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Účinnost a bezpečnost biologické léčby v terapii zánětlivých revmatických onemocnění

Effectiveness and safety of biological therapy in inflammatory rheumatic diseases

Disertační práce

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Abstrakt

Disertační práce se zabývá hodnocením účinnosti a bezpečnosti biologické/cílené léčby u chronických zánětlivých revmatických onemocnění na základě dat z registru ATTRA. Úvodní kapitoly jsou věnovány třem revmatickým onemocněním – revmatoidní artritidě (RA), psoriatické artritidě (PsA) a axiální spondylartritidě (axSpA). Práce rovněž obsahuje stručný přehled týkající se plánování, tvorby a řízení klinického registru a zmiňuje specifika spojená s analýzou dat z registru. Praktická část disertační práce cílí na dvě výzkumné otázky. V relativně nedávné době byla pro RA, PsA and axSpA definována strategie „léčby k cíli" (*treat-to-target*, T2T). Studií z reálné klinické praxe potvrzující nadřazenost T2T strategie nad konzervativním přístupem je stále nedostatek. Proto prvním cílem této práce bylo ohodnotit, zda následování strategie T2T po nedosažení alespoň nízké aktivity během prvních šesti měsíců léčby vede k vyšší šanci dosažení léčebného cíle v rámci dvanáctiměsíční kontroly. Naším druhým cílem bylo zjistit, zda existuje asociace mezi léčebnou odpovědí (dosažení remise a setrvání na léčbě) a vnímáním celkového zdravotního stavu samotnými pacienty při zahájení léčby na základě odpovědí na vybrané dvě otázky SF-36 dotazníku. Pro obě analýzy jsme zahrnuli pacienty s RA, PsA a axSpA zahajující první linii biologické/cílené léčby a aplikovali jsme metodu párování pacientů pomocí propensity skóre s cílem minimalizovat selekční zkreslení studie. Pro druhou analýzu jsme navíc použili dva různé datové soubory, abychom naše výsledky validovali. Výsledky první analýzy prokázaly vyšší účinnost strategie T2T oproti konzervativnímu přístupu u pacientů s RA (statisticky významně) a s axSpA (pouze numericky). Pacienti řídící se léčbou k cíli ukázali významně větší zlepšení stran aktivity onemocnění a kvality života mezi kontrolou v šestém a dvanáctém měsíci než pacienti, kteří se danou strategií neřídili. Dále jsme zjistili, že je strategie léčby k cíli v reálné klinické praxi v rámci ČR nedostatečně aplikována. Výsledky druhé analýzy poskytly silný důkaz, že to, jak pacienti s RA vnímají svoje zdraví při zahájení léčby, je možné použít k predikci remise při dvanáctiměsíční kontrole. Pacienti, kteří očekávají, že se jejich zdraví zhorší, a pacienti, kterým se zdá, že onemocní snadněji než jiní lidé při zahájení léčby, měli vyšší šanci na dosažení léčebné odpovědi během prvního roku léčby než pacienti, kteří si to nemysleli. U diagnóz PsA a axSpA podobně silný důkaz získán nebyl.

Klíčová slova: revmatoidní artritida, psoriatická artritida, axiální spondyloartritida, léčba k cíli, biologická/cílená léčba, remise, nízká aktivita, klinický registr, ATTRA, propensity skóre, SF-36

Abstract

This thesis focuses on evaluating the effectiveness and safety of biological/targeted treatment in chronic inflammatory rheumatic diseases based on data from the ATTRA registry. The introductory chapters of the thesis give an overview of three rheumatic diseases – rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), characterising clinical manifestation, diagnosis, therapeutical options and current treatment guidelines. The work also contains a brief summary of information about planning, creating and maintaining a clinical registry and characterises specifics related to the analysis of registry data. The practical part of the thesis was aimed at two research questions. Recently, a treat-to-target (T2T) strategy was established for RA, PsA and axSpA. Studies from daily clinical practice concerning the advantage of following T2T over usual care are still lacking. Thus, the first goal of the thesis was to evaluate whether following a treat to target strategy after not reaching low disease activity within the first six months leads to a higher chance of meeting the treatment target at the twelve-month visit. Our second goal in the thesis was to evaluate the association between therapeutic response (achieving remission and drug retention) and patients' self-perceived general health status at the treatment initiation based on answers in the SF-36 questionnaire. For both analyses, we included patients with RA, PsA and axSpA starting their first-line biological/targeted therapy and employed the propensity score matching to reduce selection bias. For the second analysis, we used two different datasets to validate our findings. The results of the first analysis showed that the T2T strategy was more effective than the conservative approach in patients with RA (statistically significantly) and with axSpA (only numerically). Patients following the T2T strategy showed significantly bigger improvements in disease activity and quality of life within the period from the 6- to 12-month visit than patients not following the strategy. We have also found that the application of the T2T is underused in the Czech Republic. The second analysis results provided strong evidence that self-perceived general health at the start of TNFi therapy predicts reaching remission at 12 months in patients with RA. We showed that both patients who expected their health to get worse and patients who seemed to get sick a little easier than other people at treatment initiation had higher odds of treatment response within the first year than patients who did not think that. In the other two diagnoses, the evidence was not strong.

Keywords: rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, treat-to-target, biological/targeted treatment, remission, low disease activity, clinical registry, ATTRA, propensity score, SF-36

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Contents

1 Introduction

Over the past two decades, a significant advance in the therapy of patients with inflammatory rheumatic diseases came with new drugs (conventional / targeted synthetic and biologic disease-modifying drugs), the development of new classification criteria, and the application of new treatment strategies. Although complete remission (or at least low disease activity) is today‘s therapeutic goal, many patients do not reach this target or achieve it but remain dependent on medication (Smolen et al. 2016). Thus, new therapies are still needed.

The effectiveness and safety of new drugs are primarily evaluated in randomised clinical trials. However, clinical trials are focused on a target patient group with strict inclusion and exclusion criteria. Therefore, they are not able to provide information, such as treatment response within the real-world practice. Clinical registries collecting data of a wide range of (not pre-selected) patients can answer the treatment effectiveness and safety questions in a real-world setting. The information provided by clinical registries is crucial for both pharmaceutical companies and global regulatory authorities.

Recently, a new treatment strategy called the treat-to-target strategy was established for patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis (see chapters 2.1.3, 2.2.3 and 2.3.3). According to the strategy, patients should be treated toward a target of remission or at least low disease activity, and the target should be reached within six months since treatment initiation. Otherwise, the drug should be switched. The efficacy of the treat-to-target approach in patients with rheumatoid arthritis has been evaluated in many randomised controlled clinical trials (Schipper et al. 2010; Stoffer et al. 2016) and several studies concerning real-life data (Schipper et al. 2012; Versteeg et al. 2018; Brinkmann et al. 2019; Ramiro et al. 2020; Vermeer et al. 2011; Steunebrink et al. 2016). Even though the T2T strategy has been widely applied in patients with rheumatoid arthritis nowadays, studies from daily clinical practice concerning the advantage of following T2T over usual care are still required (especially for psoriatic and axial spondyloarthritis). Thus, the first goal of the thesis was to evaluate whether following a treat-to-target strategy after not reaching a treatment target within the first six months leads to a higher chance of meeting the treatment target at the twelve-month visit.

One of the main therapy targets in patients is an optimisation of the quality of life. Several instruments were developed to evaluate patients’ quality of life and functioning. Patient-reported outcomes (PROs) provide reports directly from patients about their own health, quality of life, or functional status associated with the health care or receiving treatment

(Weldring a Smith 2013). One of the most widely used PRO instruments is the SF-36 (Short Form 36) questionnaire which evaluates the patient's health status using eight dimensions and includes 36 questions in total (Brazier et al. 1992). PROs have been shown to predict various disease outcomes (Jarnagin et al. 2021; Vámosi et al. 2020; Kuusalo et al. 2017). Our second goal in the thesis was to evaluate the association between therapeutic response (achieving remission and drug retention) and patients' self-perceived general health status at the treatment initiation based on answers to two selected questions in the SF-36 questionnaire.

Both goals were assessed within patients diagnosed with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis based on data from the ATTRA registry.

The thesis is divided into two parts – theoretical and practical. The theoretical part focuses on the characterisation of three rheumatic diseases (2) – rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. Clinical manifestation, diagnosis, therapeutical options and current treatment guidelines for the diseases are presented. The subsequent chapter (3) briefly summarizes information about planning, creating and maintaining a patient registry and characterises specifics related to the analysis of registry data. The bridge between the theoretical and practical section is chapter (4) devoted to the ATTRA registry. This national, prospective, observational cohort study aims to evaluate the safety and effectiveness of biological/targeted therapy for patients with chronic inflammatory rheumatic diseases. The subsequent chapters are dedicated to the goals of the statistical analyses (5), followed by a description of used methods (6), results (7), discussion (8), conclusions (9) and summary (10).

2 Rheumatic diseases

This work deals with data of patients with **rheumatoid arthritis** (RA), **psoriatic arthritis** (PsA) and **axial spondyloarthritis** (axSpA; i.e. ankylosing spondylitis AS and non-radiographic axial spondyloarthritis nr-axSpA). Therefore, this part focuses on these diagnoses. We will briefly describe the nature of the disease, treatment strategies and treatment recommendations created by the European League Against Rheumatism (EULAR).

2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterised by an uncontrolled proliferation of synovial tissue in joints. Over time, bone erosion, cartilage destruction, deformities and full loss of joint integrity can occur (Rindfleisch a Muller 2005; Kumar et al. 2016). A huge advance in the treatment of patients with RA was recorded with the introduction of new drugs (biologics), the development of new classification criteria, and the application of new treatment strategies. Nevertheless, complete remission is not very frequent and is usually closely related to concomitant therapy (Smolen et al. 2016).

2.1.1 Clinical presentation, aetiology and risk factors

First symptoms most likely arise in 35–50 years of age (Kumar et al. 2016; Pavelka et al. 2018). Morning stiffness, tenderness, joint swelling and pain are the most common manifestations. Polyarthritis of large and small joints can occur (especially in hands and feet). Practically any joint can be affected, but the pattern is usually bilateral and symmetric, and the joints are usually not erythematous (Rindfleisch a Muller 2005; Pavelka et al. 2018; Majithia a Geraci 2007). Even though RA primarily involves joints, it can manifest extra-articularly as well. It is connected with a wide array of comorbidities, often affecting the heart and lungs. Therefore, the disease should be considered as a syndrome or systematic disease (Smolen et al. 2016; Kumar et al. 2016). Extra-articular manifestations may include rheumatoid nodules, vasculitis, osteoporosis, anaemia, carpal tunnel syndrome, pulmonary involvements or dry conjunctivitis. RA has also been associated with an increased risk of lymphoma, cardiovascular disease, depression and increased mortality (Pavelka et al. 2010; Smolen et al. 2016).

The precise aetiology of this autoimmune disease is not fully understood (Rindfleisch a Muller 2005). A triggering event (combination of environmental and infectious factors) initiates

joint inflammation (Majithia a Geraci 2007). Over time, inflamed synovial tissue begins to grow and form invasive granular pannus tissue. Pannus then invades and destroys cartilage and bone. Further joint destruction is caused by released cytokines, interleukins, proteinases and growth factors. These cells and molecules often represent the treatment target (Rindfleisch a Muller 2005).

Risk factors for developing RA include female sex, positive family history, older age, low socioeconomic status, and smoking (Rindfleisch a Muller 2005). For seropositive RA, the estimated heritability is 40–65%. Genome-wide association studies characterised more than a hundred loci associated with the risk of RA. The HLA system (HLA-DRB1 gene mainly) plays a crucial role (Smolen et al. 2016). Further, apart from genetic changes, epigenetic modifications (e.g. acetylation and DNA methylation) contribute to disease development (Klein a Gay 2015). Lately, the microbiome's effect on disease risk and progression has been the focus of studies (Scher et al. 2016; Smolen et al. 2016). The disease affects approximately 1% of the adult population worldwide (Kumar et al. 2016; Pavelka et al. 2010).

2.1.2 Diagnosis and treatment

Early diagnosis is key to therapeutic success (Smolen et al. 2016). However, there is no single test that confirms the diagnosis (Rindfleisch a Muller 2005). Therefore, diagnosis is based on clinical assessment supported by radiological imaging, blood and serology marker assessment (Kumar et al. 2016). The initial laboratory tests consist of complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) (Majithia a Geraci 2007; Pavelka et al. 2018). Next, baseline renal and hepatic function tests are recommended to guide medication choices.

Early treatment is crucial to decrease the rate of disease progression. Therapeutic goals include minimising inflammation and pain, preserving physical function, quality of life, social and work capacity, protecting joints from structural damage and controlling systemic complications (Rindfleisch a Muller 2005; Smolen et al. 2020). Treatment decisions should be based on disease activity, safety issues, comorbidities and progression of structural damage. We distinguish two main treatment forms – pharmacological and surgical (arthroscopy, arthroplasty), and those two can be supplemented by non-pharmacological treatment (e.g. yoga or massage therapy).

Pharmacological treatment generally involves the treatment of symptoms, e.g. with nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs) and disease-modifying

antirheumatic drugs (DMARDs) (Majithia a Geraci 2007; Kumar et al. 2016). **NSAIDs** (e.g. aspirin, diclofenac, ibuprofen, nimesulide) reduce joint pain and swelling, but they should not be used alone as they do not change the disease course (Majithia a Geraci 2007). **GCs** (e.g. prednisone, methylprednisolone) may slow joint damage and relieve symptoms. They should be prescribed only at a low dose and for a short duration because of the high risk of side effects (Rindfleisch a Muller 2005). Treatment with **conventional synthetic DMARDs** (csDMARDs) should be initiated as soon as possible, ideally at the time of diagnosis. Early use slows disease progression and improves overall long-term prognosis. Methotrexate (MTX) represents the first choice of treatment. In case of side effects of MTX, leflunomide, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, or gold salts may be considered. When the response to the first csDMARD is inadequate, adding another DMARD drug in combination therapy may be the right choice (Majithia a Geraci 2007; Rindfleisch a Muller 2005).

Biologics (i.e. bDMARDs) represents a significant advance in therapy. Biologics come with new molecular mechanisms that target cytokines, signalling molecules and cells involved in inflammation and joint destruction (Majithia a Geraci 2007). These include, e.g. tumour-necrosis factor inhibitors (TNFi), interleukin-1 antagonists, interleukin-6 antagonists, anti-B cell antibodies and down-regulators of T-cell co-stimulation.

Targeted synthetic DMARDs (tsDMARDs) have been developed to modulate a particular target involved in the generation of inflammation (Smolen et al. 2016). An example of tsDMARDs is Janus kinase inhibitors (JAKi), such as tofacitinib, baricitinib or upadacitinib.

Despite all benefits of bDMARDs/tsDMARDs, serious adverse events are not rare (increased risk of infection, tuberculosis reactivation and cardiovascular diseases) (Majithia a Geraci 2007). Early use of DMARDs (biologics) has improved outcomes of the disease but requires close monitoring of disease course and medication side effects (Majithia a Geraci 2007). Treatment algorithms involve measuring disease activity with composite indices and applying a treat-to-target strategy (see following subchapter 2.1.3). In real clinical practice, the most frequently used composite indices for measuring disease activity are DAS28 (disease activity score using 28 joint counts) and the simplified disease activity index (SDAI). They provide continuous numerical scales measuring disease activity and can be further caregorized based on validated cut-offs (Smolen et al. 2016).

2.1.3 EULAR treatment recommendations for RA management

In 2010, the European League Against Rheumatism (EULAR) developed its first recommendations for the management of RA with DMARDs (Smolen et al. 2010). Over the years, there have been several updates, with the last update so far at the end of 2019 (Smolen et al. 2020). Treating toward a target of remission (REM) or at least low disease activity (LDA) has become the standard of care for patients and requires switching between drugs. According to EULAR recommendations, therapy with csDMARDs should be started as soon as the diagnosis is made, and MTX should be the first choice. A short-term combination with GC is advised. In the absence of poor prognostic factors (i.e., presence of RF/ACPA, persistently moderate/high disease activity, high ESR/CRP, early erosion, failure of two or more csDMARDs), other csDMARDs should be considered. If the treatment target (TT) is not reached with the first csDMARDs, and poor prognostic factors are present, a bDMARD or tsDMARD should be added. Biological DMARDs and tsDMARDs should be combined with a csDMARD if possible. If there is no improvement within three months after the start of treatment or if patients have not reached the TT by six months, therapy should be adjusted, and treatment with another bDMARD/tsDMARD should be considered. If a patient is in lasting remission after having tapered GCs, tapering bDMARDs/tsDMARDs may be considered as well. Tapering the csDMARDs comes last (Smolen et al. 2020).

The currently recommended approach for RA treatment involves titrating medication dosages until pre-specified disease activity targets have been met and maintaining these targets over time. Such so-called **treat-to-target strategy** (T2T) has proven to be more effective and generates better outcomes than usual care (Schoels et al. 2010b; Schipper et al. 2012). Many randomised controlled clinical trials have evaluated the efficacy of the T2T approach (Grigor et al. 2004; Verstappen et al. 2007; Goekoop-Ruiterman et al. 2005; Schipper et al. 2010; Stoffer et al. 2016; Schoels et al. 2010b). Even though the T2T strategy has been widely applied in daily clinical practice nowadays, studies from daily clinical practice concerning the advantage of following T2T over usual care are still required. Several studies concerning the efficacy of T2T in real clinical practice have been already conducted, but more evidence through real-life data is needed to support the T2T implementation (Schipper et al. 2012; Versteeg et al. 2018; Brinkmann et al. 2019; Ramiro et al. 2020; Vermeer et al. 2011; 2013; Steunebrink et al. 2016).

The increasing number of effective drugs has increased the likelihood of reaching the TT for RA patients, but high drug costs still limit widespread use. However, approval of **biosimilar** (**bs**) **DMARDs** led to a considerable reduction in bDMARD costs (Smolen et al.

2020). In the Czech Republic, there are available biosimilar counterparts to bio-original (bo) adalimumab, etanercept, infliximab and rituximab at the beginning of the year 2022.

2.2 Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis, usually characterised by seronegativity for rheumatoid factor. PsA is included in the group of **spondyloarthritis** (e.g. ankylosing spondylitis or reactive arthritis). The disease is complex and heterogeneous due to a wide range of disease manifestations (Scotti et al. 2018).

2.2.1 Clinical presentations, aetiology and risk factors

The first symptoms of this chronic musculoskeletal disease usually occur at the age 30–55 (Pavelka et al. 2018; Cantini et al. 2010). Even though the joint distribution is highly variable, asymmetric oligoarthritis (≤ 4 joints involved) is the most frequent pattern at disease onset. With time, the number of involved joints usually increases (polyarticular form). Arthritis is typically peripheral, less often axial (Cantini et al. 2010). Other musculoskeletal manifestations may include spondylitis[1] and sacroiliitis (similarly to ankylosing spondylitis), dactylitis[2] and enthesitis[3]. Skin manifestations comprise psoriasis[4] and nail disease (nail dystrophy). Up to 30% of patients with psoriasis may develop PsA throughout their lives (Ogdie et al. 2020). Approximately 70% of PsA patients develop psoriasis before articular involvement (Cantini et al. 2010). Although psoriasis usually appears before arthritis, both symptoms can sometimes manifest simultaneously (Pavelka et al. 2010). In more severe cases, the development of articular erosions and deformities may occur (Cantini et al. 2010).

Apart from joint and skin manifestations, there are often present comorbidities, such as metabolic syndrome, hypertension, diabetes mellitus, dyslipidemia, obesity, cardiovascular disease, inflammatory bowel disease (IBD), uveitis[5], infections, kidney and fatty liver disease, osteoporosis, fibromyalgia, gout, anxiety or depression. Patients with PsA also experience physical function limitations, fatigue, reduced work capacity and social participation (Perez-Chada a Merola 2020; Ogdie et al. 2020).

[1] Spondylitis is an inflammation of the spinal bones, or vertebrae.
[2] Dactylitis is defined as an inflammation of the whole digit, also called as the ‘sausage-shaped digit‘ (Ogdie et al. 2020; Cantini et al. 2010).
[3] Enthesitis is an inflammation at sites where ligaments, tendons, and joint capsules are attached to the bone (McGonagle et al. 1998).
[4] Most common type is psoriasis vulgaris or plaque psoriasis (Ogdie et al. 2020).
[5] Uveitis is an inflammation of the uveal tract (i.e. middle layer of the eye) (Muñoz-Fernández a Martín-Mola 2006).

The aetiology of PsA is still unknown. PsA originates in the complex interplay of genetic factors, environment (e.g. infection or stress) and immune mechanisms (clonally expanded CD8+ T-cells), where cytokines play a crucial role (Cantini et al. 2010). The disease is often associated with human leukocyte antigen (HLA) class I. HLA-B27 is present in approximately 50% of cases and is also a marker of disease severity (Pavelka et al. 2010; Cantini et al. 2010). Men and women are affected in the same measure (Scotti et al. 2018). A family history of psoriasis/PsA is associated with increased disease risk. Environmental factors – trauma, infections, vaccinations and low socioeconomic status play a role in developing PsA in genetically predisposed individuals (Solmaz et al. 2018).

2.2.2 Diagnosis and treatment

Screening tools and imaging methods helped to increase the recognition of the disease. However, there is still a relatively high prevalence of undiagnosed patients (Solmaz et al. 2018). Similar to RA, there is no specific laboratory test for PsA diagnosis (Cantini et al. 2010). Typically, RF and ACPA are absent in patients with PsA (Pavelka et al. 2010). Early diagnosis can improve the diseases' prognosis because early treatment has shown to be connected with better long-term outcomes (Solmaz et al. 2018).

In 1973, Moll and Wright first developed specific classification criteria for PsA to distinguish the disease from RA (Moll a Wright 1973). In 2006, more structured criteria were published by the Classification Criteria for Psoriatic Arthritis (CASPAR) study group, with 98,7% specificity and 91,4% sensitivity (Taylor et al. 2006). Involvement of more than five joints at the onset, elevated ESR, higher age, HLA-B27 positivity and specific polymorphism alleles have been identified as predictors of disease severity (Cantini et al. 2010).

Daily management of PsA patients includes non-pharmacological (e.g. education, physical exercises, weight loss, massage therapy) as well as pharmacological interventions (Gossec et al. 2020). Similarly to RA, treatment for PsA patients includes GCs, NSAIDs and b/cs/tsDMARDs. While GCs and NSAIDs are indicated in mild cases, DMARDs should be started in non-responding patients or patients with more severe disease (Cantini et al. 2010). From csDMARDs, sulfasalazine, leflunomide and methotrexate are recommended. Biologics approved for PsA treatment in the Czech Republic at the beginning of 2022 include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab (all TNFi), secukinumab and ixekizumab (both interleukin inhibitors). From tsDMARDs, tofacitinib and newly upadacitinib have been introduced in the Czech Republic. The treatment target is the

elimination of inflammation and optimisation of the quality of life. When choosing the right therapy for a patient, individual disease characteristics and comorbidities have to be considered to balance efficacy and safety (Gossec et al. 2020).

2.2.3 EULAR treatment recommendations for PsA management

In 2011, EULAR developed recommendations for pharmacological management of PsA and updated them in 2015 (Gossec et al. 2012; 2016). In 2019, EULAR published the latest update (Gossec et al. 2020). According to these recommendations, treatment should be aimed at reaching the target of REM or LDA by regular monitoring and appropriate therapy adjustments (Gossec et al. 2020). This co-called **T2T strategy** is already well-validated in RA. The benefit of the T2T strategy compared to routine care in PsA has been shown in the TICOPA clinical trial (Coates et al. 2015). However, more studies, especially from real clinical practice, are needed.

NSAIDs may be used to relieve musculoskeletal symptoms. Local injections of GCs should be considered as adjunctive therapy. Systemic GCs can be used only for a short period and at a low dose. In patients with polyarthritis, a csDMARD should be quickly initiated (MTX is preferred). In patients with oligoarthritis and poor prognostic factors (i.e. structural damage, high ESR/CRP, dactylitis, nail involvement), csDMARD should be considered as well. In patients with peripheral arthritis and an insufficient response to at least one csDMARD, therapy with a bDMARD should be started. If patients have an inadequate response to at least one csDMARD and at least one bDMARD or bDMARD is inappropriate, a JAKi may be considered. In patients who do not respond adequately or are intolerant of a bDMARD, switching to another bDMARD/tsDMARD should be considered. In patients with enthesitis and insufficient response to NSAIDs or local GC injections, therapy with bDMARD should be considered. In patients with predominantly axial active disease with insufficient response to NSAIDs, therapy with a bDMARD should be considered. In patients with sustained remission (at least for six consecutive months), cautious tapering of DMARDs may be considered (Gossec et al. 2020). Response to treatment is defined as at least 50% improvement of the composite measure within three months and achieving a treatment target (i.e. REM or LDA) within six months (Gossec et al. 2016). Disease activity index for psoriatic arthritis (DAPSA) or minimal disease activity (MDA) is recommended to assess the achievement of the treatment target (Smolen et al. 2018).

2.3 Axial Spondyloarthritis

Axial spondyloarthritis (axSpA) belongs to a seronegative spondyloarthritis group with a predominantly affected axial skeleton (i.e. spine and sacroiliac joints) and presents typically with inflammatory back pain. AxSpA is an umbrella term including both **ankylosing spondylitis** (AS; also called radiographic axSpA) and **non-radiographic axSpA** (nr-axSpA). The difference between the two conditions is the presence of radiographic sacroiliitis (i.e. structural damage in the sacroiliac joints or spine). In nr-axSpA, there is no definitive radiographic sacroiliitis and can be regarded as an earlier or milder part of axSpA with possible future development of structural damage in the axial skeleton (Kumthekar a Deodhar 2021; Sieper a Poddubnyy 2017).

2.3.1 Clinical presentation, aetiology and risk factors

Patients with axSpA present with chronic back pain and stiffness, mainly in the lower back and pelvis, but any part of the spine can be involved. Back pain usually gets better with exercise, not with rest (Kumthekar a Deodhar 2021). Inflammation and structural damage can occur in the axial skeleton, and this can lead to spinal mobility restriction (Sieper a Poddubnyy 2017). Spinal disease in patients with axSpA is characterised by syndesmophytes formation (bony bridges) at vertebrae bodies. In advanced axSpA, the classical bamboo spine can be seen as a result of vertebral body fusion (Kumthekar a Deodhar 2021). The most common peripheral manifestations are enthesitis and (oligo)arthritis in an asymmetrical pattern (predominantly lower limbs). Less frequently, dactylitis may occur. The most frequent extra-articular manifestation is uveitis, less often psoriasis and IBD. Comorbidities such as osteoporosis and cardiovascular diseases can also occur (Sieper a Poddubnyy 2017; Pavelka et al. 2010). As a result of chronic back pain and stiffness, fatigue connected with sleep disturbances is often present (Kumthekar a Deodhar 2021).

The disease usually occurs in the second or third decade of life. Ankylosing spondylitis affects men two or three times more often than women. In nr-axSpA, men and women are diseased more or less equally (Sieper a Poddubnyy 2017). In Europe, the prevalence estimate of AS is around 0.25% (Stolwijk et al. 2016). The exact cause of the disease is still unknown (genetic and environmental factors). AxSpA is closely associated with the HLA-B27 gene, with more than 90% of AS patients having the HLA-B27 antigen (Pavelka et al. 2010). Apart from the HLA-B27 gene, genome-wide association studies have detected several other genes associated with AS (Sieper a Poddubnyy 2017). More than 90% heritability for AS was estimated within

twins' studies (Brown et al. 1997). The epicentre of inflammation in axSpA is represented by IL-23/IL-17 pathway, which yielded several potential target options for treatment (Ritchlin a Adamopoulos 2021).

2.3.2 Diagnosis and treatment

Early diagnosis of axSpA is important because it is associated with better outcomes in terms of disease activity, function, spinal mobility and radiographic damage. The diagnosis can be quite challenging as back pain in the population is frequent; therefore, a delay in diagnosis often occurs (Ritchlin a Adamopoulos 2021; Kumthekar a Deodhar 2021). Nevertheless, inflammatory back pain or chronic pain in the lower back in individuals younger than 45 years of age is an important clue that should raise suspicion of axSpA and subsequent testing for HLA-B27, CRP, and imaging should be performed (Ritchlin a Adamopoulos 2021).

While progressive changes on X-rays of sacroiliac joints are required for the diagnosis of AS, in nr-axSpA, a radiographic sacroiliitis is absent (Ritchlin a Adamopoulos 2021). The modified New York criteria are widely used in clinical practice for making the diagnosis (van der Linden et al. 1984). However, they do not allow capturing the early phase in the absence of radiographic changes in the sacroiliac joints, which can take years to manifest (Sieper a Poddubnyy 2017). The Assessment in SpondyloArthritis International Society (ASAS) published new classification criteria for axSpA (Rudwaleit et al. 2009a; 2009b). They include imaging (besides radiography, MRI included) and a genetic arm, thus enabling the classification of patients as nr-axSpA (Ritchlin a Adamopoulos 2021). However, these criteria were not developed to make a diagnosis but for research purposes (Kumthekar a Deodhar 2021). As separate diagnostic criteria are generally not available, classification criteria are often wrongly used for diagnostic purposes (Sieper a Poddubnyy 2017).

The therapy can be divided into non-pharmacological (physical therapy, exercise, quitting smoking) and pharmacological. Both musculoskeletal and extra-articular manifestations should be taken into account when choosing a drug (Heijde et al. 2017).

NSAIDs are recommended as the first line of treatment in patients with axSpA (both AS and nr-axSpA). They reduce back pain and stiffness. **Conventional synthetic DMARDs** are not effective in axial disease (Kumthekar a Deodhar 2021). Long-term use of **GCs** should be avoided (Ritchlin a Adamopoulos 2021). TNF inhibitors represent the main group of **bDMARDs** and are used to control the symptoms after the NSAIDs' failure. All TNFi have

proved to be effective in the improvement of musculoskeletal manifestations in axSpA (Kumthekar a Deodhar 2021; Karmacharya et al. 2020). Predictors of a good response to TNFi is a young age, elevated CRP and active MRI inflammation (Poddubnyy a Sieper 2020). At the start of 2022, in the Czech Republic, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab from TNFi and secukinumab or ixekizumab (IL-17A inhibitors) are administered. Similarly to RA and PsA, biosimilars are available. From **tsDMARDs** (particularly JAK inhibitors), upadacitinib was approved to treat AS patients in the Czech Republic.

2.3.3 EULAR treatment recommendations for axSpA management

The ASAS/EULAR recommendations for axSpA management were first created in 2006, with the following updates in 2010 and 2016 (Zochling et al., 2006; Braun et al., 2011; Heijde et al., 2017). The T2T strategy previously mentioned in the text for RA (see 2.1.3) and PsA (see 0) diagnosis was established for axSpA patients as well (Smolen et al., 2018). Several T2T trials have been carried out or are currently ongoing in axial SpA, e.g. TICOSPA trial (Moltó et al., 2020) or AScalete study (Poddubnyy et al. 2020).

Treatment should be monitored and investigated whether the treatment target defined as remission or low disease activity is reached (Heijde et al. 2017; Smolen et al. 2018). Disease activity is usually evaluated through composite scores Bath Ankylosing Spondylitis Disease Index (BASDAI) (Garrett et al. 1994) or the Ankylosing Spondylitis Disease Activity Score (ASDAS) (Machado et al. 2011). While the BASDAI is a fully patient-reported outcome, the ASDAS combines patient-reported outcomes and CRP/ESR and, thus, is the preferred measure (Heijde et al. 2017; Smolen et al. 2018). ASDAS inactive disease (< 1.3) is a clinical remission-like definition and corresponds to a primary treatment target. An alternative target is moderate disease activity (corresponds to LDA), defined as ASDAS < 2.1 (Smolen et al. 2018).

According to ASAS/EULAR recommendations, the primary goal of axSpA treatment is to maximise the long-term quality of life through control of symptoms, inflammation, prevention of progressive structural damage and normalisation of function and social participation. Treatment should always be individualised based on current disease symptoms, patient characteristics and the presence of comorbidities. Patients with pain and stiffness should use NSAIDs as a first-line drug. Local GCs injection may be considered; systemic GCs should not be administered. Patients with purely axial disease should not be treated with csDMARDs; sulfasalazine may be given to patients with peripheral arthritis. Biological DMARDs are considered in patients with persistently high disease activity (ASDAS ≥ 2.1 or BASDAI ≥ 4)

despite conventional treatments. It is recommended to start with TNFi and switch to another TNFi or IL-17 inhibitor (i.e. secukinumab) in case of failure. In bDMARDs, a failure is defined as not reaching a clinically important improvement ($\Delta\downarrow$ ASDAS $\geq$ 1.1) within three months or not achieving the treatment target within six months. In patients with sustained remission (for at least six months), tapering of bDMARDs may be considered (Heijde et al. 2017; Smolen et al. 2018).

3 Clinical registries

Since this work is focused on the analyses of real-world data from the clinical registry ATTRA, this chapter is dedicated to clinical registries. This whole chapter will briefly summarise clinical registries in terms of planning, registry creation, registry maintenance and finally, processing and analyzing registry data.

First, it is important to distinguish between clinical trials and registries. Clinical registries (also called patient registries) can be defined as ‘organised systems that use observational methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serve one or more predetermined scientific, clinical, or policy purposes‘ (Gliklich a Dreyer 2010). Clinical trials are experiments in which an intervention intended to change a human subject’s outcome is implemented, usually through a randomisation process that takes away the decision-making from practitioners. In contrast, registries use an observational study design that does not control the treatment plan. A well-designed patient registry collects data about the care that is actually provided. There are usually fewer inclusion and exclusion criteria and that allows studying a wider range of patients (results can be generalised). Although the evaluation of registry data is similar to the evaluation of clinical trial data, they differ in certain areas. Therefore, it is necessary to use different constructs when processing clinical data from registries (Gliklich a Dreyer 2010). Even though regulators prefer data from randomised controlled trials, these data can be limited or are not ethical/feasible in some situations. Patient registry data may provide crucial support for regulatory decision-making, and they represent a useful tool for health-related real-world evidence (McGettigan et al. 2019). Therefore, patient registries provide valuable data, contribute to evidence-based medicine (EBM) and fill the gaps in EBM that cannot be addressed by randomised clinical trials (Gliklich a Dreyer 2010).

The following subchapters are based mainly on publications (Gliklich a Dreyer 2010; Chrápavá et al. 2018) and my own work experience in the field of clinical registries.

3.1 Registry types

We can **classify** registries based on defined populations. Product registries include patients exposed to biopharmaceutical products (e.g. drugs) or medical devices. Disease/condition registries consist of patients with the same diagnosis (e.g. rheumatoid arthritis or chronic lymphocytic leukaemia). Another group, health services registries, is

defined by patients who have had the same/similar procedure, clinical encounter or hospitalisation. Populations registries are based on geographical areas and are used only for public health reporting, not for evaluating outcomes (Gliklich a Dreyer 2010).

Further, in this text, we will mainly focus on **clinical registries** (also called disease or patient registries). The data are collected in a real-life clinical practice, where the care results from a joint decision of a clinician and a patient (not assigned by the registry protocol).

3.2 Planning a registry

Before creating a registry, several key steps are needed. We have to decide what the registry's purpose will be; we have to define target populations, means for addressing the research questions, identify stakeholders[6], assess the feasibility and ensure funding. It is crucial to establish a registry team (e.g. project managers, data managers, quality managers or data analysts) and a scientific board for the registry (healthcare specialists, scientists) based on their experience and expertise. Another essential thing is to plan how and when the registry will end.

3.2.1 Scope of the registry

The **purpose** of different registries may vary and is closely related to the registry's design. The aim of a registry can be, e.g. description of the natural history of the disease, monitoring and evaluation of clinical effectiveness, quality of life of patients, cost-effectiveness of health care products (e.g., drugs) or monitoring drug safety (Gliklich a Dreyer 2010). Overall, most registries' mission is to improve the quality of patient care and improve patients' health (Chrápavá et al. 2018).

As was already mentioned, a patient registry should be **designed** with respect to its major purpose. A research question should be formulated first, followed by choosing a study design. Next, questions of clinical interest have to be translated into measurable exposures and outcomes (Gliklich a Dreyer 2010). Researchers and clinicians, in cooperation with analysts, have to create a set of collected variables and put them into case report form (CRF). Each objective is usually described by one primary endpoint or by one or more secondary endpoints if needed (Chrápavá et al. 2018). The variables can be collected at registry entry or during follow-up visits. The standard set of variables collected across various clinical registries usually

[6] Stakeholders include patients, clinicians, providers, product manufactures, authorization holders or payers (Gliklich a Dreyer 2010).

include basic demographic characteristics (e.g., ID, date of birth, sex or date of diagnosis), symptoms, clinical and laboratory characteristics, treatment characteristics, adverse events and patient status (alive, dead, lost to follow-up). Patient-reported outcomes measures (PROMs) represent another common group of collected parameters. These data are taken directly from patients and depict real-life information about patients‘ quality of life (e.g., SF-36 questionnaire). Many variables used in data analyses can be derived from collected data, for example, age at diagnosis, overall survival or treatment duration.

It is essential to collect enough information to answer the registry objectives but not overwhelm clinicians and patients with too many required variables. The attitude that everything about patients should be collected is not always the best solution considering the registry‘s long-term sustainability and the costs of data collecting (Chrápavá et al. 2018).

Other steps when creating registry design include choosing patients for the study, determining the follow-up length and frequency of visits, how many patients need to be studied and whether a comparator group is needed (Gliklich a Dreyer 2010; Dixon et al. 2010). It has to be decided whether the registry will have a short-term course or whether continuous data collection will be planned. Usually, clinical registries are continual projects and do not limit to certain follow-up periods (Chrápavá et al. 2018). However, the sample size and follow-up duration should be large enough to address the registry aims. Registries can provide valuable information about product safety and often function as post-authorisation safety studies (PASS). Therefore, it is necessary to ensure that the information about adverse events will reach the right stakeholders (Gliklich a Dreyer 2010).

3.2.2 Stakeholders and experts of the registry

The main stakeholders involved in the registry creation and functioning of the registry include professional society, clinicians, researchers, contract research organisation (CRO), patient organisation representatives, pharmaceutical industry representatives, regulatory authorities, healthcare providers and healthcare payers. Engaging healthcare specialists and scientists (‘opinion makers’) in the registry project and formating a scientific board for the registry is a critical step for the registry‘s future success (Chrápavá et al. 2018). Another crucial thing is creating an internal project team. The key team members consist of the project manager, data manager, data analyst, pharmacovigilance manager, helpdesk (i.e. registry support) and quality manager.

3.2.3 Ethics, data ownership, funding and privacy

As the creation and use of a clinical registry for research purposes constitute "research involving human subjects ", there are some legal requirements that registries have to fulfil.

Patient data are highly confidential, and it is crucial to ensure patients' privacy. Anonymisation and pseudonymisation of data ensure the information entered in the registry cannot lead to identifying individual patients by third parties. The **Anonymisation** procedure completely removes any information in data that could lead to an individual being identified (e.g. names, or addresses). The **pseudonymisation** procedure involves replacing identifying items with artificial identifiers/pseudonyms (i.e. personal ID number) when patients enter the registry. Since anonymisation does not allow certain registry functionalities (e.g. integrating data from various sources, more follow-up records per patient), pseudonymisation brings an advantage (Chrápavá et al. 2018; Zaletel a Kralj 2015). Using personal ID numbers allows the sharing of data while confidentiality is ensured. The key to re-identification of a patient is possible only at the patient's treatment centre (Chrápavá et al. 2018). In the case of pseudonymised data, the data have to be processed in compliance with the **General Data Protection Regulation** (GDPR)[7]. According to GDPR, data collected in a registry belong to a special category of personal data and can be processed only based on explicit patient consent in a written form. The informed consent should be signed before participation in the registry at the time of recruitment (Chrápavá et al. 2018).

The registry data should be protected by password and encoding and stored securely on dedicated servers with limited access by authorised registry personnel. Further reports or analytical results from the registry should not contain any information that might disrupt either patient or a physician's anonymity (Chrápavá et al. 2018).

The registry, of course, needs financial support for its existence and contracts with the sponsors specifying the exact conditions of sponsorship have to be negotiated. A multi-financial approach can be advantageous (e.g. government grants, professional societies, insurance and pharmaceutical companies or patient organisations) (Chrápavá et al. 2018).

[7] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)

3.2.4 Patients‘ and site recruitment

While planning a clinical registry, the sponsor, guarantor, professional society, and CRO must identify suitable centres and physicians for participation. The entire site selection and recruitment process should be described in the protocol. It is useful for future analyses to determine a reasonable number of recruited sites and ensure enough patient-years (Chrápavá et al. 2018).

What motivates the centres to participate are interesting scientific objectives, data and analytical results about the centre’s performance and finally, offered remuneration. The motivation for patients‘ participation can be the desire to help other patients as well himself/herself to achieve better treatment results. Inclusive and exclusive criteria for patient selection in the registry are generally broad, and often, no selection criteria are made (except diagnosis). Some registries can aim at individuals with a specific diagnosis treated with a defined therapy (e.g. targeted therapy) or limit patients by age (e.g. over 18 years old). Patient recruitment is most commonly done by the treating physician, who provides the patients with the necessary information about participation in the registry. Patients then, after careful reading, sign the informed consent (Chrápavá et al. 2018).

3.2.5 Technical feasibility

Once the dataset and data source (patients and sites) is defined, an instrument for data collection should be selected. Traditionally, data collection focused on paper-based case report forms (CRF) followed by double data entry in a relational database. Nowadays, an ideal means of data collection is through the **Electronic Data Capture** (EDC) system into electronic CRF. The EDC system enables collecting, cleaning, storing, monitoring and reporting of registry data in real-time. A significant advantage of the EDC system is implementing online data validation checks when entering data (Walther et al. 2011). Apart from various EDC systems, other IT solutions for the facilitation of data management exist, e.g. Clinical Trial Management Systems (CTMS) frequently used by pharmaceutical companies and medical research institutes in clinical research (Leroux et al. 2011).

3.2.6 Quality assurance

Another necessity when creating a registry is a control body of relevant processes. Quality assurance consists of the control that all registry-related activities were appropriately planned and documented, and everything is performed in compliance with the study protocol

and other adequate documents (see 3.2.7); the study is processed in compliance with the legal and normative requirements, and that potential risks were considered, evaluated and prevented.

3.2.7 Project documentation

An essential part of a registry project is a registry **protocol** containing all information about the registry. All participating sides must approve the protocol written by members of the project team. After internal approval, the protocol is submitted to the ethics committee and regulatory authority for official approval. All centres should receive the protocol before data collection starts (Chrápavá et al. 2018).

A **project management plan** represents a tool describing the primary purpose and scope of the project (i.e. new registry establishment). It also includes a sequence of goals, tasks and needed procedures, registry budget and timelines (Chrápavá et al. 2018).

A **data management plan** is another important document that should be prepared once the protocol and basic projects attributes are known. It describes the activities corresponding to data collection and processing. Some of the things a data management plan should include are project scope (number of countries/sites/estimated number of patients), number of language mutations, requirements on eCRF structure (e.g. form statuses, user roles, validations, adverse event reporting, translation/coding), the structure of collected data and medical coding. Other necessary data management documentation is represented by a **data validation plan** that describes all checks and validations planned to be performed on collected data (Chrápavá et al. 2018).

A **statistical analysis plan** (SAP) contains a detailed description of the analytical methods to be performed after the project completion and the corresponding lock of the database. However, the preparation of SAP does not apply to projects such as long-term registries because their objectives are more general and usually not focused on one endpoint. The SAP is applicable only if hypotheses are conducted within a clinical registry (Chrápavá et al. 2018).

Other necessary documentation when creating a registry includes a **communication management plan** (defining the registry communication), a **cost management plan** (defining both operational costs and payments to investigators), a **quality management plan** (describing the implementation of quality policies and quality requirements[8]) and a **risk management plan** (including actions, plans and activities designed to monitor, assess, prevent or solve any risks).

[8] Non-interventional studies have to follow rules called Good Pharmacoepidemiology Practice (GPP) created in 1996 (https://www.pharmacoepi.org/resources/policies/guidelines-08027/).

3.3 Registry creating

While planning a registry is mainly the project manager's responsibility, a registry's actual creation falls under the data managers. After the finalisation of CRF, the database has to be set up, tested and validated. Instructions for data entry have to be created, followed by the generation of user accounts and training of data entry personnel (Chrápavá et al., 2018).

3.3.1 Case report form creation

CRF is a printed or electronic document designed to record information about patients based on the protocol. In the case of paper questionnaires, subsequent digitisation is required to allow statistical evaluation. The process of converting data into an electronic form is connected with the potential human errors during transcription. Other disadvantages are the impossibility of setting validations (e.g. for values outside the range), problems with the readability of written data, and slower progress from data entry to data evaluation. The electronic version of CRF is, therefore, highly recommended (Chrápavá et al. 2018).

When creating CRF, we have to think through which elements are necessary for answering the main research questions and which are desirable but not essential. Parameters crucial for subsequent analyses (i.e. core set) should be marked as mandatory. Overall, the choice of data elements should be guided by parsimony, validity and the registry's purpose (Gliklich a Dreyer 2010; Chrápavá et al. 2018). As the CRF serves as a template for database creation, it is crucial to think about the visit's structure from the beginning. Individual parameters (i.e. variables) should be grouped into paragraphs (i.e. question groups, set of similar/related questions), and these paragraphs create a form (i.e. page). Visits (i.e. phases) consist of a set of forms; a set of visits forms an arm (Chrápavá et al. 2018).

3.3.2 Database setup

The protocol, CRF, data management plan and data validation plan form the basis for database development. Apart from CRF structure, the detailed registry design, schedule of planned visit and flow of collected data have to be considered. Moreover, special requests for database functionalities (e.g. reporting, data transfer, randomisation, language mutations or criteria for payments to investigators) have to be included during the development process (Chrápavá et al. 2018). The first things a data manager has to know are the registry name, the

website address, the registry's primary language, the presence of pharmacovigilance reporting, and the connection between form statuses and investigators' payments (Chrápavá et al. 2018).

Usually, the first form to be created is a **subject form** that has to be completed for each patient enrolling in the registry. This form includes basic patient data (e.g. date of birth, gender, initials) and the question of fulfilment inclusion/exclusion criteria if applicable. After completing this form, a new patient is created (the patient ID is automatically generated), and filling of other forms may start. In the case of multi-centre registries, the **site form** containing the hospital or the physician's name may also be required (Chrápavá et al. 2018).

Data managers distinguish between different arms and phases in the database. Different **arms** are typically used for different diagnoses. Different **phases** can be used for particular parts of the subject's follow-up (e.g. baseline and follow-up visits). One phase contains one or more forms that are logically composed together (e.g. in the same time period). **Phase forms** record the information from individual visits and represent the biggest part of the collected information. The mandatory questions in forms are usually marked (e.g. with an asterisk), and the form cannot be saved as completed until these questions are answered. Some variables may be automatically calculated from other questions in the database (e.g. composite indices). Others can be hidden (used only for calculations) or read-only (e.g. BMI calculated from previously filled weight and height). Some questions can be dependent on previous answers. In that case, skip logic is used to hide questions that do not have to be filled for all patients. This step helps forms be more comprehensible and easy to follow. Further, hidden description texts displayed above or below particular variables may be helpful (Chrápavá et al. 2018). The most frequently used **data field types** (see **Figure 1**) include

- *text* (string)
- *numbers* (integer – without decimal places; real – with decimal places)
- *code list* – list of more options where only one (radio button or drop-down list) or more than one (multi-select) can be chosen
- *checkbox* (a box that can be marked with a check by clicking or left blank)
- *analogue scale* (the desired value is chosen optically in an analogue scale)
- *picture map* (the desired value is chosen optically from a picture divided into parts)
- *date* (entering date or/and time in pre-defined format)

Question groups consisting of somehow related parameters (e.g. clinical parameters, genetics or concomitant therapy) allow better orientation and enable creating relationships between the questions. As an example, for treatment regimens or concomitant therapy, repeating question

groups can be used. Sometimes, it can be useful to transfer values between individual forms, especially if we do not expect those values to change (e.g. medication during individual visits). This is particularly convenient for physicians who do not have to list all items from previous visits but only check the transferred values and modify them if needed (Chrápavá et al. 2018).

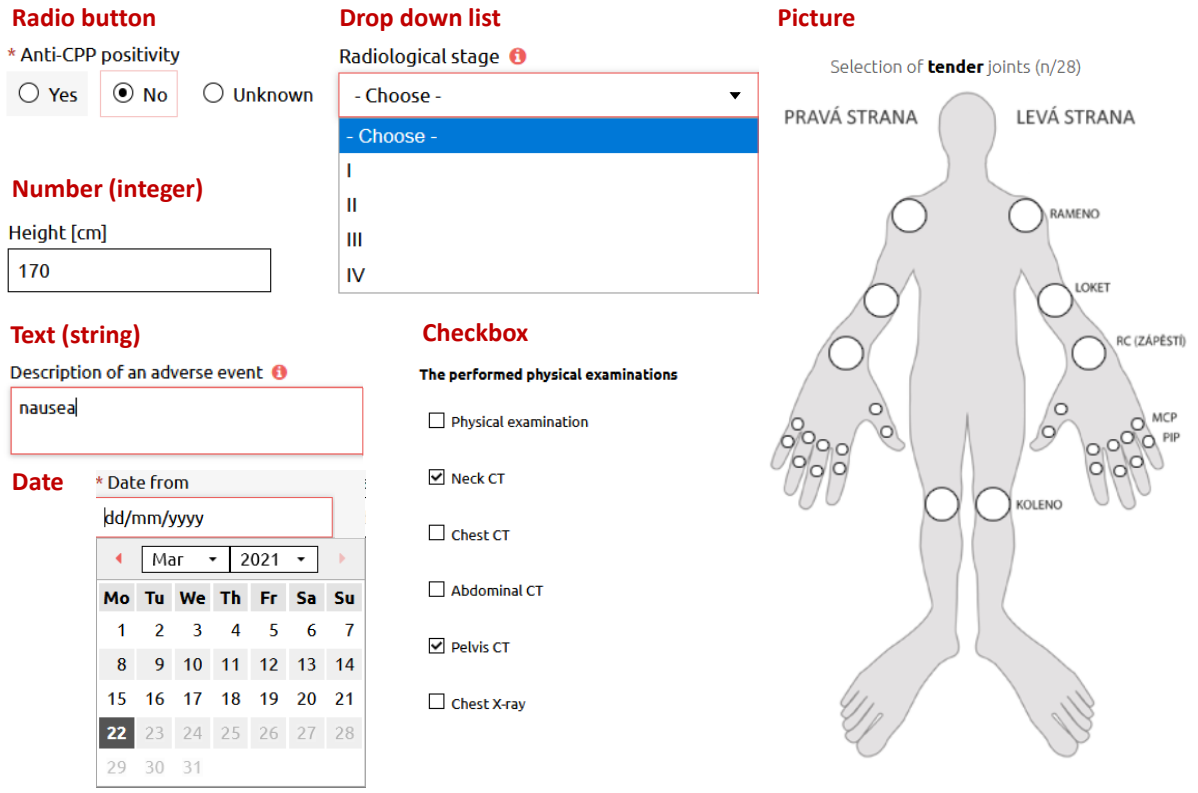


Figure 1 *Example of data field types in a database*

It is good to assign a **status** to each form based on the filling state. If the values in the form are not final and can be changed, the status of the form would be „pending“. If all mandatory variables are filled, and the submitter wants to save the form as finished, the status can be changed to „completed“. When the form is completed, validation tools check the entered data whether they meet all pre-defined conditions (e.g. values range, correctness). If so, the form status automatically switches to „valid“; otherwise, error messages appear, and the form switches to „pending“ (Chrápavá et al. 2018).

An integral part of database setup are **validations** that should be implemented to ensure the correctness and consistency of data in the registry. Future registry outputs (i.e. reports, statistical analyses) are significantly affected by data quality; therefore, it is necessary to have valid data. Apart from data format control, length, boundaries, and future dates are checked during the data entry process. Data checks can be set across different forms as well (e.g. date

of diagnosis cannot be later than the baseline visit or earlier than the date of birth). All programmed checks have to be tested and validated afterwards (Chrápavá et al. 2018).

Another important part of the registry setup is **reporting**. Reports can be viewed online in real-time, or alternatively, reports can be sent to predefined email addresses once per agreed period. Several different types of reports can be generated, e.g. enrolment reports showing data growth (patients, forms) in the registry, overview reports of entered data indicating data quality, queries' reports showing the data quality. Clinical registries often monitor real-life drug safety, and such data needs to be analyzed and reported. The most efficient way is to directly generate an adverse event report from the database once the adverse event enters the database. Ideally, the EDC system allows setting up an automatic mail to the pharmacovigilance department once the adverse event form is saved with valid status. Information on safety outcomes should be collected in a comparable, internationally agreed manner, e.g. through the Medical Dictionary for Regulatory Activities coding system for adverse events[9] (Chrápavá et al. 2018; Dixon et al. 2010).

3.3.3 Database testing

It is essential to test the database before its launch to prevent any future errors and database changes. Testing has to be done after each database modification as well. The functionality of the database is tested by entering the complete data of at least one patient. Testing usually includes checking the database structure, validations and verification of reports and compliance with the protocol, CRF, data management and validation plans. In addition to internal testing, more comprehensive revision is recommended (by the investigators, project manager and analyst). After signing all documents by all parties, the database can be launched, and user access (the login, password, web address) can be sent to relevant investigators and the project team members. Sometimes it can be convenient to create patients' access to the database as well. However, the patients' access is limited to either one specific form that the particular patient has to fill (e.g. quality of life questionnaire) or the single patient data in read-only mode to see his/her data (Chrápavá et al. 2018).

3.3.4 Training

Training of investigators and data entry staff (or other staff involved) is an essential part of a well-functioning registry. Initial training during the registry setup, training of new users

[9] https://www.meddra.org/

and training after updating the database structure should be done. All investigators in all sites should put the data in the registry consistently and in the same manner (Chrápavá et al. 2018).

A **technical manual** represents a fundamental tool for registry users to help them handle the database (e.g. login, data entry). It should include, e.g. information about creating new patients in the database and data entry, searching for submitted patients (e.g. by ID), reading the registry's structure or working with the forms. Another helpful document is a **clinical manual** with information related to individual data entry (Chrápavá et al. 2018).

3.4 Registry maintenance

When the registry is set up, and all preparation activities mentioned in previous chapters are finished, the first patient can be entered into the registry. The majority of the registry processes should then run automatically. However, there are still some things that have to be dealt with. Data entered in the registry are continuously validated, and investigators are encouraged (through error messages and queries) to correct any inconsistencies. In addition to continual data review connected with possible registry modifications, reporting is another integral part of registry maintenance. Finally, data imports and data export have to be established.

3.4.1 Data validation and data review

In chapter 3.3.2, we have mentioned the need for **data validations** to obtain quality data. The system generates error messages based on the validation checks programmed within the registry setup during the data entry. Therefore, investigators receive instant feedback if any inconsistency compared to the programmed validations is found. An example of error messages that can occur during the data entry is shown in **Figure 2**.

The next step of the validation process consists of coherence checks validating parameters across the whole database. These checks usually result in the generation of queries regarding data corrections. Investigators can respond to those queries and, for example, clarify the rare cases (special parameter values) for which those validations should be manually overridden. Besides automatic checks, manual queries are also needed because not everything can be checked automatically (or can, but it is too complicated). Since the number of queries is very informative in terms of users‘ (sites‘) activity and data quality, it is recommended to monitor queries (number and statuses) in different sites and provide relevant feedback to given sites through query

reporting. For long-term registries, the **data review** process is recommended, e.g. before critical milestones such as interim analysis. (Chrápavá et al. 2018).

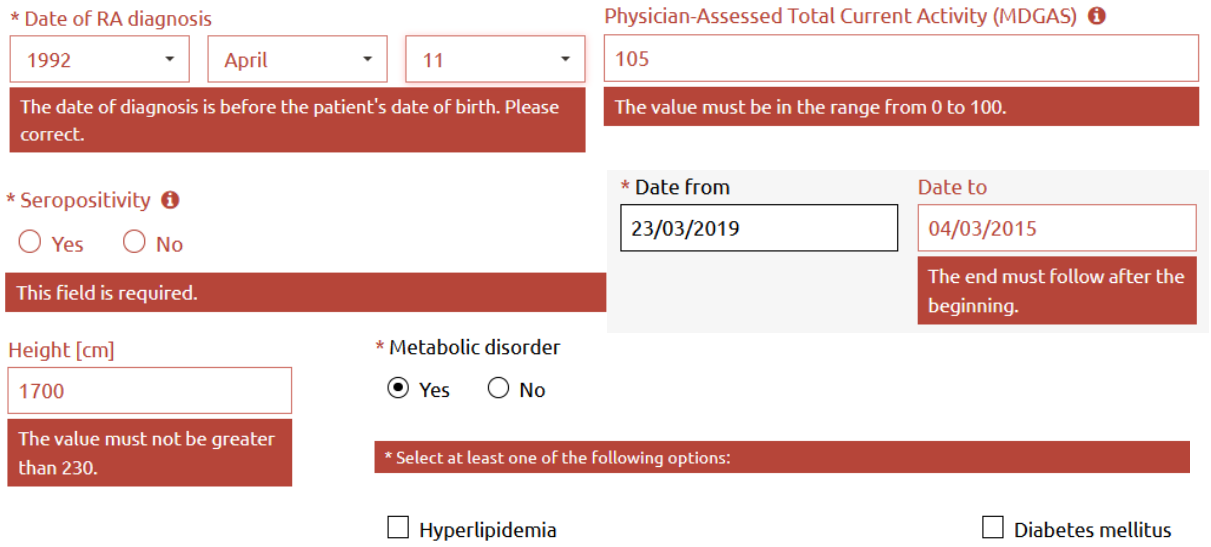


Figure 2 *Examples of error messages during data entry*

3.4.2 Data import and data export

During the registry's existence, **data import** both occasionally and on a regular basis may be needed. The reasons for one-time data import can be the joining of new sites with their own data registry or the joining of several registries into one central registry. Parameters from the source database have to be matched to the parameters in the target database. This mapping process involves creating rules for the EDC system and transforming the source data into the target database. Regular import of external data (e.g. laboratory, form questionnaires) can also be established. Data quality control after each import has to be performed to ensure that everything has been imported completely and correctly (Chrápavá et al. 2018).

The unnecessary process in the registry leading to data analyses is **data exporting**. We have to decide what data we want to export (e.g. data from specific sites, only data from valid forms) and what export format we wish to receive. Most common formats include Microsoft Office Excel format (XLS, XLSX), a comma-separated value (CSV) file, a plain text (TXT) file or other alternative formats for statistical analyses (e.g. SAS). The data analyst may also have specific data requirements that will subsequently facilitate him/her work with data (Chrápavá et al. 2018).

Unlike investigational clinical studies, clinical registries are observational and are generally not limited to a specific time period. Therefore, the database lock is usually not planned. In any case, when the registry comes to its end, the database has to be locked. After the cancellation of all investigators‘ accesses, the data manager generates the complete export, which is provided to the data analyst for final statistical analyses (Chrápavá et al. 2018).

3.5 Analysis of registry data

The data collected within clinical registries can be processed in different ways, but all analyses' primary goal should be more or less the same – to contribute to a better quality of patient care. Typical registry outputs include already mentioned periodical reports, articles, abstracts, posters, conference papers, presentations or online visualisations.

3.5.1 Specific aspects of clinical registry data

As previously mentioned, clinical registries reflect real clinical practice, where the treatment of patients is not strictly regulated by the protocol. Unlike clinical trials, clinical registries include a wider population (including elderly patients or patients with multiple comorbidities); thus, the results have high external validity (Vandenbroucke et al. 2007). Further, randomisation is not present in clinical registries. Treatment selection, care and evaluation fall under the clinician’s decision and the treatment can be changed based on current clinical outcomes. Therefore, more complex statistical methods should be applied when analyzing registry data to minimise confounding. We can partially overcome the problem of missing randomisation by performing multivariable analyses (see subchapter 3.5.3) containing confounders[10] or by employing matching techniques, such as propensity score matching (Rosenbaum a Rubin 1983).

Propensity score matching is frequently employed in cohort (or case-control) studies to make studied groups comparable in baseline characteristics, thus reducing selection bias. The principle of this statistical technique is matching patients from one study group (treatment *A* further in the text) to patients from the other group (treatment *B* further in the text) based on each patient's propensity score. The propensity score (PS) is defined as the probability of receiving treatment *A* based on measured covariates (baseline characteristics):

$$P(group = 1 \mid \mathbf{X})$$

[10] Counfounding factor (i.e. confounder) is a factor that is associated both with the exposure and the outcome and cause a spurious association between the two (Vandenbroucke et al. 2007).

where P is a probability, group = 1 a grouping variable with values 0 for treatment B and 1 for treatment A in our example, the symbol | stands for conditional on, and **X** is a set of observed covariates (characteristics). Matching patients with a similar estimated PS creates an approximate balance for all studied confounders resulting in unbiased treatment effect estimates. The selection of proper covariates is key, and we should make sure that we do not omit any unobserved confounders. The PS estimates are usually obtained using logistic regression with the treatment assessment (1 – treatment A, 0 – treatment B) as the outcome variable and the selected covariates as predictors. Other possibilities to get estimates are, for instance, discriminant analysis or regression trees. The actual matching can be performed in several different ways. The most common technique is the nearest neighbour matching with 1:1 matching ratio, which means that a single patient from the A group is matched to a single patient from the B group with the most similar estimated PS. We can determine a maximum allowable difference (*caliper*) between two individuals to prevent bad matches. In case both groups vary greatly in size, we can prefer 1:*n* matching ($n>1$) instead. After matching, we should check the model adequacy and evaluate whether balance on the selected covariates has been achieved (e.g. standardized mean differences should be close to 0 and variance ratio close to 1). Finally, the treatment effect (A vs B) can be estimated through tests or models within the matched dataset (Thoemmes 2012; Randolph et al. 2014; Benedetto et al. 2018). In case we want to compare three patient (treatment) groups instead of two, Rassen et al. proposed an effective way through PS matching (Rassen et al. 2013). Other PS-based alternatives to propensity score matching are stratification, inverse probability weighting or regression adjustment (Benedetto et al. 2018).

Missing data are highly prevalent in observational research (e.g. missing visits or incompletely filled forms). Missing data are always connected with some loss of information, leading to lower accuracy of estimates and lower power in general (Fitzmaurice et al. 2011). There are several approaches to address missing data, and some techniques require certain assumptions about missing values. A typology of missing data has been developed (Little a Rubin 2019). We call data *missing completely at random* (MCAR) if the probability that a particular observation is missing does not depend on any observable variables' values. We describe data as *missing at random* (MAR) if, given the observed data, the probability that the observation is missing is independent of the missing data's actual values. Lastly, data are defined as *missing not at random* (MNAR), if the probability of missing observation still depends on the missing values even after taking the available data into account (Little a Rubin

2019; Vandenbroucke et al. 2007). However, it is often difficult or even impossible to identify the actual mechanism of missing data (Everitt a Hothorn 2011).

We can restrict analyses only to individuals with complete data on all required variables. Such complete-case analyses can sometimes be biased (unless we have MCAR data) and inefficient. The bias arises if individuals with missing values are not typical of the whole sample, and the inefficiency arises due to reduced samples size. An alternative is to perform an available-case analysis, which makes better use of data, but it can cause bias as well. Generally, complete-case and available-case analyses are all right if the number of missing values is small. Another option is using the last observation carried forward for repeated measures. However, this can distort trends over time, and it can bring bias if we insert a missing category indicator for a confounder. The missing values can also be imputed with assumed or estimated values (e.g. mean or median value), but it can hide or exaggerate the association of interest and produce small standard errors (Vandenbroucke et al. 2007; Everitt a Hothorn 2011). A more appropriate way to deal with missing values is by multiple imputations suggested by Rubin (Rubin 1987). This method is based on a Monte Carlo technique replacing missing values by *m* simulated versions, where *m* is typically from 3 to 10. Each of *m* simulated complete datasets is analysed with appropriate methods, and the results are then combined to produce final estimates and confidence intervals (Everitt a Hothorn 2011). In all analyses, we should report the number of missing values for each analysed variable at each step of the analysis, and we should give reasons for missing values if possible. If we account for missing data, we should always describe the used method (e.g. multiple imputations) (Vandenbroucke et al. 2007).

The general workflow of statistical analyses of registry data includes data import, missing data processing, data validation and derivation, descriptive summary and visualisation, hypotheses testing and modelling, and multivariable analysis to adjust for confounding factors. Making a flow diagram showing individual steps leading to the final dataset is always good. It should include the number of individuals at each stage of the study.

3.5.2 Descriptive statistical summary and testing

The first step in any analysis is to summarise or display data to obtain basic information about the analysed patients‘ population. We have to distinguish two types of variables: categorical (e.g. gender, line of therapy or presence of comorbidities) and continuous/quantitative (e.g. age, disease duration or weight).

Categorical parameters are usually described through absolute and relative frequencies (i.e. percentages) presented in frequency and contingency tables (see **Table 1**). Tables can be accompanied by pie charts or bar plots (see **Figure 3**). If we wish to visualise two categorical variables within one graph, we can draw clustered/stacked bar plots (see **Figure 4**).

Table 1 *Example of a frequency table (left) describing absolute (n) and relative frequencies (%) of patients according to a line of therapy and example of a contingency table (right) showing absolute (n) and relative frequencies (%) of men and women among patients treated with drug A and drug B*

Line of therapy	*n* (%)
1	10 (10.6%)
2	16 (17.0%)
3	26 (27.7%)
4 or higher	42 (44.7%)
Total	94 (100.0%)

Gender	**Drug A**	**Drug B**
Men, *n* (%)	56 (57.1%)	84 (56.0%)
Women, *n* (%)	42 (42.9%)	66 (44.0%)

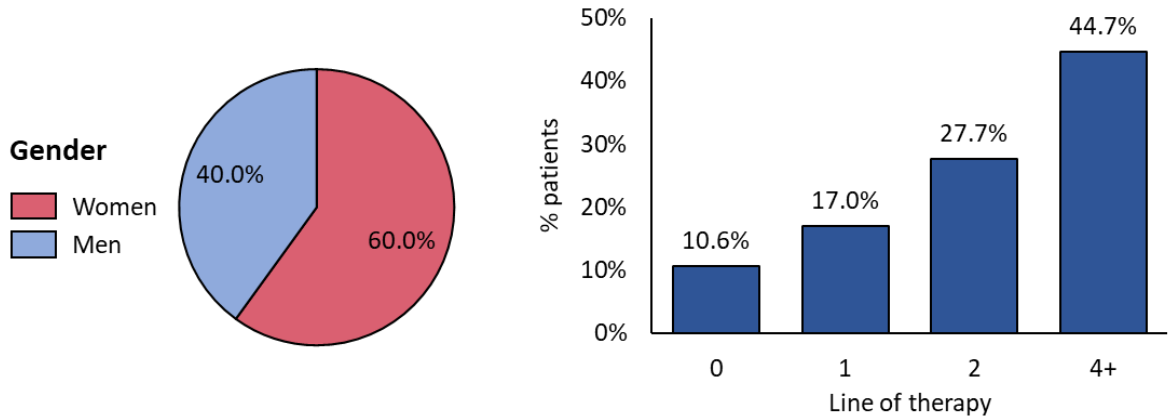


Figure 3 *Example of a pie chart (left) displaying frequencies of men and women and bar plot (right) showing relatives frequencies of patients according to a line of therapy*

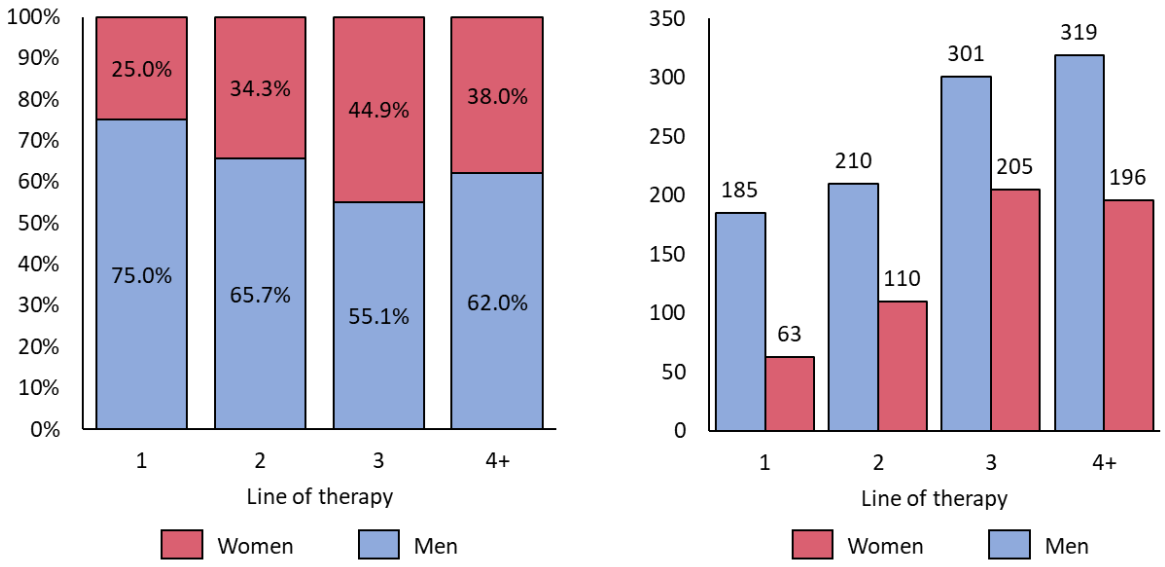


Figure 4 *Example of a 100% stacked bar plot (left) and clustered bar plot showing a representation of lines of therapy according to gender*

Continuous (quantitative) data are standardly summarised by measures of central tendency (e.g. mean or median) and measures of dispersion (e.g. standard deviation, variance, percentiles or range). The choice of appropriate statistics depends on data symmetry. In practice, if data follow a normal (or at least symmetrical) probability distribution, we can characterise continuous data through means and standard deviations or ranges (minimum and maximum). Otherwise, we should prefer medians with percentiles (5^{th} and 95^{th} or interquartile range) instead since they are not affected by atypical values. Most frequently, we visualise continuous/quantitative data through histograms (for aggregated data) and boxplots (see **Figure 5**). If we want to explore the relationship between two continuous variables, we can draw a scatter plot.

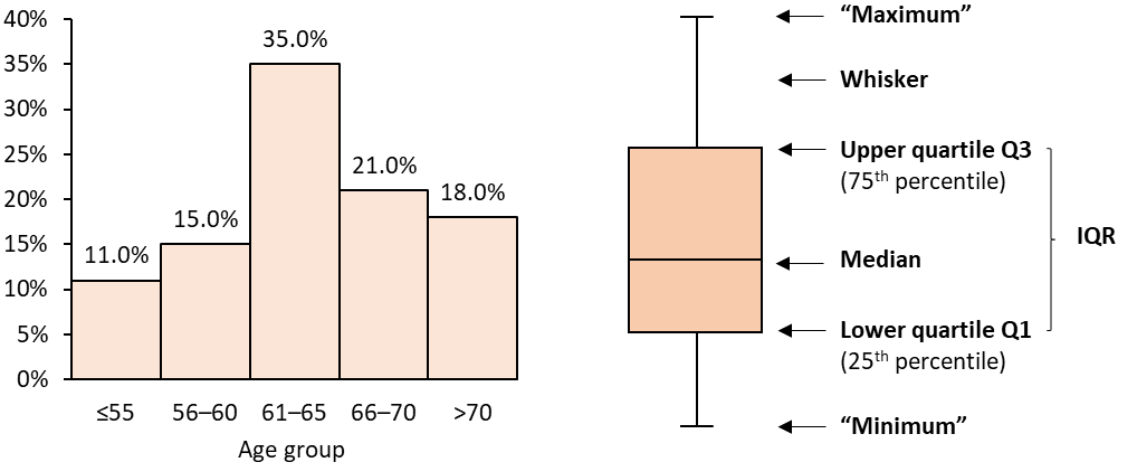


Figure 5 *Example of a histogram (left) and a box plot (right)*

Very often, we want to compare patient subgroups concerning their characteristics. Descriptive statistics (e.g. means, medians, counts) and graphs are valuable but not sufficient to discover statistically significant differences between compared subgroups. Therefore, formal testing is inevitable. The choice of statistical test depends both on the data type and study settings.

For continuous variables, we distinguish two groups of tests: parametric and non-parametric. The former mentioned require data (approximately) following a normal distribution and equal variances across tested subgroups. The normality assumption can be checked graphically (histograms, boxplots or normal-quantile plots) or formally by tests, such as the Shapiro-Wilk test or the Kolmogorov-Smirnov test (Shapiro, Wilk, 1965; Massey, 1951; Yap, Sim, 2011). The equality of variance in subgroups can be formally tested through the F-test, the Levene test, the Bartlett test or the Brown-Forsythe test (Wang et al., 2017). In terms of violation of assumptions (e.g. skewed data) or small sample size, non-parametric tests represent a great alternative. Such tests work with signs or value ranks; therefore, they are not affected by outliers and do not require a certain shape of the probability distribution of data. On the other hand, they have smaller power when testing (Kaur, Kumar, 2015). Test selection further depends on the study setting. If we want to compare the same patients at baseline and after six months, the data in these two time points are not independent and paired tests should be employed. Finally, different tests have to be chosen when comparing one group vs reference value, two subgroups and three or more subgroups. An overview of different tests for continuous variables is presented in **Figure 6**.

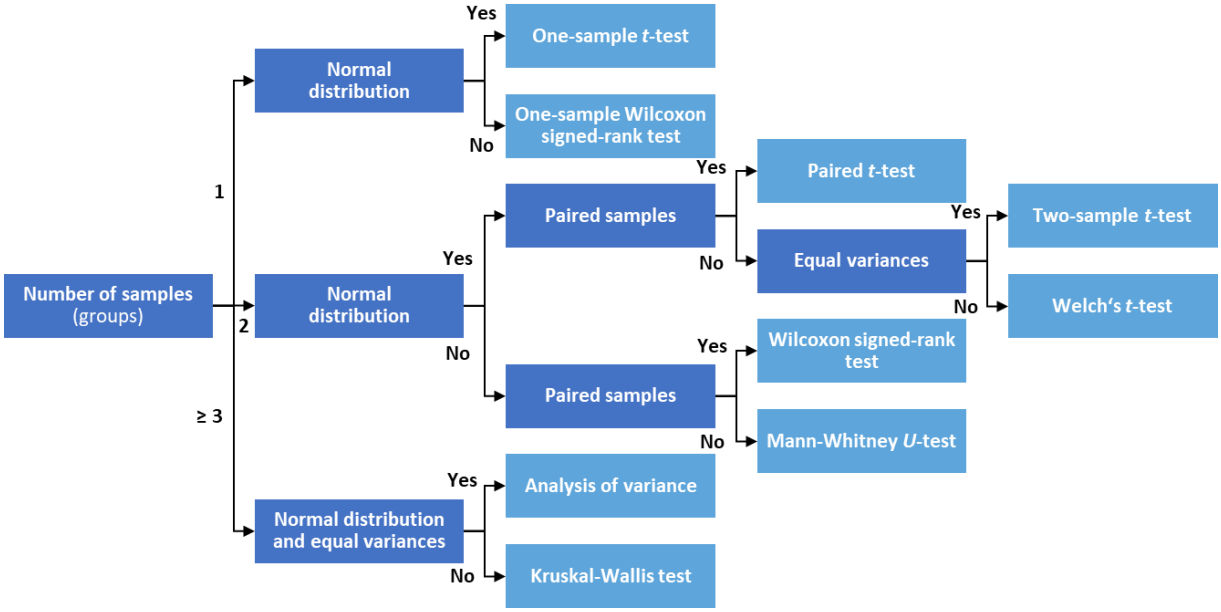


Figure 6 *Overview of common statistical tests for continuous variables*

When we compare three or more groups, and the test reveals the overall difference between the groups, it is useful to include post-hoc tests[11] to discover which particular pairs differ. The resulting p-values should be corrected for multiple testing afterwards, for example, through Bonferroni, Holm-Bonferroni or Benjamini-Hochberg correction techniques (Holm, 1979; Benjamini, Hochberg, 1995; Streiner, Norman, 2011).

We can also be interested in whether the proportions of one variable's categories differ depending on the other categorical variable's values. Such comparison can be made using Pearson's chi-squared test and Fisher's exact test. Pearson's chi-squared test assumption is that at least 80% of contingency table's cells have expected counts five or higher and 100% of cells two or higher. In case of violation of this assumption, Fisher's exact test should be used instead (Kim, 2017). Fisher's exact test was originally designed for 2×2 contingency tables but can be generalised to an arbitrary table (Mehta, Patel, 1983). If we wish to compare counts in the categories within related samples (e.g. pre-treatment and post-treatment), we can apply McNemar's test (McNemar, 1947).

3.5.3 Correlation and regression analysis

Very often, we want to evaluate the strength of a relationship/association between two or more variables. **Correlation analysis** can be used to quantify the association between two continuous variables. Pearson's correlation coefficient can be applied when data do not contain outliers and are not skewed (ideally normal probability distribution). Otherwise, non-parametric Spearman's correlation coefficient should be used. While Pearson's correlation coefficient measures the linear correlation between parameters, Spearman's correlation coefficient evaluates the monotonic relationships[12] of parameters. The common feature of both coefficients is that they take values between –1 (total negative correlation) and +1 (total positive correlation), with zero value indicating no relationship (Mukaka, 2012). A positive correlation means that with the increasing values of the first variable, the values of the other variable increase as well (see the left scatter plot in **Figure 7**). A negative correlation shows the opposite trend (see the right scatter plot in **Figure 7**). Generally, an absolute correlation coefficient value between 0 and 0.3 is considered as a negligible correlation (Mukaka, 2012). It is important to remember that even if

[11] Tukey's or Scheffé's method can be used as post-hoc test for ANOVA testing and Conover-Inman test or Mann-Whitney test when testing with Kruskal-Wallis test (CHEN et al., 2018; Ostertagová et al., 2014).

[12] In a monotonic relationship, the variables tend to move in the same relative direction, but not necessarily at a constant rate as opposed to linear relationship. As one variable rises, the other variable either rises continously (positive correlation) or sinks continously (negative correlation) (Schneider et al., 2010).

both Pearson's and Spearman's correlation coefficients are equal to zero, it does not necessarily mean there is no relationship between the variables (the relationship can be, e.g., quadratic).

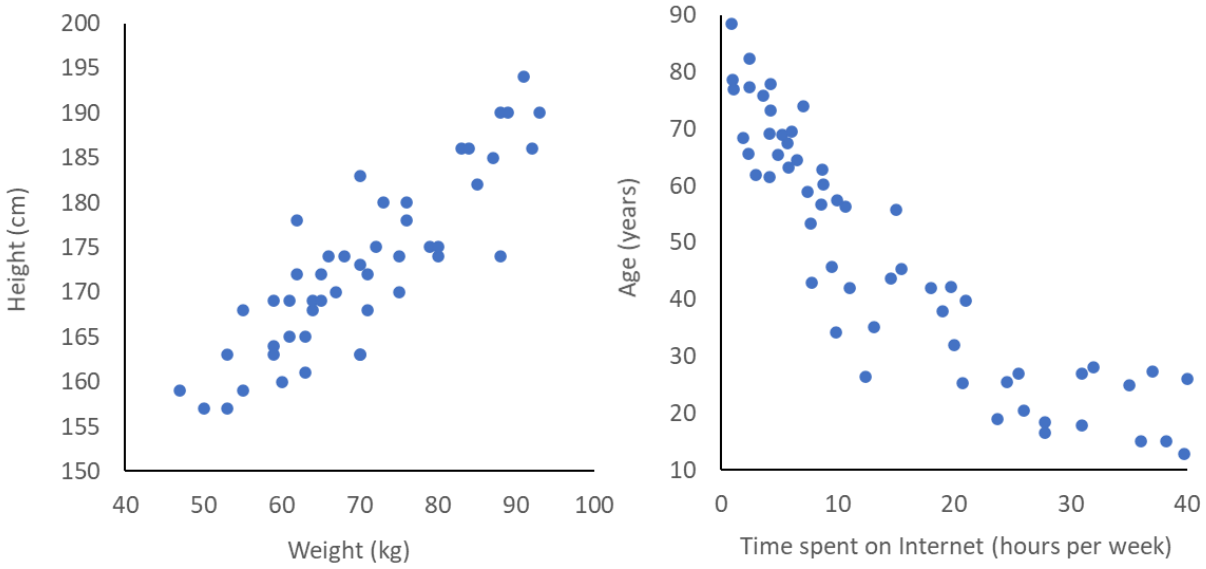


Figure 7 *Example of scatterplots showing positive (left graph) and negative (right graph) correlation between variables*

The relationship between two or more categorical variables can be illustrated through contingency tables, and the presence of a statistically significant association can be tested through Pearson's chi-squared test or Fisher's exact test (see 3.5.2). To quantify this relationship, we can employ measures, such as the **risk ratio** (RR, also called relative risk) or **odds ratio** (OR). These measures are usually applied to assess the strength of the association between a given exposure (e.g. poor prognostic factor presence) and specific outcome (e.g. remission). Risk ratio can be calculated as the ratio of two probabilities – the probability of a specific outcome (e.g. adverse event) in a group with and without given exposure (e.g. new vs standard treatment). Odds are defined as the ratio of two probabilities – the probability of the occurrence and non-occurrence of an outcome of interest (e.g. remission). The odds ratio is a ratio of odds in the two groups (Stare, Maucort-Boulch, 2016). Computational formulas for both statistics are shown in **Table 2**.

Table 2 *Example of a contingency table with formulas for the calculation of risk ratio (RR) and odds ratio (OR)*

		Partial remission (/adverse events)		
		Yes	**No**	**Total**
Treatment combination	**New**	a	b	a + b
	Standard	c	d	c + d
	Total	a + c	b + d	a + b+ c + d

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} \qquad OR = \frac{\frac{a/(a+b)}{b/(a+b)}}{\frac{c/(c+d)}{d/(c+d)}} = \frac{\frac{a}{b}}{\frac{c}{d}}$$

If the RR (resp. OR) results in 1, it indicates no difference in risks (resp. odds) between the groups. Values higher than 1 mean that the outcome is more likely to occur in the exposed group; values lower than 1 mean the opposite. If the probability of an event is generally small (typically less than 0.1), both RR and OR give similar results. However, if the probability of the event occurrence is high, then both measures differ. In retrospective (case-control) studies, ORs should be computed instead of RRs. In prospective (cohort) studies, both measures can be used (Stare, Maucort-Boulch, 2016; Ranganathan et al., 2015).

Another essential statistical technique is **regression analysis** which enables us to study how one or more variables affect another variable. The variable to be explained or predicted through a set of other variables is called the outcome variable, dependant or response variable. Variables that explain/predict it are called independent variables, regressors, predictors or covariates. Regression models can be explanatory or predictive, depending on our goal. Based on the regression model, we can describe the relationship between dependant and independent variables, estimate future values of the dependent variable from the observed independent variables, or identify risk (prognostic) factors influencing the outcome variable (Schneider et al., 2010).

Based on the number of predictors, we divide models into **univariable** and **multivariable**. In univariable models, we only model one variable's effect on the outcome variable. Multivariable models contain more than one predictor. As previously mentioned (in chapter 3.5.1), clinical registry data include a wide spectrum of patients. Therefore, we should adjust the effect estimate of the studied variable for potential confounders through multivariable models as well. Depending on the character of the outcome variable, we distinguish different types of regression models. The most common types include **linear regression** (continuous or quantitative dependant variable), **logistic regression** (binary dependant variable) or **Poisson regression** (count data). Independent variables can be either continuous, categorical or binary.

The linear models (LMs) assume that residuals[13] follow normal probability distribution with zero mean value and constant variance (i.e. residuals are unsystematic, homogenous in variance and independent). The linear model can be described as

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}\,,$$

where $\mathbf{Y}$ is a vector of observed values of the dependent variable, $\mathbf{X}$ is a matrix containing values of independent variables in columns, $\boldsymbol{\beta}$ is a vector of regression coefficients that we wish

[13] Residuals (errors) are differences between estimated and observed values of dependent variable (Zvára et al., 2013).

to estimate, and $\boldsymbol{\varepsilon}$ is a vector of residuals (Zvára et al., 2013). The resulting estimates of regression coefficients represent the change in the dependent variable per unit change in the continuous independent variable. In the case of binary/categorical independent variables, the regression coefficient characterizes the change in the dependent variables for individual predictor's categories against the reference category (Schneider et al., 2010).

Generalized linear models (GLMs) represent an extension of the standard linear models that cannot handle non-normal response variables, such as counts or proportions. Each GLM model is specified by the probability distribution from the exponential family (e.g. normal, binomial or Poisson) and link function, which defines the relationship between the transformed mean value of the dependent variable and the linear combination of predictors η (Faraway, 2006). A widely used GLM model within clinical studies is the logistic regression model with the logit link function g defined as

$$\eta = g(\mu) = ln\frac{\mu}{1-\mu},$$

where η is a linear combination of predictors (i.e. linear predictor), g is a link function, and μ is a mean value of the dependent variable. The resulting regression coefficient estimates can be interpreted through odds ratios computed as exponentials from regression coefficients of studied predictors (Faraway, 2006; Fitzmaurice et al., 2011).

In certain situations, it may be necessary to use **random-effect models** (also called mixed models). Typically, if we have repeated measurement data/longitudinal data or clustered data, the assumption of independent observations no longer holds, and such correlation among observations needs to be taken into account (West et al., 2007).

3.5.4 Survival analysis

Survival data are very frequent in clinical registries, and traditional statistical methods (such as *t*-test or logistic regression) cannot be used for analyses due to the presence of incomplete data. Therefore, specialized statistical techniques have to be considered instead.

We typically want to analyze the time to an event of interest (e.g. death, progression, relapse or treatment discontinuation). We can be interested, for instance, in whether a new treatment prolongs survival time after the diagnosis or what proportion of patients will survive a certain amount of time. A unique feature of survival data is that not all patients experience the event by the end of the observation period, and this condition is called **censoring**. The actual

survival time is unknown for patients who reach the end of the follow-up period without the studied event. We only know that the survival time is longer than the observation time (Schober, Vetter, 2018). These observations are called right-censored (the most common type of censoring, see **Figure 8**). Right censoring can also be seen in patients that dropped out of the study or were lost to follow-up. The censoring time should not be related to the event time to get unbiased inferences (i.e. non-informative censoring). Other less frequent censoring types are left[14] and interval[15] censoring (Schober, Vetter, 2018).

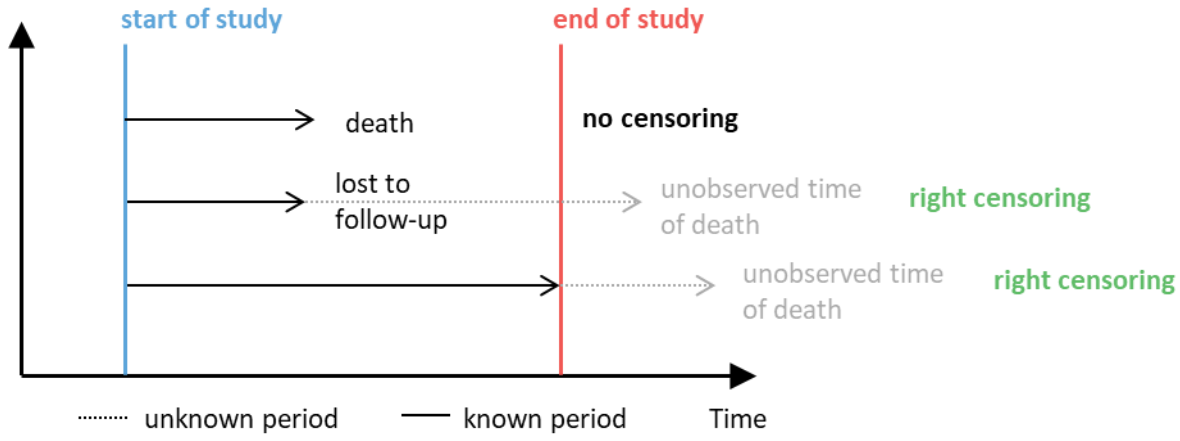


Figure 8 *Illustration of right censoring in overall survival analysis*

In every survival analysis, we have to clearly define the event of interest[16] and the starting point (e.g. diagnosis, treatment initiation) from which we will follow the occurrence of events (Schober, Vetter, 2018). Further, we should report the number of events for each studied group and the extent of loss to follow-up, ideally with reasons, as incomplete follow-ups may bias the results (Vandenbroucke et al., 2007).

The real probability distribution of survival data is not usually known, and non-parametric estimators represent frequently-used means of estimating that do not require a distribution specification. The most commonly used estimation technique of the survival function is the **Kaplan-Meier method** (Kaplan, Meier, 1958). The Kaplan-Meier estimator is based on the probability of surviving until a given time point conditional to the probability of being alive in previous intervals. The assumptions of the Kaplan-Meier method are the knowledge of exact time

[14] Left censoring occurs when the patient has the event before the observation period, but the exact time is unknown (Schober, Vetter, 2018).
[15] Interval censoring happens when the event occurrs between two time points but we do not know the exact time (Schober, Vetter, 2018).
[16] Apart from death, the event of interest can also be, for example, progression, the start of first-line treatment, discontinuation of treatment and many others. The term survival analysis is being used even if the studied event is not death. Alternatively, the term *time-to-event analysis* can be used as well (Schober, Vetter, 2018).

points of event occurrence and the independence of censoring and event rate. An example of the Kaplan-Meier curve is shown in **Figure 9**. The vertical axis represents the estimated probability of survival (values 0–1), and the horizontal axis displays the time since the starting observation point. The curve is a step function in which each vertical drop indicates the occurrence of one or more events. The Kaplan-Meier curve is usually accompanied by the median survival time corresponding to the time duration, after which 50% of patients have reached an event (red dashed line in **Figure 9**). We can also obtain the *x*-year survival rate, which shows the proportion of patients that survived *x* years (see green dashed line in **Figure 9**). Both median survival time and x-year survival rates should be accompanied by the corresponding confidence intervals. It is also useful to provide, together with the Kaplan-Meier plot, the number of patients at risk[17] at various time points in a table underneath the graph. We should keep in mind that survival is estimated less precisely at time points with few subjects at risk (usually close to the follow-up end). It is also helpful to summarise the follow-up time through medians since dissimilar follow-ups in compared groups could lead to bias (ElHafeez et al., 2012; Schober, Vetter, 2018; George et al., 2014).

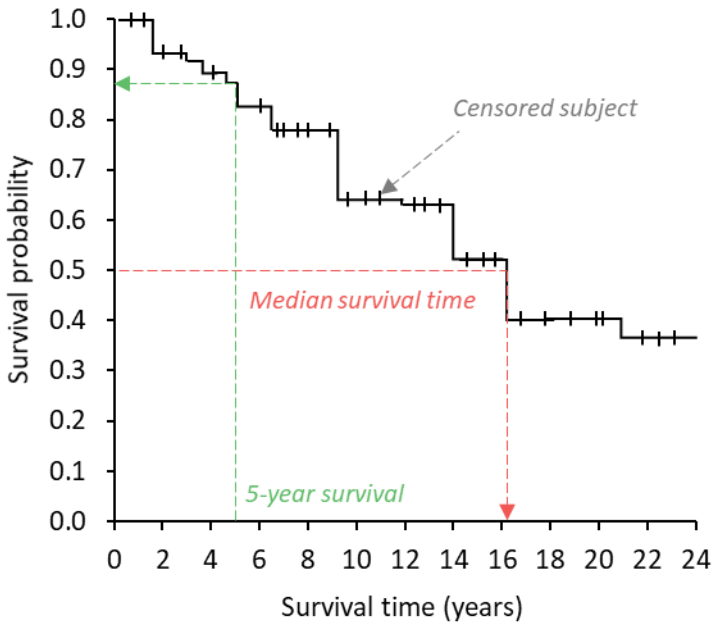


Figure 9 *Kaplan-Meier curve for survival; the red dashed line denotes the median survival time (16.2 years), the green dashed line shows the probability of 5-year survival (0.88), the black vertical line segments represent censoring*

[17] Patients are 'at risk' at any time point since the follow-up start, on the condition that they are still alive and the event has not yet occurred at that time.

Very often, it is desirable to compare two Kaplan-Meier curves corresponding to two or more subgroups of patients. This comparison can be made by the non-parametric Log-rank test, which tests that there is no difference in the probability of an event at any time point (Bland, Altman, 2004). The assumptions of the Log-rank test are the same as in the Kaplan-Meier method. In the case of crossing survival curves of different groups, the power of the test to detect such differences is very low (Schober, Vetter, 2018; Bland, Altman, 2004).

Another essential quantity beside the survival function is the hazard function which is an indicator of the risk of experiencing the event of interest at a given time point (George et al., 2014). The **Cox proportional hazards regression model** enables us to investigate the relationship between predictors (e.g. treatment type) and survival through the hazard function (Cox, 1972). While testing through the Log-rank test tells us whether the difference in survival exists or not, the Cox regression model can quantify the size of the difference (i.e. quantify the effect of predictors on survival). The advantage of the Cox regression model is that it does not require a definition of a particular survival distribution. The Cox proportional hazards model assumes proportional hazards for different values of predictors. In other words, the effects of predictors should be constant over time. The Cox regression models belong to a group of semi-parametric[18] methods. The results of the model (i.e. exponentiated regression coefficients) can be interpreted through hazard ratio, defined as the ratio of the predicted hazard function under two different values of a predictor (e.g. treatment *A* vs *B*). Similarly to the odds ratio or relative risk (see 3.5.3), the hazard ratio value higher (resp. lower) than 1 tells us that the event's occurrence is more (resp. less) likely. Hazard ratio estimates can be presented graphically through forest plots (Kim, 2017; George et al., 2014). As well as in other regression models, both univariable (unadjusted hazard ratios) and multivariable models (adjusted hazard ratios) can be made. The latter mentioned allows controlling for the effects of other covariates in the model (e.g. age, sex, comorbidities). This enables us to study prognostic factors independently.

Sometimes, we have to deal with the **competing risks data**. A competing risk can be defined as an event whose occurrence precludes the occurrence or changes the probability of occurrence of another examined event. An example of competing risks can be, for instance, the relapse of leukaemia as an event of interest and non-relapse mortality as a competing risk event (i.e. a death without relapse prevents achieving relapse). If we want to describe the cumulative probability that the event has occurred throughout follow-up, we can calculate it simply as one

[18] Semi-parametric methods do not require assumptions regarding the distribution of surivval times but do assume aspecific relationship between covariates and hazard function (Schober, Vetter, 2018).

minus the Kaplan-Meier function in the absence of competing risks. However, if there are more dependent event types, Kaplan-Meier estimates become biased (individuals experiencing a competing event are removed from the risk set). The cumulative incidence method represents a suitable alternative to the Kaplan-Meier method (Kim, 2007; Zhang, 2017). We can compare cumulative incidence curves between different patient groups in the presence of competing risks with Gray's test (Gray, 1988). An analogy to the Cox regression models is the Fine-Gray models (Fine, Gray, 1999). Another option (but less appropriate) is to use Cox regression models for cause-specific hazards (Kim, 2007; Zhang, 2017).

Sometimes, we can be interested in analysing events that can occur more than once (i.e. recurrent events) or analysing series events. We can model such events through recurrent event models (Amorim, Cai, 2015). In the case of clustered data, random effects need to be incorporated as individuals within a cluster (e.g. family) tend to be more 'similar' to each other. Frailty models account for these nonindependent observations and represent an analogy to mixed effect models mentioned earlier (Schober, Vetter, 2018a).

4 ATTRA registry

The practical part of the thesis consists of statistical analyses of data from the ATTRA registry. Therefore, this chapter focuses on a brief description of the registry.

The ATTRA registry[19], established in 2001, is a non-interventional, prospective, national, observational cohort study. Its main purpose is to evaluate the safety and effectiveness of bDMARDs (and lately also tsDMARDs) in patients with chronic inflammatory rheumatic diseases. Patients with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE) starting bDMARDs or tsDMARDs are recruited from fifty-six practices sites (private or academic) for adult patients and further eight practices sites for children (see picture **Figure 10**). Since the ATTRA registry captures more than 95% of patients with RA treated with bDMARDs/tsDMARDs in the Czech Republic, the registry can be regarded as nationwide.

The expert guarantor for this project is the Czech Rheumatological Society; the Institute of Biostatistics and Analyses, Ltd. (IBA; a spin-off company of Masaryk University in Brno) provides management and data processing. Contributions from pharmaceutical companies finance the project. Patients provide their written consent at the entry to the registry, and the data are pseudonymised by replacing identifying items with artificial identifiers to prevent the identification of patients. Data collection is planned for the long term.

Initially, the data was collected in paper form, but later, the data collection became fully electronic. IBA develops and runs information systems for data collection and validation, using both local (desktop) and online (web-based) technologies. Specifically, the EDC system (see chapter 3.2.5) IBA uses is CLADE-IS (*Clinical Data Warehousing Information System*), one of the most modern and progressive EDC systems. The data are regularly analyzed, and the results are provided to both sponsors (pharmaceutical companies) and investigators (research publications). Apart from regular reports (annual, quarterly) and research analyses, the ATTRA registry collaborated in several international projects, such as the collaboration focused on rituximab treatment CERERRA (Chatzidionysiou et al., 2012; 2016), tocilizumab treatment TOCERRA (Lauper et al., 2018), and abatacept treatment MEDACTA (Finckh et al., 2015). Currently, ATTRA collaborates in the international project focused on JAK inhibitors - JAK-POT study (Lauper et al., 2020), the project studying various research questions related to SpA patients – EuroSpA (Lindström et al., 2021; Ørnbjerg et al., 2019), and the project focused on comorbidities occurring in RA patients – FOREUM (Burn et al., 2020).

[19] https://attra.registry.cz/

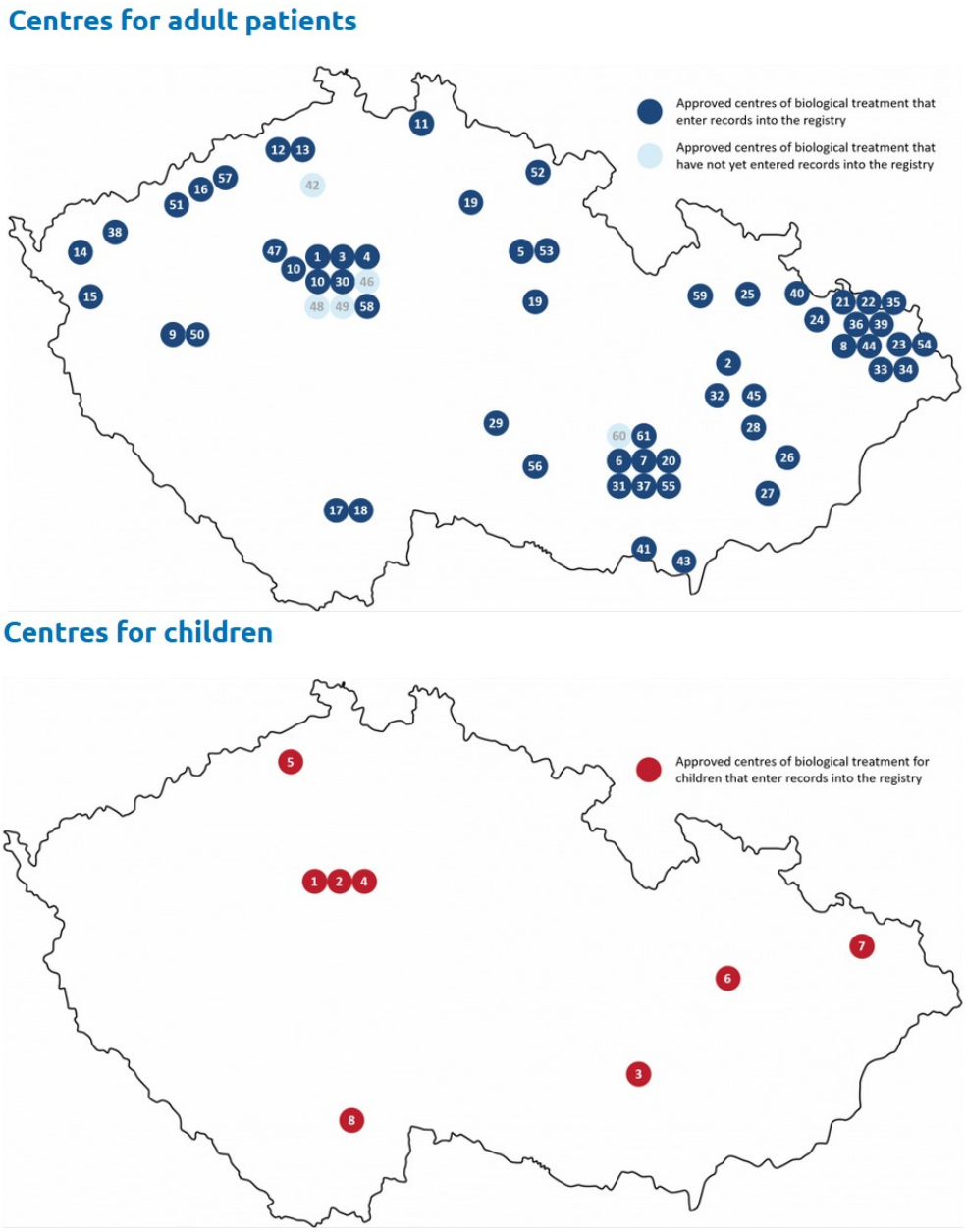


Figure 10 *Approved centres of biological treatment for adult patients (upper) and children (lower); fifty-six centres for adults already entered data in ATTRA registry (dark blue), five centres have not entered data so far (light blue)*

At the beginning of 2021, the ATTRA database included information on 6071 patients with RA, 1621 patients with PsA and 3987 patients with axSpA with a record of b/tsDMARDs treatment (see **Figure 11**). Together 4858 RA patients, 3509 axSpA patients and 1411 PsA patients are currently (start of 2021) treated with b/tsDMARDs (see **Figure 12**). Biological/targeted DMARDs approved for treating patients with RA, PsA and axSpA include adalimumab, certolizumab pegol, etanercept and golimumab. RA patients can also be treated with abatacept, anakinra, baricitinib, rituximab, sarilumab, tocilizumab, tofacitinib (PsA as well) or upadacitinib. PsA patients can be further given ixekizumab and secukinumab (axSpA

as well). The representation of mentioned drugs within currently treated patients for all three diagnoses is shown in **Figure 13**.

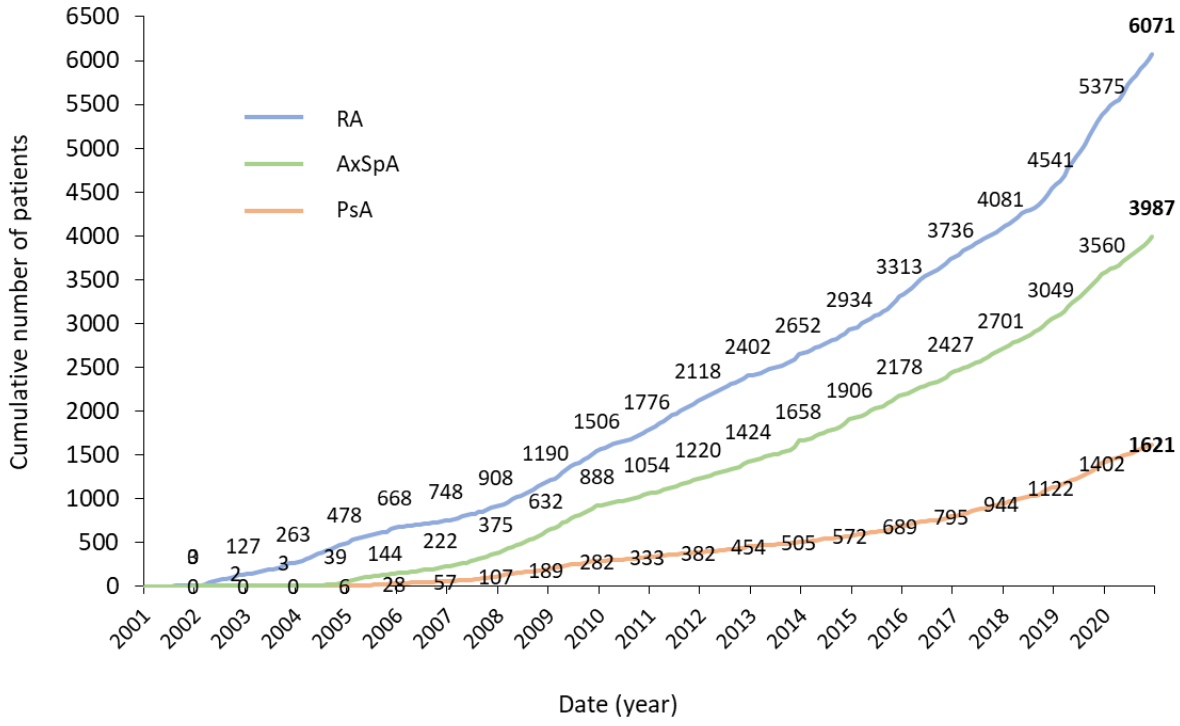


Figure 11 *Cumulative number of patients with a record about b/ts DMARDs therapy in ATTRA registry throughout the years*

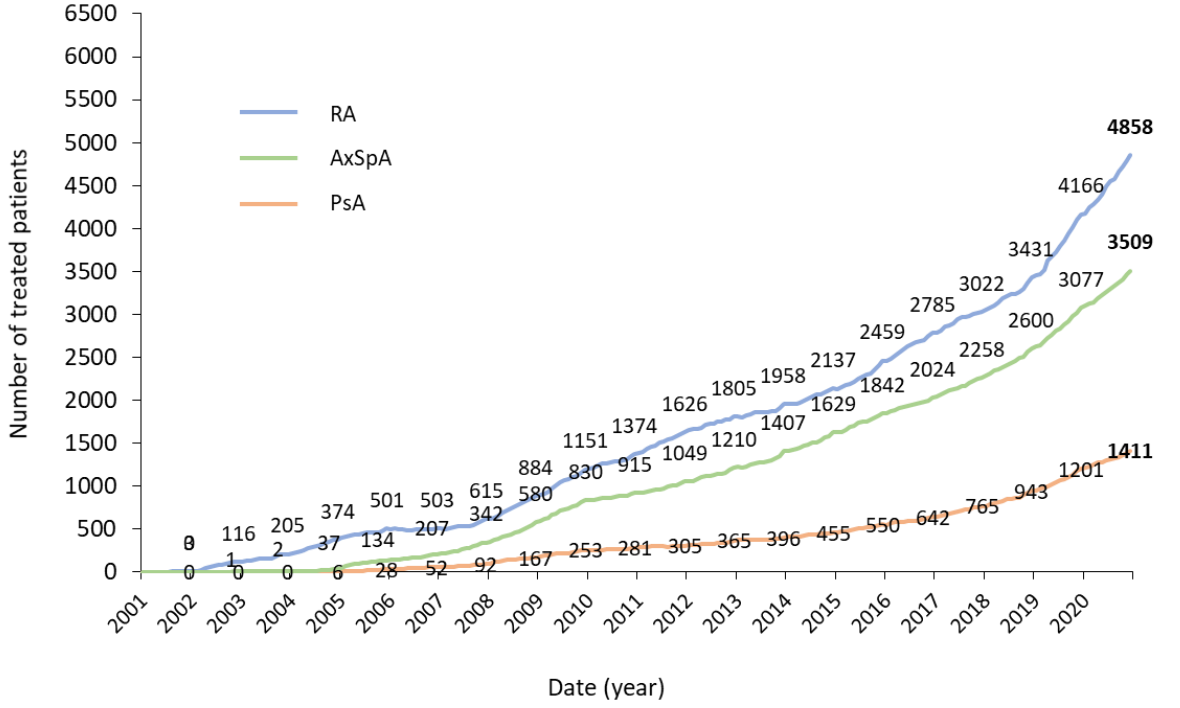


Figure 12 Number of currently treated patients with RA, axSpA and PsA within ATTRA registry throughout years

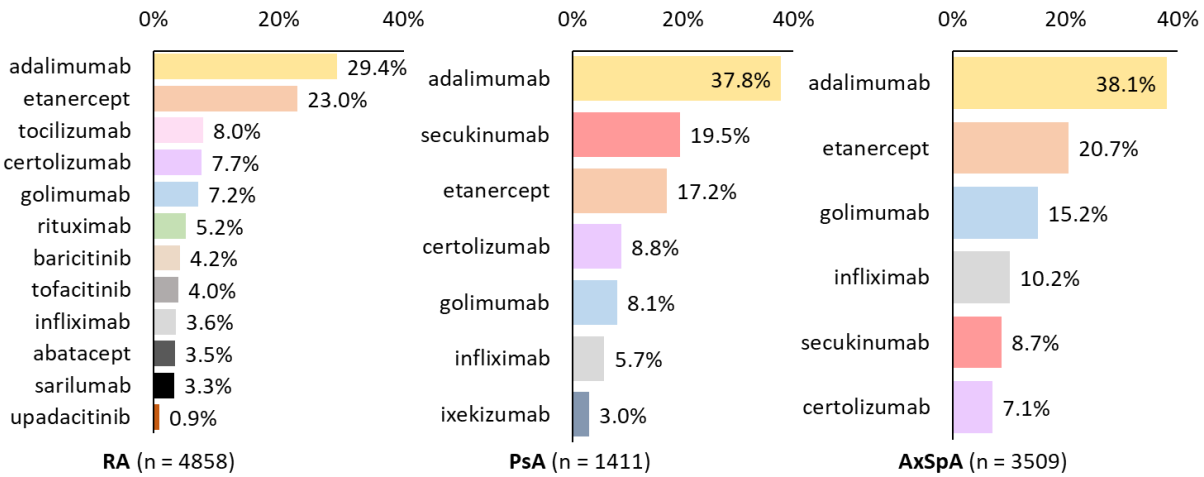


Figure 13 *Frequency of b/ts DMARDs in currently treated patients with RA, PsA and axSpA in ATTRA registry (at the beginning of 2021)*

Already said, the ATTRA registry consists of five individual databases for all five diagnoses. In addition to the cohort of patients treated with b/ts DMARDs, ATTRA includes a control cohort containing patients without b/ts DMARD therapy. Databases ATTRA-RA, ATTRA-AS and ATTRA-SLE also contain patients with an early phase of the disease.

Data are continuously recorded in eCRFs. The entry form and performing entrance control for treatment initiation have to be filled for each patient entering the registry. Then, follow-up data on disease activity, disease function and anti-rheumatic therapies are collected at regular intervals (3, 6, 12, 18, 24, 30, 36 months and annually after that). At the treatment initiation, baseline data are collected, including demographics (e.g., gender, age, height, weight, BMI, education, smoking status and presence of comorbidities), disease characteristics (e.g. disease duration, presence of RF, anti-CPP, HLA-B2, joint deformities, extra-joint manifestations, psoriasis etc.), disease activity (e.g., number of swollen or tender joints, patient and physician global assessment of disease activity, erythrocyte sedimentation, C-reactive protein, disease activity scores), quality of life, patient function, workability, current and previous therapy (b/cs/ts DMARDs, GCs). Some parameters are collected across all diagnoses (e.g. age, height and weight, concomitant therapy or gender), other parameters are specific to each diagnosis (e.g. information about HLA-B27 gene is recorded for PSA and AS, but not for RA diagnosis). Further, information about adverse events, termination of monitoring or treatment within clinical trials are collected. Adverse events are coded through the system of MedDRA codes.

5 Aims of thesis

In the practical part of the work, we focused on two main research questions. Therefore, the rest of the work is divided into two parts.

5.1 T2T strategy vs conservative approach

First, we aimed to evaluate adhesion to treat-to-target strategy (T2T) within the three diagnoses – RA, PsA and axSpA. We were interested in whether patients following the T2T strategy showed better results than patients not following the T2T strategy. Specifically, we aimed to assess whether following a T2T strategy after not reaching the treatment target (REM/LDA) within the first six months leads to a higher probability of meeting the treatment target at the 12-month visit in daily clinical practice. We also described four groups of patients based on different treatment courses with the first bDMARD/tsDMARD. More detail about the T2T strategy for RA, PsA and axSpA diagnoses can be found in subchapters 2.1.3, 2.2.3 and 2.3.3.

5.2 Predictive ability of self-perceived general health at TNFi therapy start

Second, we dealt with evaluating the predictive ability of two SF-36[20] questionnaire questions (Qs) from dimension *General Health*, specifically Q 11A '*I seem to get sick a little easier than other people*', and Q 11C '*I expect my health to get worse*'. We hypothesized that positive responses to these questions might correspond to a more fragile, self-perceived general health status, thus serving as possible predictors of future patient disease outcomes. We aimed to investigate whether these two questions could predict therapeutic response in patients with RA, PsA and axSpA starting their first TNFi therapy.

[20] The Short Form-36 Health Survey (SF-36) questionnaire is an instrument for measuring health perception. It is widely used for evaluating individual patients health status (Brazier et al. 1992).

6 Methods

6.1 T2T strategy vs conservative approach

6.1.1 Study population

In this study, we included all bio-naive adult patients diagnosed with RA/PsA/axSpA starting b/ts DMARDs within a period from 1 January 2012 to 31 December 2017 (for RA patients) or from 1 January 2012 to 31 December 2019 (for PsA and axSpA patients). Patients without available DAS28-ESR (for RA), DAPSA (for PsA) and ASDAS (for axSpA) at baseline, 6-month and 12-month visits or without HAQ and EQ-5D at baseline and 12-month visits were excluded from analyses (see **Figure 14**).

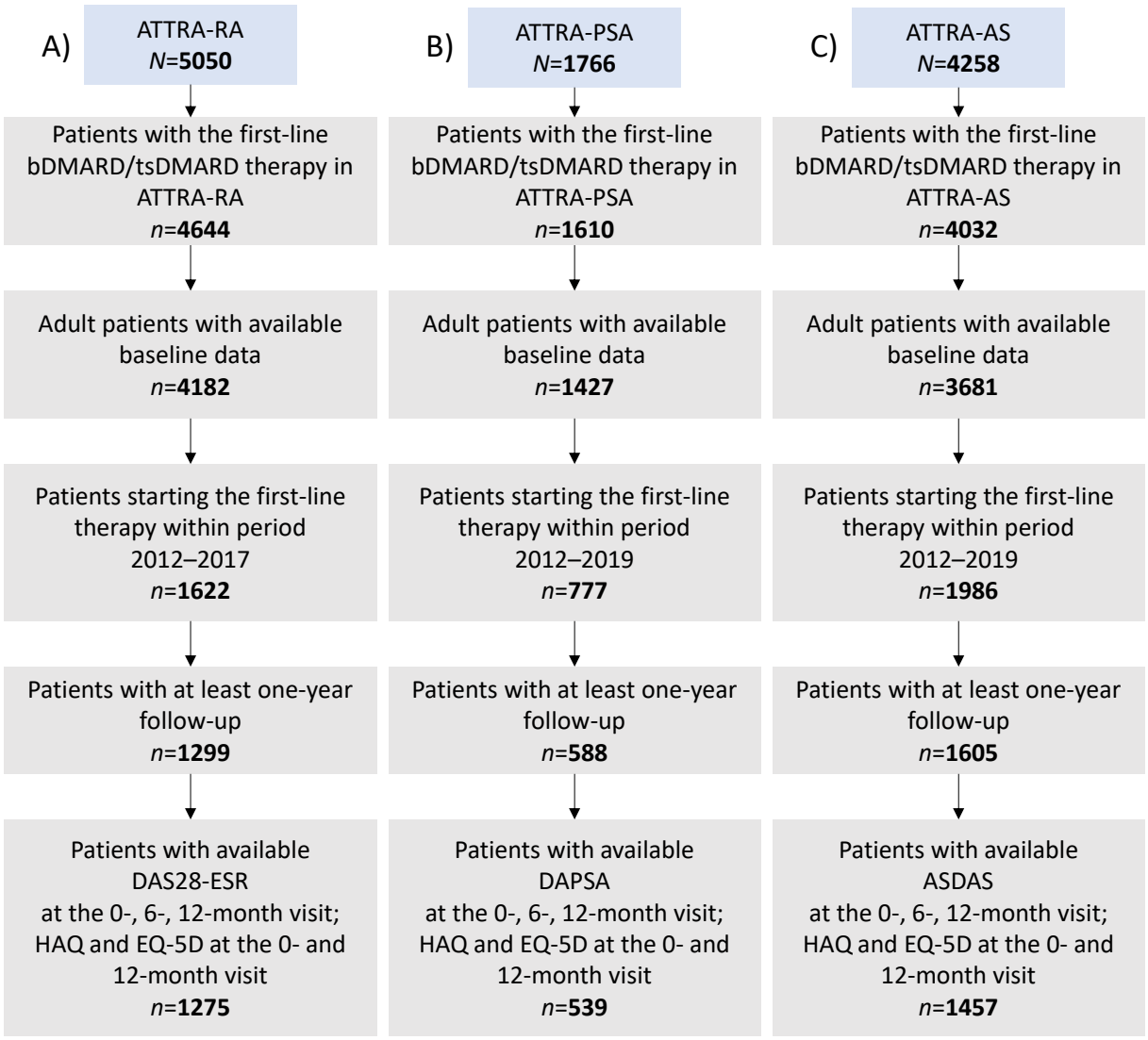


Figure 14 *Flow chart showing individual steps to the final dataset for RA (left), PsA (middle and axSpA (right) patients*

Data were collected in the ATTRA registry (see 4). Ethics approval for ATTRA was granted by the Czech Multicentre Research Ethics Committee, no. 201611 S300 and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic, no. 10113/2016. No additional ethical approval was required for the current analysis. All subjects provided their written consent for collecting and storing data before participation. All procedures were performed following the Declaration of Helsinki.

6.1.2 Study design

We divided patients into four cohorts based on treatment results at the 6-month visit and based on switches to another therapy during the first year of the treatment with b/tsDMARDs (see **Figure 15**).

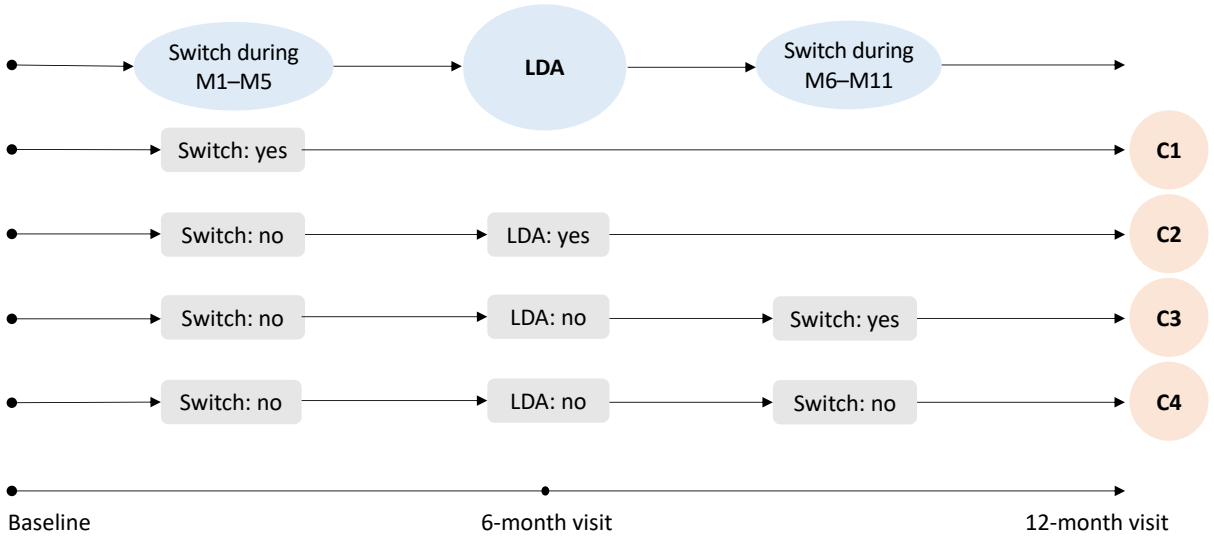


Figure 15 *Definition of studied cohorts C1 ('early switchers'), C2 ('responders'), C3 ('switchers following T2T principle') and C4 ('non-switchers not following T2T principles') based the achievement of treatment response at the 6-month visit and based switching within the first year; LDA – low disease activity; M – month*

First, we evaluated whether patients switched to another therapy within the first five months of the treatment. Next, we assessed if patients reached remission or low disease activity (LDA) at the 6-month visit (defined through disease activity score as DAS28-ESR ≤ 3.2, DAPSA ≤ 14, ASDAS < 2.1). Finally, we checked whether patients changed the therapy within months 6–11 provided they did not achieve the treatment target. Cohort *C1* includes patients that changed bDMARD/tsDMARD therapy during the first months (usually at a 3-month visit) before evaluating treatment response at the 6-month visit. These patients were either not responding to the treatment at all or were not tolerating the treatment (e.g., side effects) within

the first months of the first-line therapy. Cohort *C2* consists of patients ideally responding to the treatment because they achieved the treatment target after six months of therapy without a need to switch. Cohort *C3* comprises patients not responding to the treatment because they did not achieve the treatment target after the first six months of therapy. Following T2T principles, they switched to a different treatment. The last cohort *C4* is represented by patients not responding to the treatment since they did not achieve the treatment target (similarly to *C3* cohort). Regardless of T2T principles, they continued with the same treatment.

6.1.3 Outcome measures

Previously mentioned in 5.1, the primary objective of this study was to compare odds for the achievement of remission (REM) or at least low disease activity (LDA) after one year of the treatment between patients following (group *C3*) and not following (group *C4*) T2T strategy[21]. We assessed disease activity through composite indices, particularly DAS28-ESR (Prevoo et al. 1995), DAPSA (Schoels et al. 2010a) and ASDAS (Lukas et al. 2009).

DAS28-ESR (Disease Activity Score using 28 joint counts) is a measure of disease activity for patients with RA. It can take values between 0 and 9.4 (the higher, the worse). According to the values of the DAS28-ESR score we can define remission (REM; DAS28 ESR < 2.6), low disease activity (LDA; 2.6 ≤ DAS28-ESR ≤ 3.2), medium disease activity (MDA; 3.2 < DAS28-ESR ≤ 5.1) and high disease activity (HDA; DAS28-ESR > 5.1). The score is composed of tender joint count (TJC; 0–28), swollen joints count (SJC; 0–28), patient's global assessment of disease activity (PtGA) on a visual analogue scale (VAS; 0–100 mm) and erythrocyte sedimentation rate (ESR) (Fransen et al., 2003). DAS28 score can be calculated using CRP instead of ESR; however, other cut-off values for disease activity categories should be used when using CRP (Fleischmann et al. 2017; Greenmyer et al. 2020). In this work, we use the version including ESR. The DAS28-ESR can be calculated through the formula:

$$DAS28\ ESR = 0.56 * \sqrt{TJC} + 0.28 * \sqrt{SJC} + 0.70 * \ln ESR + 0.014 * PTGA.$$

DAPSA (Disease Activity index for PSoriatic Arthritis) score measures the disease activity in PsA patients. It consists of tender joints count (TJC; 0–68), swollen joints count (SJC; 0–66), CRP (mg/dL), patient's assessment of disease activity (PtGA) and pain (PtPain) on a 10-cm VAS (0 - not active/no pain, 10 - very active/very severe). Patients' disease activity can be classified based on the DAPSA values as REM (0–4), LDA (4.1–14), MDA (14.1–28)

[21] See chapters 2.1.3, 2.2.3 and 2.3.3 for more information about the T2T strategy recommended by EULAR.

and HDA (>28) (Gonçalves et al. 2020; Schoels et al. 2016). DAPSA index is simply defined as a sum:

$$DAPSA = TJC68 + SJC66 + PtGA\ (0\text{–}10\ cm) + PtPain\ (0\text{–}10\ cm) + CRP(mg/dL).$$

ASDAS (Ankylosing Spondylitis Disease Activity Score) is a measure of disease activity for patients with axSpA. It combines patient-reported outcomes (PROs) and CRP (or ESR) into one index. Specifically, it consists of acute-phase reactant (CRP/ESR), back pain, duration of morning stiffness, peripheral pain/swelling and PtGA. All PROs are reported on a 0–10 cm VAS. Based on the index values, disease activity can be classified as an inactive disease (ASDAS <1.3, analogy to REM), moderate disease activity (1.3 ≤ ASDAS < 2.1, analogy to LDA), high disease activity (≤ 2.1 ASDAS ≤ 3.5, analogy to MDA) and very high disease activity (ASDAS > 3.5, analogy to HDA). The ASDAS using CRP can be calculated through the formula (Machado et al. 2015):

$$ASDAS = 0.12 * Back\ pain + 0.06 * Duration\ of\ morning\ stiffness + 0.11 * PtGA + 0.07 * Peripheral\ pain/swelling + 0.58 * \ln(CRP(mg/L) + 1).$$

In terms of the secondary outcomes, we compared treatment results based on the disease activity score after 12 months between all studied cohorts. The proportion of patients with remission, low disease activity, medium disease activity and high disease activity at baseline and 12-month visits were compared across the studied cohorts C1–C4. Next, we compared changes in parameters related to disease activity (DAS28-ESR, SDAI[22], DAPSA, ASDAS, BASDAI[23], TJC and SJC, CRP, ESR, PtGA, MDGA) and quality of life (HAQ-DI, EQ-5D) after 6 and 12 months of the bDMARDs/tsDMARDs treatment between cohorts *C3* and *C4*.

HAQ-DI (Health Assessment Questionnaire Disability Index) is a comprehensive outcome measure assessing the self-reported functional status (disability). It ranges between 0 and 3, with higher values meaning worse disability. HAQ includes eight sections in total - dressing, arising, eating, walking, hygiene, reach, grip, and activities (Bruce a Fries 2005). **EQ-5D** (EuroQol) is an instrument that evaluates the quality of life. The EQ-5D questionnaire includes five dimensions that are rated by patients: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It also contains a VAS (0–100) for respondents' perceived health status, with higher values meaning better health status. An EQ-5D summary

[22] Simplified Disease Activity Index (range 0–84) measuring disease activity in RA. It includes TJC, SJC, PtGA, MDGA (medical doctor global assessment) and CRP (Smolen et al. 2003).
[23] Bath Ankylsoing Spondylitis Disease Activity Index is a measure of disease activity for ankylosing spondylitis. It contain evaluation of fatigue, spinal pain/swelling, enthesitis, morning stiffness duration and severity (Garrett et al. 1994).

index, derived by applying a formula that attaches weights to each dimension's levels, ranges between –0.59 and 1 (the higher, the better quality of life) (EuroQol Group 1990).

6.1.4 Statistical methods

A descriptive summary of patients' demographic and treatment characteristics and disease activity measurements was performed for all four studied cohorts *C1–C4*. For continuous variables, we calculated the median with interquartile range (IQR, 25^{th}–75^{th} percentiles). For a description of categorical variables, we used absolute and relative frequencies (i.e., percentages). We performed the non-parametric Mann-Whitney U test for continuous variables (after normality checks) and Pearson's chi-squared test for categorical variables to test differences between two patients' groups. The magnitude of changes in parameters over two visits was tested through the paired Wilcoxon test. For all tests, P values < 0.05 were considered to be statistically significant. We did not impute missing data in this analysis. The percentage of missing data in outcome variables (i.e. DAS28-ESR, DAPSA, ASDAS, HAQ and EQ-5D at baseline, 6 and 12 months) was relatively small; we excluded 1.8% of RA patients, 8.3% of PsA patients and 9.2% of axSpA patients in total.

We used propensity score matching to match patients not switching to another therapy after not reaching the treatment target at 6-month visit (*C4*) to patients switching to a different treatment after not reaching the treatment target (*C3*). For matching, we performed logistic regression with outcome variable *C3* (=1) vs *C4* (=0) and selected baseline covariates. The covariates were chosen based on statistically significant differences in baseline characteristics with respect to clinical relevance and multicollinearity. We chose the matching ratio 1:1 (for RA and axSpA) and 1:2 (for PsA). Further, we set the caliper to 0.2. The adequacy of the final propensity score model was checked through the balance diagnostics (standardized mean differences should be less than 0.1 to ensure balance in selected covariates). We used matching to make both groups comparable in characteristics at the 6-month visit and to minimise confounding by other factors in the evaluation of achieving REM/LDA at the 12-month visit. After we carried out propensity score matching, we employed binary logistic regression to determine the odds for reaching REM/LDA at the 12-month visit in cohorts *C3* and *C4*. We did all descriptive statistics and testing using IBM SPSS Statistics 25.0. The propensity score model was performed in R (version 3.5.3).

6.2 Predictive ability of self-perceived general health at TNFi therapy start

6.2.1 Study population

In this study, we used two separate datasets for analyses to validate our results – primary (older cohort) and validation dataset (newer cohort). The primary dataset included all bio-naive adult patients diagnosed with RA/PsA/axSpA starting TNFi therapy within a period from the registry data collection start (2001/2004/2002 for RA/PsA/axSpA) until 31 December 2017 (data export on 1 January 2018). The validation dataset consisted of all bio-naive adult patients with RA/PsA/axSpA diagnosis starting TNFi therapy between 1 January 2018 and 1 January 2020 (data export on 31 March 2021). Patients without filled the SF-36 questionnaire at baseline and without at least one-year follow-up with available 6-month and 12-month visits were excluded from the analysis (see flow charts **Figure 16**, **Figure 17** and **Figure 18**). Additionally, in the primary axSpA dataset, patients with missing ASDAS scores at baseline, 6-month and 12-month visits were excluded from further analyses. The number of missing values was extensive in this cohort because the collection of ASDAS within the ATTRA registry started in 2012.

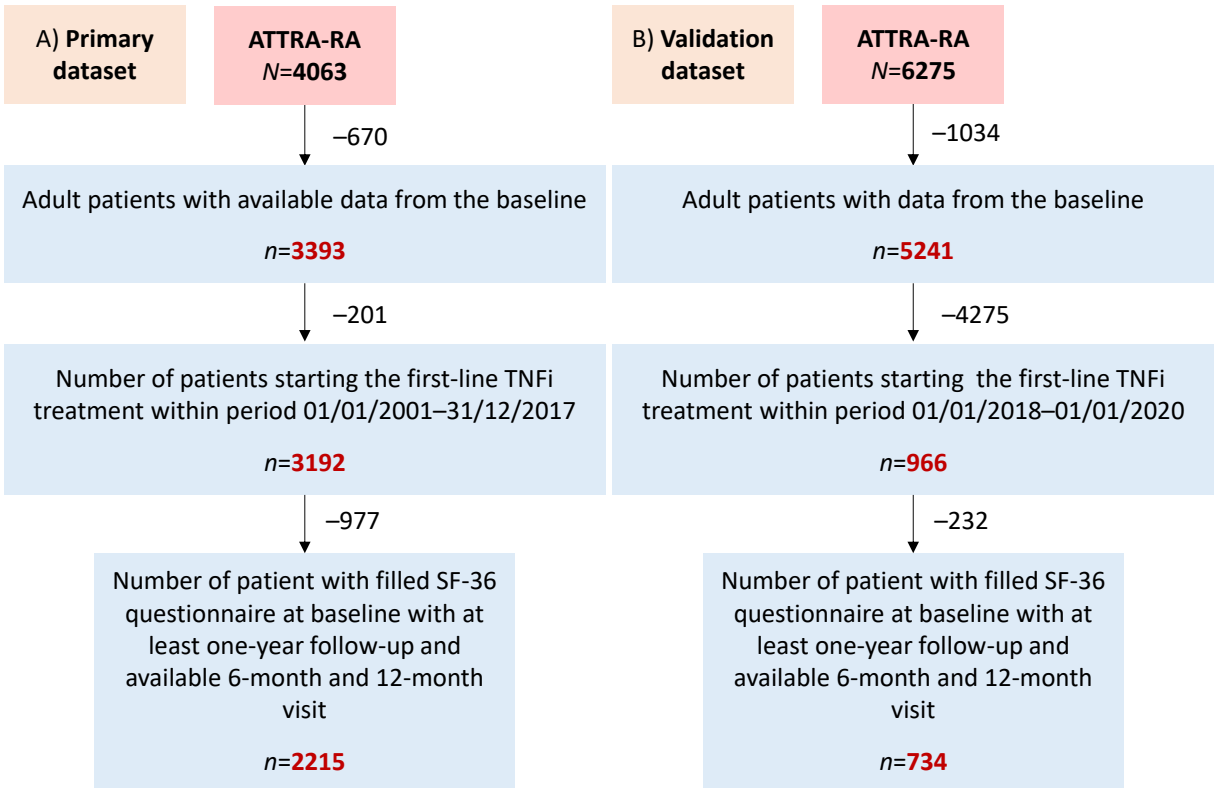


Figure 16 *Flow chart showing individual steps to final datasets both for the primary dataset (A) and validation dataset (B) within RA diagnosis*

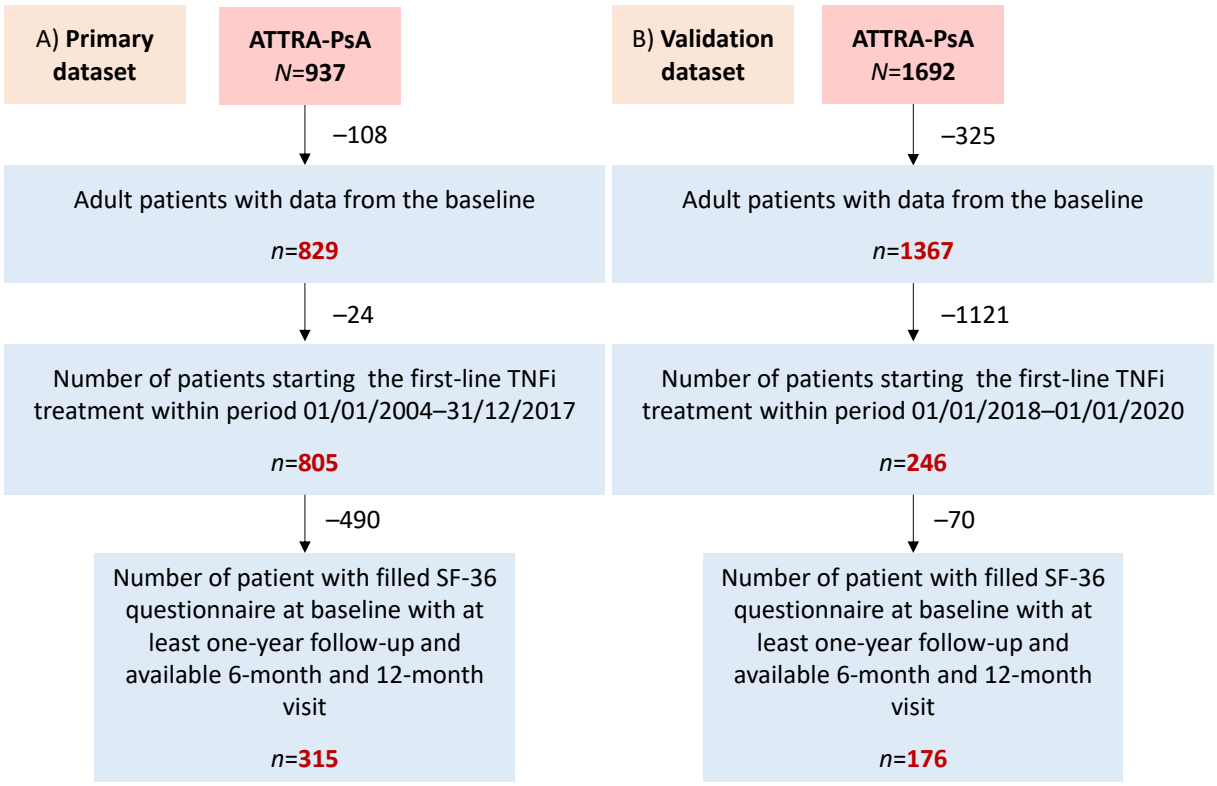


Figure 17 *Flow chart showing individual steps to final datasets both for primary (A) and validation (B) datasets within PsA*

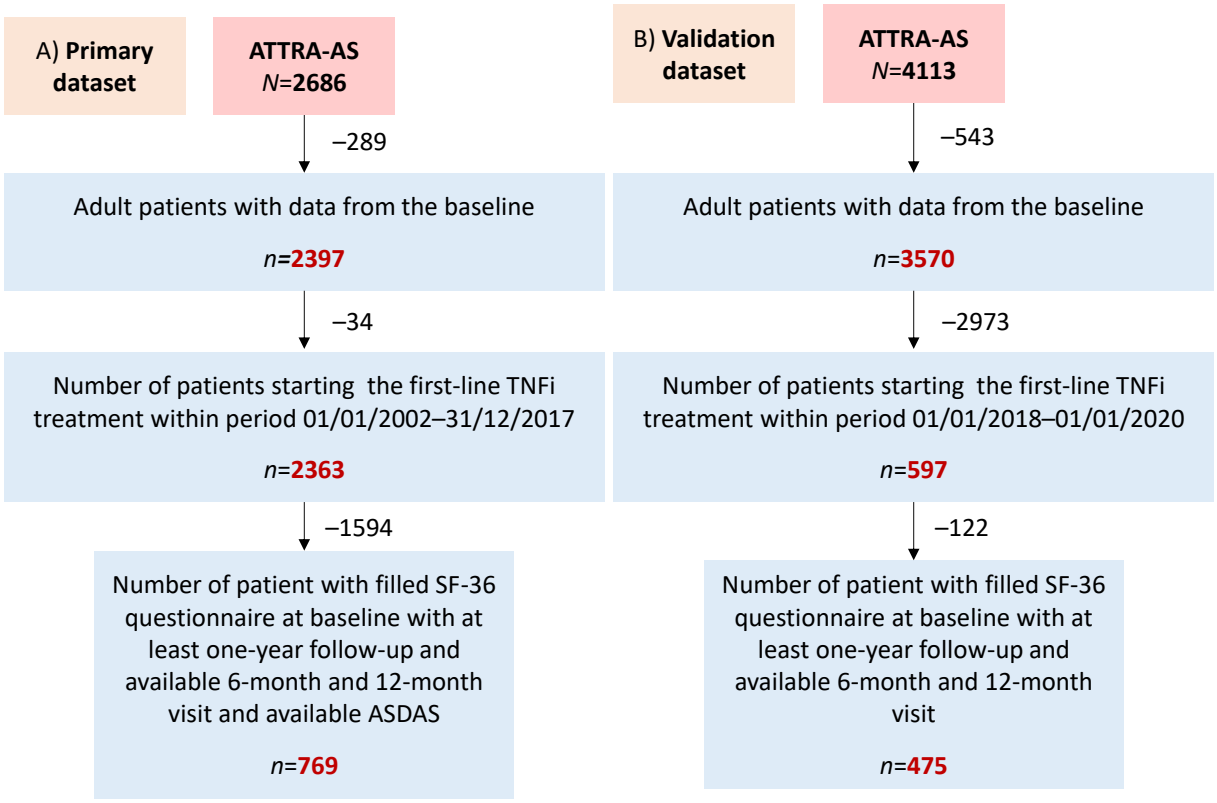


Figure 18 *Flow chart showing individual steps to final datasets both for the primary (A) and validation dataset (B) within axSpA patients*

Data were collected in the ATTRA registry (see 4). Ethics approval for ATTRA was granted by the Czech Multicentre Research Ethics Committee, no. 201611 S300 and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic, no. 10113/2016. All subjects provided their written consent for collecting and storing data before participation. All procedures were performed following the Declaration of Helsinki.

6.2.2 Study design

We divided patients meeting the inclusion criteria specified in the previous chapter (6.2.1) according to their response (definitely/mostly yes, definitely/mostly no, don't know) to Q11A '*I seem to get sick a little easier than other people*', and Q11C '*I expect my health to get worse*' at baseline. We further analyzed only patients who answered definitely/mostly yes/no, because we wanted to focus only on decisive patients. Patients who responded '*definitely yes'* and 'mostly yes' were analyzed together (as well as patients responding '*definitely no*' and '*mostly no'*). Patients' subgroups based on their responses are shown in pie charts **Figure 19** (RA), **Figure 20** (PsA)and **Figure 21** (axSpA). We used two separate datasets (primary and validation) for each diagnosis to validate our results. As part of a sensitivity analysis, we performed the whole analysis on the PS matched datasets as well.

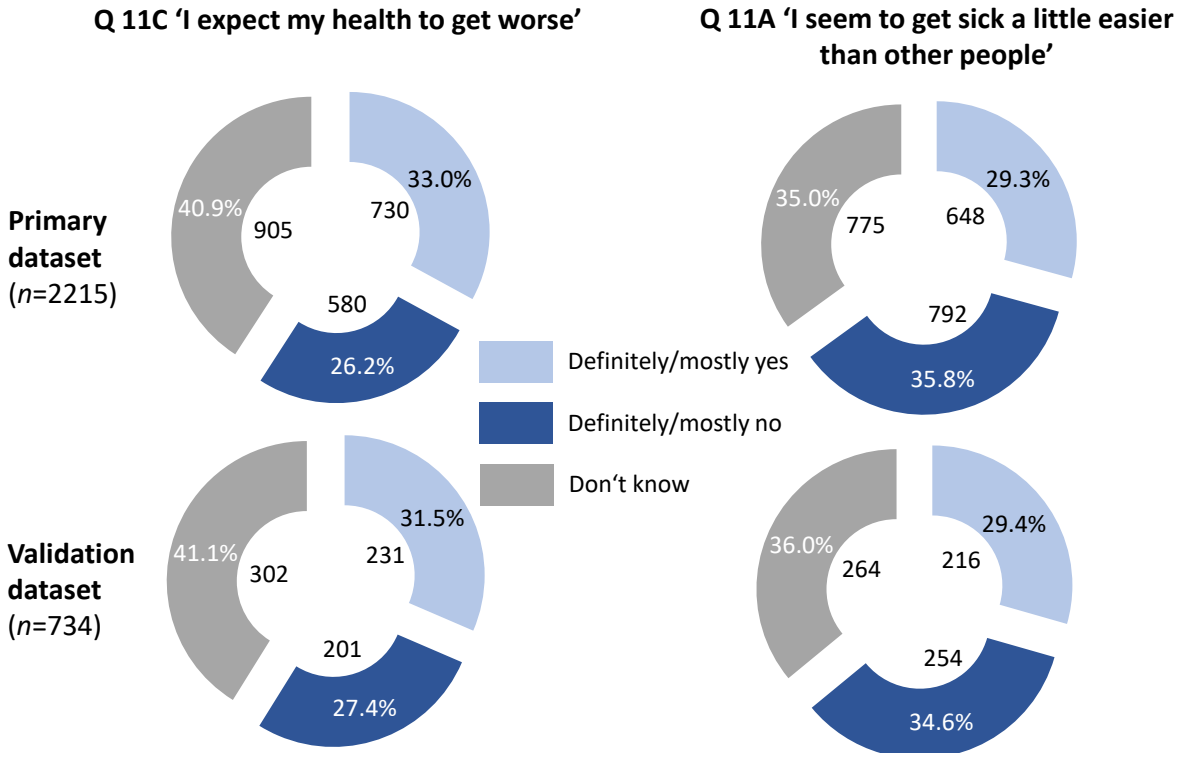


Figure 19 *Division of RA patients based on their answers to studied SF-36 questions*

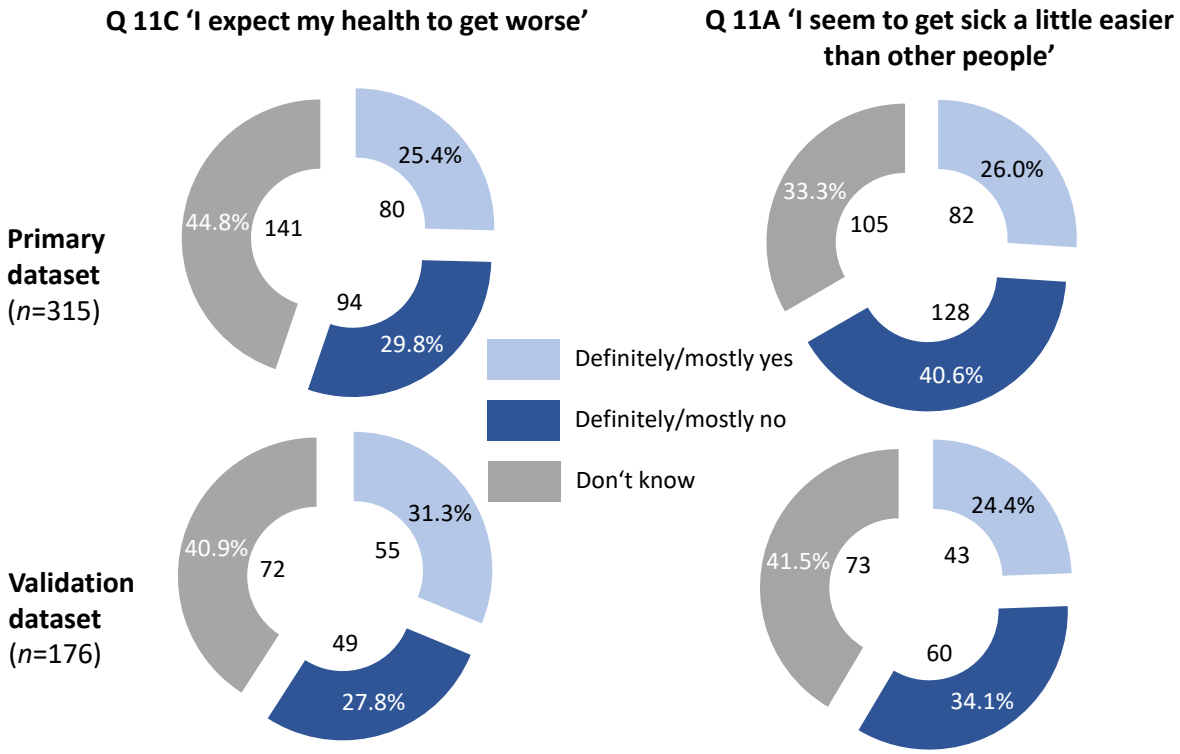


Figure 20 *Division of PsA patients based on their answers to studied SF-36 questions*

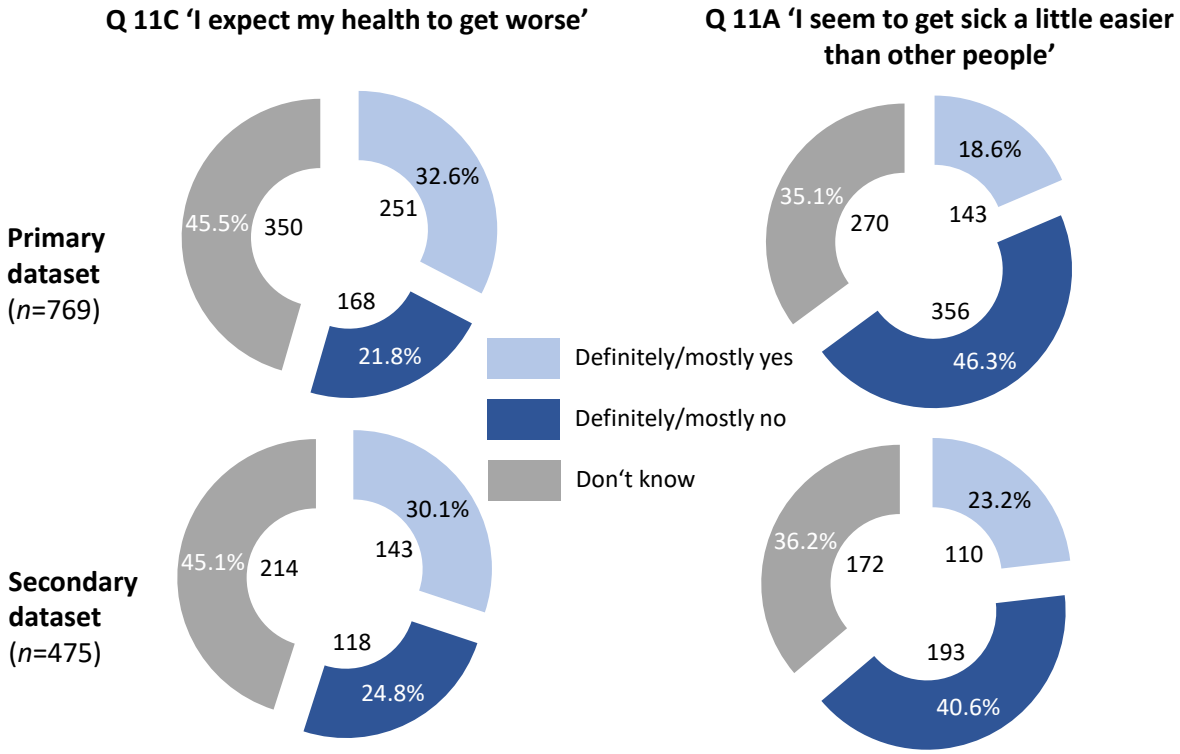


Figure 21 *Division of axSpA patients based on their answers to studied SF-36 questions*

6.2.3 Outcome measures

In this study, our goal was to investigate whether the two selected SF-36 questions could predict therapeutic response in patients starting their first anti-TNF therapy. The therapeutic response was evaluated through remission achievements and drug retention.

Our primary outcome was remission (REM) at 6 and 12 months since TNFi treatment initiation. Remission was defined through disease activity indices as DAS28-ESR < 2.6 (for RA), DAPSA ≤ 4 (for PsA) and ASDAS < 1.3 (for axSpA). For more information about these composite indices, see 6.1.3. Our secondary outcome was drug retention. These two outcomes were evaluated across studied subgroups ('*definitely/mostly yes*' vs '*definitely/mostly no*') in both datasets (primary and validation) for each diagnosis.

6.2.4 Statistical methods

A descriptive summary of patients' demographic and treatment characteristics and disease activity measurements was performed for patients answering '*definitely/mostly yes*' and '*definitely/mostly no*' to Q11A and Q11C. For continuous variables, we calculated the median with interquartile range (IQR, 25^{th}–75^{th} percentiles). For a description of categorical variables, we used absolute and relative frequencies (i.e., percentages). We performed the non-parametric Mann-Whitney *U* test for continuous variables (after normality checks), and Pearson's chi-squared test for categorical variables to test differences between two patients' groups. In case the assumption of Pearson's chi-squared test was violated, Fisher's exact test was used instead. For all tests, P values < 0.05 were considered to be statistically significant. We did not impute missing data in this analysis and performed an available-case analysis instead.

We computed univariable logistic regression models to obtain odds ratios for remission achievement after 6/12 months of treatment for patients answering '*yes'* vs '*no'* to studied questions. Next, we performed multivariable logistic regression models with baseline HAQ and DAS28-ESR/DAPSA/ASDAS to obtain odds ratios adjusted for potential confounders.

Drug retention was computed through the Kaplan-Meier survival method. Drug survival time was computed as the time from the first-line TNFi initiation until the date of drug discontinuation (for any reason) or the last update of patients in the registry. Drug survival probabilities were displayed through Kaplan-Meier curves and supplemented by numbers of patients at risk beneath the graphs. We also present numbers of discontinuations, one-year and two-year survival rates and median survival time with corresponding confidence intervals. The

probabilities of drug discontinuations were compared across the studied groups through the Log-rank test. In case the curves were crossing, we also computed the Breslow test and Tarone-Ware test. We employed Cox regression models to estimate hazard ratios for treatment discontinuation for patients answering '*yes'* vs '*no'*. Besides crude hazard ratios, we obtained adjusted versions with baseline HAQ and DAS28-ESR/ASDAS/DAPSA as confounders.

For the sensitivity analysis, we created balanced datasets for both subgroups (answering '*yes'* and '*no'*). We used propensity score matching to match patients answering '*yes'* to patients answering '*no*' within each studied question. We performed logistic regression with the outcome variable '*yes'* (=1) vs '*no'* (=0) and selected baseline covariates for matching. The covariates were chosen based on statistically significant differences in baseline characteristics with respect to clinical relevance and multicollinearity. We chose the matching ratio 1:1 and set the caliper to 0.2. The adequacy of the final propensity score model was checked through the balance diagnostics (standardized mean differences should be less than 0.1 to ensure balance in selected covariates). We used matching to make both groups comparable in baseline characteristics and to minimise confounding by other factors in the evaluation of achieving REM at the 6-/12-month visit and in the evaluation of drug retentions. After we carried out propensity score matching, we employed binary logistic regression to determine the odds for reaching REM at the 6-/12-month visit in cohorts '*yes'* and '*no'*, and we calculated drug retentions as well. We did all descriptive statistics and testing using IBM SPSS Statistics 25.0. The propensity score model was performed in R (version 3.5.3).

7 Results

7.1 T2T strategy vs conservative approach

7.1.1 Patients‘ characteristics at baseline

In total, we included 1275 patients with RA, 539 patients with PsA and 1457 patients with axSpA fulfilling the inclusion criteria in the analysis (see **Figure 14**). For RA diagnosis, cohort C1 was represented by 62 (4.9%) patients, C2 consisted of 598 (46.9%) patients, C3 included 124 (9.7%) patients and 491 (38.5%) patients belonged to C4 subgroup (see **Figure 22**). Within patients with PsA, cohort C1 included 11 (2.0%) patients, C2 consisted of 395 (73.3%) patients, C3 included 29 (5.4%) patients, and C4 consisted of 104 (19.3%) patients (see left diagram in **Figure 23**). In axSpA diagnosis, 25 (1.7%) patients belonged to the C1 group, 938 (64.4%) patients belonged to the C2 group, 90 (6.2%) patients fell into the C3 group, and 404 (27.7%) patients represented C4 (see right diagram in **Figure 23**).

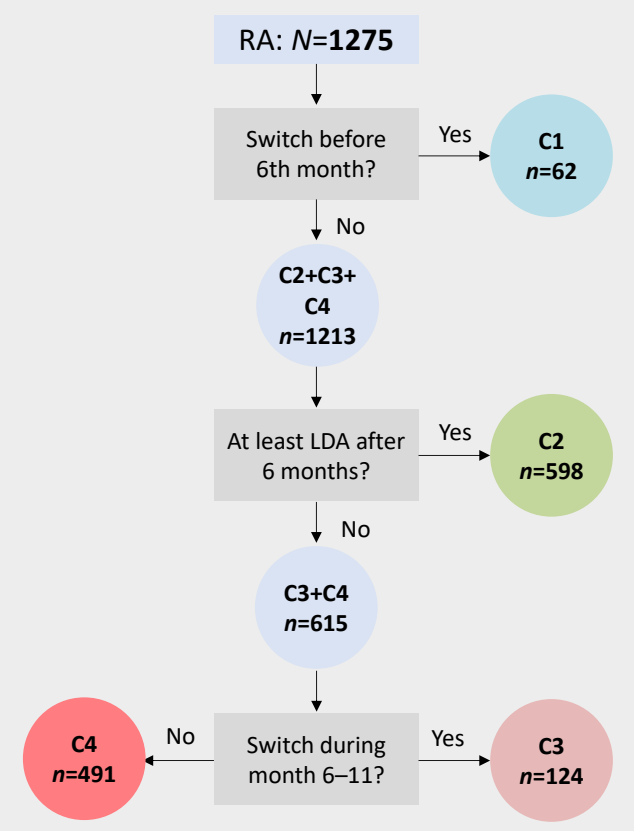


Figure 22 *Division of RA patients into four study cohorts; LDA – low disease activity*

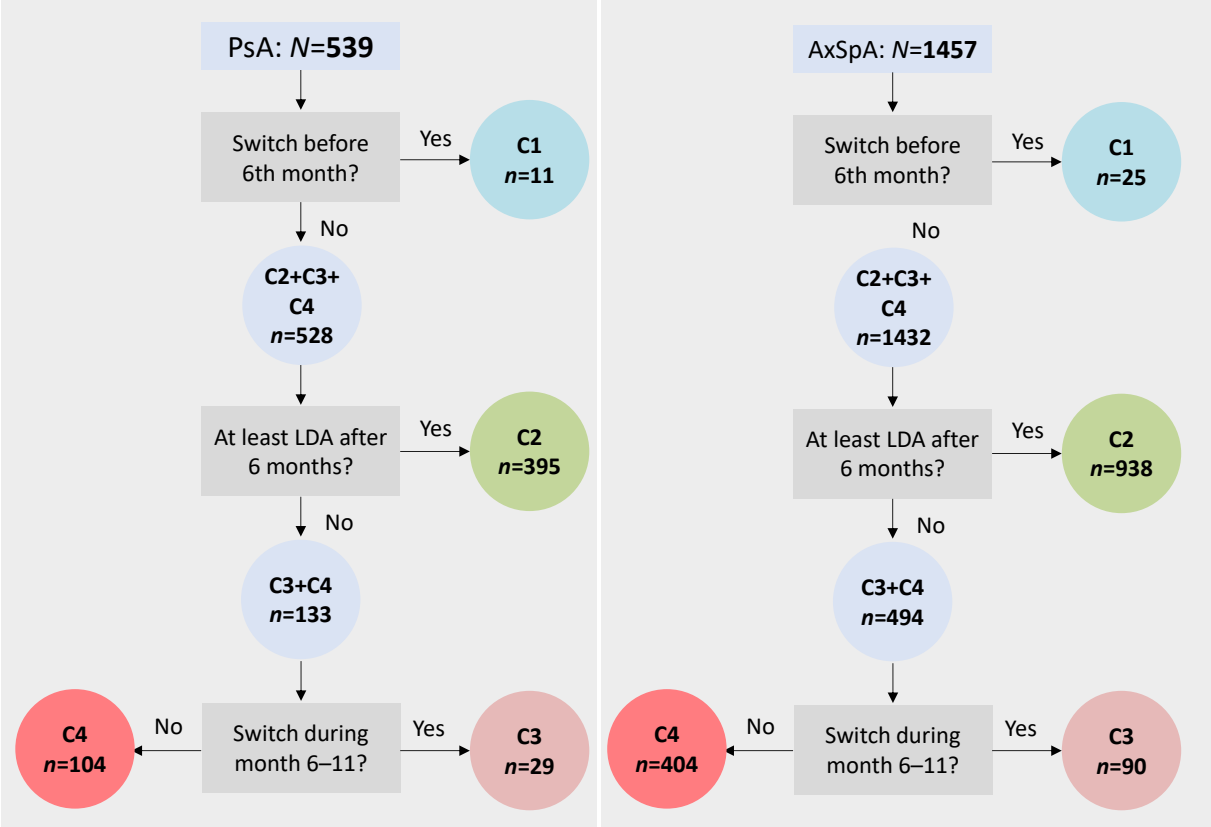


Figure 23 *Division of PsA (left) and axSpA (right) patients into four study cohorts; LDA – low disease activity*

The most frequently administered drug in the **RA cohort** was adalimumab (ranging from 27.4% to 40.3% in studied cohorts), etanercept (from 15.3% to 35.5%) and golimumab (from 6.5% to 15.5%). Tofacitinib, as the only Janus kinase inhibitor administered in analysed patients, was present only in one patient from C2 and one patient from C4. Out of 61 patients from C1 treated with TNFi in the first line, 42 (68.9%) switched before the six-month visit to another TNFi, 11 (18.0%) switched to an interleukin-6 inhibitor (tocilizumab or sarilumab), 7 (11.5%) switched to abatacept, and 1 (1.6%) switched to rituximab. One patient from C1 who was treated with tocilizumab in the first line switched to anakinra. Out of 120 patients from the C3 cohort that were treated with TNFi, 72 (60.0%) patients switched after the six months to another TNFi, 28 (23.3%) switched to an interleukin-6 drug (tocilizumab or sarilumab), 13 (10.8%) switched to abatacept and 7 (5.8%) switched to rituximab. Out of two C3 patients with tocilizumab, one switched to rituximab and the other to abatacept. Out of two C3 patients with rituximab, one switched to etanercept and the other to abatacept. We present baseline characteristics of all four studied cohorts within RA diagnosis in **Table 3**.

Table 3 *Baseline characteristics of RA patients in cohort C1–C4 (N=1275)*

	C1 (*n*=62)	C2 (*n*=598)	C3 (*n*=124)	C4 (*n*=491)
Female, *n* (%)	52 (83.9%)	431 (72.1%)	102 (82.3%)	390 (79.4%)
Age at diagnosis, years	44.0 (34.0–52.0)	43.5 (33.0–52.0)	45.0 (34.0–51.5)	47.0 (38.0–54.0)
Age at start of 1st line, years	51.0 (42.0–58.0)	53.0 (41.0–60.0)	52.0 (44.5–61.0)	55.0 (48.0–63.0)
Disease duration, years	5.6 (3.0–7.8)	6.0 (2.5–11.8)	5.0 (2.2–12.1)	6.2 (3.0–12.9)
RF positive	47 (75.8%)	428 (71.6%)	92 (74.2%)	389 (79.6%)
ACPA positive	44/61 (72.1%)	399/587 (68.0%)	91/120 (75.8%)	348/480 (72.5%)
Presence of erosions	25/38 (65.8%)	210/295 (71.2%)	46/67 (68.7%)	22/290 (76.6%)
Currently smoking	10/53 (18.9%)	102/504 (20.2%)	26/103 (25.2%)	93/413 (22.5%)
Presence of comorbidities	44 (71.0%)	364 (61.0%)	77 (62.1%)	334 (68.0%)
BMI	24.9 (23.1–28.1)	25.6 (22.6–29.4)	25.5 (22.9–30.4)	26.1 (22.8–30.1)
Previous csDMARDs				
0	0 (0.0%)	8/592 (1.4%)	2 (1.6%)	6/484 (1.2%)
1	13 (21.0%)	226/592 (38.2%)	27 (21.8%)	131/484 (27.1%)
2	18 (29.0%)	147/592 (24.8%)	30 (24.2%)	165/484 (34.1%)
3	17 (27.4%)	112/592 (18.9%)	35 (28.2%)	113/484 (23.3%)
4+	14 (22.6%)	99/592 (16.7%)	30 (24.2%)	69/484 (14.3%)
GCs in previous history	56 (90.3%)	519/597 (86.9%)	112 (90.3%)	442 (90.0%)
Concomitant csDMARDs	54 (87.1%)	549 (91.8%)	107 (86.3%)	440 (89.6%)
Concomitant MTX	44 (71.0%)	454 (75.9%)	77 (62.1%)	349 (71.1%)
- MTX dose (mg/week)	15.0 (10.0; 20.0)	15.0 (15.0; 20.0)	20.0 (10.0; 20.0)	15.0 (12.5; 20.0)
Concomitant GCs	49 (79.0%)	446 (74.6%)	96 (77.4%)	402 (81.9%)
- Prednisone dose (mg/day)	7.5 (5.0; 10.0)	5.0 (5.0; 10.0)	7.5 (5.0; 10.0)	7.9 (6.1; 7.5)
DAS28-ESR (0–10)	6.4 (5.7–7.0)	5.9 (5.3–6.5)	6.2 (5.6–6.8)	6.3 (5.8–6.8)
TJC (28 joints)	14.0 (11.0–19.0)	12.0 (9.0–16.0)	14.5 (9.0–19.0)	13.0 (10.0–18.0)
SJC (28 joints)	10.0 (7.0–13.0)	9.0 (6.0–12.0)	9.5 (6.0–12.5)	10.0 (7.0–13.0)
ESR (mm/h) [a]	33.5 (16.0–53.0)	28.0 (16.0–40.0)	32.0 (18.0–50.0)	34.0 (23.0–50.0)
CRP (mg/l) [b]	22.0 (9.4–34.0)	12.0 (5.3–23.5)	15.0 (7.9–31.0)	16.8 (8.0–33.1)
SDAI (0–86) [c]	40.5 (32.7–47.8)	35.6 (29.5–42.4)	39.3 (33.0–48.2)	39.0 (32.6–45.9)
PtGA (0–100)	78.0 (69.0–84.0)	70.0 (59.0–80.0)	75.0 (62.5–81.5)	75.0 (60.0–85.0)
MDGA (0–100) [d]	74.0 (60.0–80.0)	65.0 (52.0–75.0)	70.0 (58.5–80.0)	70.0 (60.0–80.0)
HAQ-DI (0–3)	1.8 (1.3–2.0)	1.4 (1.0–1.8)	1.8 (1.4–2.0)	1.8 (1.4–2.0)
EQ-5D (-0.59–1)	0.1 (0.0–0.6)	0.2 (0.1–0.7)	0.1 (0.0–0.5)	0.1 (0.0–0.5)

RF rheumatoid factor; *ACPA* anti-citrullinated protein; TNFi tumour necrosis factor inhibitor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *GCs* glucocorticoids, *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *SDAI* Simplified Disease Activity Index; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented; if the denominator is smaller than the number of patients in given cohorts, n/total (%) are presented.

[a] *n*=62 (C1), n=573 (C2), *n*=118 (C3), *n*=486 (C4)

[b] *n*=60 (C1), *n*=576 (C2), *n*=123 (C3), *n*=480 (C4)

[c] *n*=55 (C1), *n*=560 (C2), *n*=119 (C3), *n*=465 (C4)

[d] *n*=57 (C1), *n*=582 (C2), *n*=120 (C3), *n*=476 (C4)

The median age of RA patients at the start of the first bDMARD/tsDMARD was between 51 years (C1) and 55 years (C4 cohort). Females represented from 72.1% (C2 cohort) to 83.9% (C1 cohort) patients. All patients had high baseline disease activity according to DAS28-ESR score with a median 6.4 (5.7–7.0) in C1, 5.9 (5.3–6.5) in C2, 6.2 (5.6–6.8) in C3 and 6.3 (5.8–6.8) in C4. Patients from cohorts C3 and C4 significantly differed only in age at the start of the first therapy (p=0.016) and the number of previous csDMARDs (p=0.025). The median age was 52.0 (44.5–61.0) years in C3 and 55.0 (48.0–63.0) years in C4. Cohorts C1 and C2 significantly differed in gender (84% vs 72% females; p=0.046) and in almost all parameters related to baseline disease activity and quality of life. Patients from cohort C1 had higher disease activity than C2 cohort according to DAS28-ESR (median 6.4 vs 5.9; p<0.001), TJC (median 14 vs 12; p=0.005), CRP (median 22 vs 12; p=0.002), PtGA (median 78 vs 70; p=0.008), MDGA (median 74 vs 65; p=0.015) and worse physical function and quality of life according to HAQ-DI (median 1.8 vs 1.4; p=0.001) and EQ-5D (median 0.1 vs 0.2; p=0.048), respectively.

In the **PsA cohort**, the most frequently administered drug was adalimumab (ranging from 37.9% to 47.1% in studied cohorts). Other administered bDMARDs included etanercept, infliximab, certolizumab, golimumab and secukinumab. No JAKi was present PsA cohort. There was a statistically significant difference in frequency of administered bDMARDs between cohorts C3 and C4 (e.g. infliximab 24.1% vs 3.8%; p=0.019). Out of 11 patients from C1 treated with TNFi in the first line, 10 (90.9%) switched before the six-month visit to another TNFi, 1 (9.1%) switched to an interleukin-17A inhibitor (ixekizumab). Out of 25 patients from the C3 cohort with TNFi, 18 (72.0%) patients switched after the six months to another TNFi, 7 (28.0%) switched to an interleukin-17A inhibitor (secukinumab). Out of four C3 patients with secukinumab in the first line, all switched to TNFi. Baseline characteristics of all four studied cohorts within PsA diagnosis can be found in **Table 4**.

Table 4 *Baseline characteristics of PsA patients in cohort C1–C4 (N=539)*

	C1 (n=11)	C2 (n=395)	C3 (n=29)	C4 (n=104)
Female, *n* (%)	8 (72.7%)	170 (43.0%)	13 (44.8%)	56 (53.8%)
Age at diagnosis, years	46.0 (40.0–49.0)	39.0 (32.0–49.0)	41.0 (34.0–47.0)	43.0 (31.5–50.0)
Age at start of 1st line, years	51.0 (43.0–58.0)	48.0 (39.0–57.0)	47.0 (42.0–55.0)	52.0 (42.0–57.0)
Disease duration, years	3.0 (1.7–8.0)	5.4 (2.2–11.9)	2.3 (1.5–8.7)	5.7 (1.9–11.7)
RF+/ACPA+	0 (0.0%)	19 (4.8%)	4 (13.8%)	17 (16.3%)
Psoriasis	7/8 (87.5%)	314/336 (93.5%)	26/27 (96.3%)	83/89 (93.3%)
Dactylitis	3/10 (30.0%)	148/391 (37.9%)	9/27 (33.3%)	35/102 (34.3%)
Enthesitis	6 (54.5%)	58/391 (14.8%)	5/28 (17.9%)	20 (19.2%)

Currently smoking	2/10 (20.0%)	65/369 (17.6%)	5/24 (20.8%)	25/93 (26.9%)
Presence of comorbidities	6 (54.5%)	294 (74.4%)	22 (75.9%)	83 (79.8%)
BMI[a]	27.5 (23.5–33.7)	27.8 (24.7–32.6)	26.6 (25.0–29.5)	29.7 (25.7–33.3)
HLA-B27 positivity	0/9 (0.0%)	75/306 (24.5%)	10/23 (43.5%)	19/74 (25.7%)
Nail involvement				
No	3/10 (27.3%)	166/395 (42.0%)	9/27 (31.0%)	37/101 (35.6%)
Mild	3/10 (27.3%)	94/395 (23.8%)	12/27 (41.4%)	28/101 (26.9%)
Medium	3/10 (27.3%)	110/395 (27.8%)	4/27 (13.8%)	26/101 (25.0%)
Severe	1/10 (9.1%)	19/395 (4.8%)	2/27 (6.9%)	10/101 (9.6%)
Previous csDMARDs				
0	1 (9.1%)	16/391 (4.1%)	0 (0.0%)	1/103 (1.0%)
1	4 (36.4%)	159/391 (40.7%)	7 (24.1%)	42/103 (40.8%)
2	2 (18.2%)	124/391 (31.7%)	13 (44.8%)	35/103 (34.0%)
3+	4 (36.4%)	92/391 (23.5%)	9 (31.0%)	25/103 (24.3%)
GCs in previous history	6 (54.5%)	221 (55.9%)	16 (55.2%)	68 (65.4%)
Concomitant csDMARDs	8 (72.7%)	307 (77.7%)	21 (72.4%)	82 (78.8%)
Concomitant MTX	8 (72.7%)	235 (59.5%)	15 (51.7%)	56 (53.8%)
- MTX dose (mg/week)	15.0 (10.0–15.0)	15.0 (12.5–20.0)	15.0 (10.0–20.0)	20.0 (12.5–20.0)
Concomitant GCs	3 (27.3%)	126 (31.9%)	8 (27.6%)	44 (42.3%)
- Prednisone dose (mg/day)	5.0 (5.0–5.0)	5.0 (5.0–10.0)	5.0 (5.0–7.5)	7.5 (5.0–10.0)
DAS28-ESR (0–10)	6.2 (4.8–6.8)	5.4 (4.5–6.1)	5.5 (4.6–5.9)	5.8 (5.2–6.6)
DAPSA	48.3 (34.4–69.9)	34.7 (25.6–43.1)	33.4 (28.6–49.1)	43.2 (36.8–51.7)
TJC (68 joints)	17 (9–38)	11 (7–16)	12 (10–21)	16.0 (11–24)
SJC (66 joints)	9.0 (2.0–17.0)	8.0 (4.0–12.0)	7.0 (4.0–12.0)	10.0 (5.0–12.5)
CRP (mg/l)	5.0 (4.0–12.0)	14.5 (5.6–26.2)	9.2 (4.5–19.2)	13.5 (5.7–33.5)
ESR (mm/h)[b]	30.0 (10.0–38.0)	28.0 (16.0–42.0)	20.0 (10.0–40.0)	30.0 (15.0–53.0)
PtGA (0–100)	80.0 (70.0–86.0)	70.0 (60.0–80.0)	70.0 (52.0–80.0)	75.5 (60.5–85.0)
MDGA (0–100)	70.0 (40.0–78.0)	68.0 (55.0–80.0)	64.0 (59.0–72.0)	70.0 (58.5–80.0)
HAQ-DI (0–3)	1.6 (0.9–1.9)	1.3 (0.9–1.6)	1.4 (0.9–1.8)	1.6 (1.3–1.9)
EQ-5D (-0.59–1)	0.2 (0.0–0.5)	0.2 (0.1–0.7)	0.1 (0.0–0.6)	0.1 (0.0–0.2)
PGA of psoriasis				
0–1	2 (18.2%)	91/379 (24.0%)	8/28 (28.6%)	33/99 (33.3%)
2–3	5 (45.5%)	225/379 (59.4%)	20/28 (71.4%)	47/99 (47.5%)
4–5	4 (36.4%)	63/379 (16.6%)	0/28 (0.0%)	19/99 (19.2%)

RF rheumatoid factor; *ACPA* anti-citrullinated protein; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *GCs* glucocorticoids, *DAS28-ESR* 28-joint disease activity score with ESR; DAPSA Disease Activity index for Psoriatic Arthritis; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PGA* Physician global assessment; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented; if the denominator is smaller than the number of patients in given cohorts, n/total (%) are presented.

[a] *n*=11 (C1), n=382 (C2), *n*=29 (C3), *n*=103 (C4)

[b] *n*=11 (C1), *n*=389 (C2), *n*=29 (C3), *n*=103 (C4)

The median age at the first bDMARD/tsDMARD initiation was between 47 years (C3) and 52 years (C4 cohort). Females represented from 43.0% (C2 cohort) to 73.0% (C1 cohort)

patients. Patients from all studied cohorts had high baseline disease activity according to DAPSA score with a median value of 48.3 (34.4–69.9) in C1, 34.7 (25.6–43.1) in C2, 33.4 (28.6–49.1) in C3 and 43.2 (36.8–51.7) in C4. Patients from cohorts C3 and C4 significantly differed in disease activity according to DAS28-ESR (C3 vs C4: median 5.5 vs 5.8), ESR (C3 vs C4: median 20 vs 30), PGA of psoriasis (more severe in C4), BMI (C3 vs C4: median 26.6 vs 29.7) and drug type (e.g. infliximab was present in 24.1% of C3 patients vs 3.8% of C4 patients). Cohorts C1 and C2 significantly differed in DAPSA score (C1 vs C2: median 48.3 vs 34.7), tender joint count (C1 vs C2: median 17 vs 11), CRP (C1 vs C2: median 5.0 vs 14.5) and presence of enthesitis (54.5% in C1 vs 14.8% C2). However, cohort C1 included only 11 patients. Therefore, the comparison's results should be interpreted with great caution.

In the **axSpA cohort**, the most frequently administered drug was adalimumab (ranging from 42.4% to 48.0% in studied cohorts). Other administered bDMARDs included etanercept, infliximab, certolizumab, golimumab and secukinumab. No JAKi was present axSpA cohort. There was no statistically significant difference in the frequency of administered bDMARDs between cohorts C3 and C4. Out of 25 patients from C1 treated with TNFi in the first line, 23 (92.0%) switched before the six-month visit to another TNFi, 2 (8.0%) switched to an interleukin-17A inhibitor (secukinumab). Out of 83 patients from the C3 cohort treated with TNFi, 70 (84.3%) patients switched after the six months to another TNFi, 13 (15.7%) switched to an interleukin-17A inhibitor (secukinumab). All seven C3 patients with secukinumab switched to TNFi. Baseline characteristics of four studied cohorts within axSpA diagnosis can be found in **Table 5**.

Table 5 *Baseline characteristics of axSpA patients in cohort C1–C4 (N=1457)*

	C1 (*n*=25)	C2 (*n*=938)	C3 (*n*=90)	C4 (*n*=404)
Female, *n* (%)	13 (52.0%)	237 (25.3%)	30 (33.3%)	145 (35.9%)
Age at diagnosis, years[a]	36.0 (31.5–44.5)	31.0 (25.0–39.0)	37.0 (26.0–44.0)	35.0 (28.0–43.0)
Age at start of 1st line, years	42.0 (35.0–50.0)	38.0 (31.0–46.0)	45.0 (35.0–53.0)	43.0 (36.0–52.0)
Disease duration, years[a]	4.4 (1.1–7.2)	3.9 (1.1–8.9)	4.4 (0.9–13.2)	5.1 (1.5–11.0)
Uveitis	5 (20.0%)	207/931 (22.2%)	16/89 (18.0%)	79/403 (19.6%)
Colitis	3 (12.0%)	37/931 (4.0%)	3/89 (3.4%)	26/403 (6.5%)
Psoriasis	1 (4.0%)	42/937 (4.5%)	7 (7.8%)	15 (3.7%)
Dactylitis	0/22 (0.0%)	42/905 (4.6%)	2/81 (2.5%)	11/390 (2.8%)
Currently smoking	8/23 (34.8%)	272/866 (31.4%)	32/83 (38.6%)	136/381 (35.7%)
Presence of comorbidities	18 (72.0%)	407 (43.4%)	50 (55.6%)	252 (62.4%)
BMI[b]	28.7 (23.0–33.6)	25.8 (22.9–29.0)	27.5 (25.3–31.9)	27.8 (24.5–31.7)
HLA-B27 positivity	19/24 (79.2%)	846/928 (91.2%)	79/88 (89.8%)	352/398 (88.4%)
Joint involvement				
Axial	8/23 (34.8%)	414/921 (45.0%)	30/88 (34.1%)	134/399 (33.6%)

Root	2/23 (8.7%)	209/921 (22.7%)	21/88 (23.9%)	110/399 (27.6%)
Peripheral	13/23 (56.5%)	298/921 (32.4%)	37/88 (42.0%)	155/399 (38.8%)
Previous csDMARDs				
0	11 (44.0%)	425/933 (45.6%)	41/88 (46.6%)	144/400 (36.0%)
1	11 (44.0%)	349/933 (37.4%)	31/88 (35.2%)	157/400 (39.3%)
2	1 (4.0%)	124/933 (13.3%)	9/88 (10.2%)	80/400 (20.0%)
3+	2 (8.0%)	35/933 (3.8%)	7/88 (8.0%)	19/400 (4.8%)
GCs in previous history	10 (40.0%)	254 (27.1%)	28 (31.1%)	145 (35.9%)
Concomitant csDMARDs	9 (36.0%)	304 (32.4%)	28 (31.1%)	158 (39.1%)
Concomitant MTX	3 (12.0%)	106 (11.3%)	8 (8.9%)	59 (14.6%)
- MTX dose (mg/week)	10.0 (10.0–15.0)	15.0 (10.0–20.0)	15.0 (12.5–15.0)	13.8 (12.0–20.0)
Concomitant GCs	4 (16.0%)	123 (13.1%)	13 (14.4%)	65 (16.1%)
- Prednisone dose (mg/day)	3.8 (2.5–7.5)	5.0 (5.0–10.0)	5.0 (5.0–5.0)	5.0 (5.0–10.0)
Concomitant NSAIDs	12/24 (50.0%)	541/931 (58.1%)	57 (63.3%)	260/402 (64.7%)
ASDAS	4.5 (3.8–4.9)	4.0 (3.4–4.5)	4.3 (3.7–4.8)	4.2 (3.8–4.8)
BASDAI	7.3 (6.6–7.7)	6.2 (5.0–7.5)	7.0 (5.7–8.0)	6.7 (5.5–7.9)
SJC (44 joints)[c]	0.0 (0.0–1.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–1.0)
CRP (mg/l) [d]	17.8 (9.9–37.3)	18.0 (11.0–28.3)	20.4 (12.1–38.0)	21.0 (12.2–37.7)
ESR (mm/h)[e]	32.0 (20.0–57.0)	28.0 (16.0–38.0)	30.0 (14.0–47.0)	30.0 (18.0–46.0)
BASFI[f]	7.0 (5.2–7.8)	5.0 (3.3–6.6)	6.3 (4.6–8.1)	6.4 (4.7–7.7)
MDGA (0–100) [g]	65.0 (56.0–75.0)	65.0 (50.0–77.0)	70.0 (52.0–80.0)	70.0 (55.0–80.0)
HAQ-DI (0–3)	1.5 (1.3–1.8)	1.0 (0.8–1.4)	1.4 (0.9–1.8)	1.3 (1.0–1.7)
EQ-5D (-0.59–1)	0.1 (0.0–0.2)	0.2 (0.1–0.7)	0.1 (0.0–0.3)	0.1 (0.1–0.6)
Sacroiliitis grading				
Pre-radiographic stage	1 (4.0%)	44/923 (4.8%)	4/85 (4.7%)	19/397 (4.8%)
Stage I	0 (0.0%)	24/923 (2.6%)	2/85 (2.4%)	3/397 (0.8%)
Stage II	10 (40.0%)	360/923 (39.0%)	35/85 (41.2%)	127/397 (32.0%)
Stage III	1 (4.0%)	118/923 (12.8%)	7/85 (8.2%)	41/397 (10.3%)
Stage IV	5 (20.0%)	159/923 (17.2%)	14/85 (16.5%)	84/397 (21.2%)
Stage V	8 (32.0%)	218/923 (23.6%)	23/85 (27.1%)	123/397 (31.0%)

BMI body mass index; csDMARDs conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *GCs* glucocorticoids, NSAIDs nonsteroidal anti-inflammatory drugs; *ASDAS* ankylosing spondylitis disease activity score; BASDAI Bath ankylosing spondylitis disease index; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *SDAI* Simplified Disease Activity Index; *BASFI* Bath Ankylosing Spondylitis Functional Index; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented; if the denominator is smaller than the number of patients in given cohorts, n/total (%) are presented.

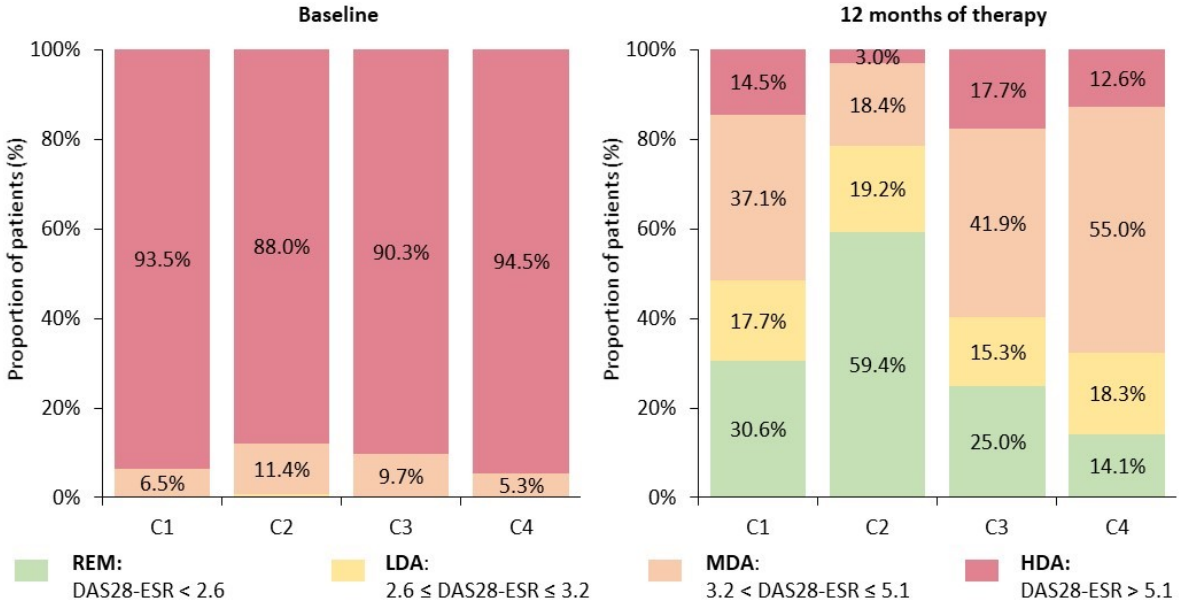
[a] *n*=24 (C1), n=911 (C2), *n*=87 (C3), *n*=396 (C4)
[b] *n*=25 (C1), *n*=921 (C2), *n*=86 (C3), *n*=390 (C4)
[c] *n*=24 (C1), *n*=935 (C2), *n*=89 (C3), *n*=402 (C4)
[d] *n*=24 (C1), *n*=923 (C2), *n*=90 (C3), *n*=400 (C4)
[e] *n*=23 (C1), *n*=926 (C2), *n*=87 (C3), *n*=391 (C4)
[f] *n*=25 (C1), *n*=923 (C2), *n*=89 (C3), *n*=402 (C4)
[g] *n*=21 (C1), *n*=920 (C2), *n*=88 (C3), *n*=393 (C4)

The median age at the first bDMARD/tsDMARD initiation was between 38 years (C2) and 45 years (C3 cohort). Females represented from 25.3% (C2 cohort) to 52.0% (C1 cohort) patients. Patients from all studied cohorts had high baseline disease activity according to ASDAS score with median 4.5 (3.8–4.9) in C1, 4.0 (3.4–4.5) in C2, 4.3 (3.7–4.8) in C3 and 6.3

4.2 (3.8–4.8) in C4. Patients from cohorts C3 and C4 significantly differed only in the number of previous csDMARDs (p=0.047), year of bDMARD administration (C3 in later years) and presence of biosimilars (35.9% in C3 vs 22.3% in C4). Cohorts C1 and C2 significantly differed in gender (52.0% vs 25.3% females), age at diagnosis (median 36 vs 31), joint involvement (peripheral more in C1 compared to C2), presence of comorbidities (72.0% vs 43.4%) and in almost all parameters related to baseline disease activity and quality of life.

7.1.2 Disease activity after 12 months in C1–C4

Comparison of disease activity according to the DAS28-ESR/DAPSA/ASDAS score after one year of treatment in cohorts C1–C4 within RA, PsA and axSpA diagnoses is illustrated in **Figure 24**, **Figure 25** and **Figure 26**.

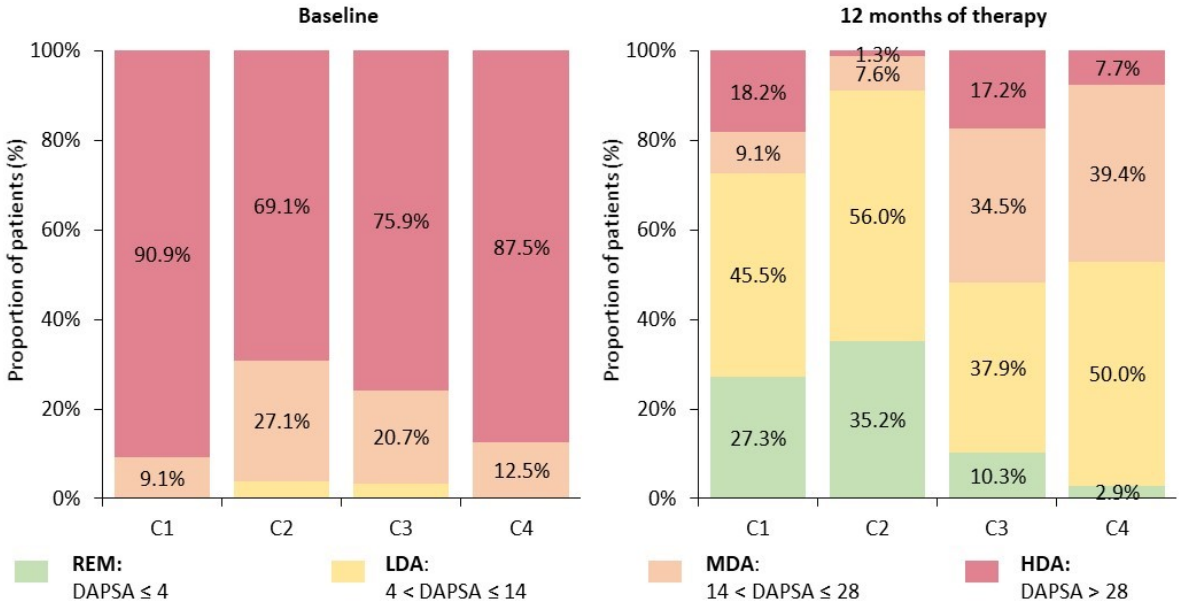


Month	DAS28-ESR	C1 (*n*=62)	C2 (*n*=598)	C3 (*n*=124)	C4 (*n*=491)
0	Median (IQR)	6.4 (5.7–7.0)	5.9 (5.3–6.5)	6.2 (5.6–6.8)	6.3 (5.8–6.8)
12	REM+LDA	30 (48.4%)	470 (78.6%)	50 (40.3%)	159 (32.4%)
	Median (IQR)	3.2 (2.4–4.3)	2.4 (1.7–3.1)	3.7 (2.6–4.7)	3.7 (3.0–4.4)

Figure 24 *Disease activity of RA patients according to DAS28-ESR at baseline and after one year of treatment; REM remission; LDA low disease activity; MDA medium disease activity; HDA high disease activity; IQR interquartile range*

In **RA** diagnosis, we could see the best treatment results after 12 months in the group C2 with almost 79% of patients with REM/LDA compared to 48% of patients in group C1 (p<0.001), 40% of patients in group C3 (p<0.001) and 32% in group C4 (p<0.001). Although there was no statistically significant difference in the proportion of patients with REM/LDA

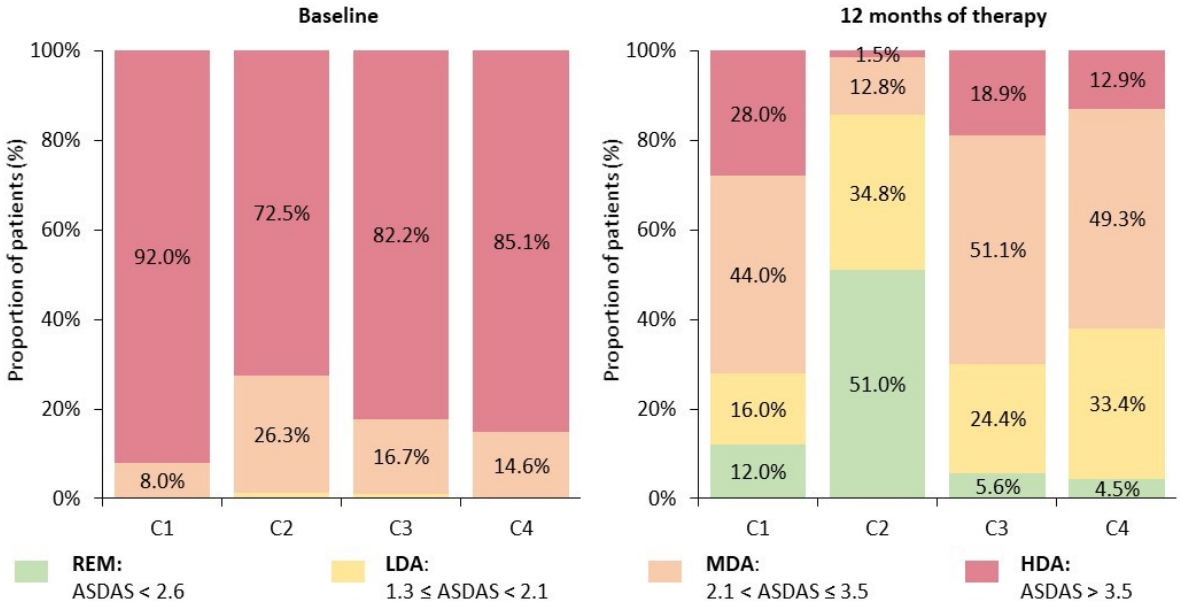
between groups C3 (following T2T strategy) and C4 (not following T2T strategy) after 12 months (p=0.095), we could observe slightly better results in the group C3 (40% vs 32% with REM/LDA). We observed the lowest median value of DAS28-ESR in group C2, and it falls within the level of remission. The median value of DAS28-ESR in group C1 corresponded to the upper bound of low disease activity. Median DAS28-ESR values in groups C3 and C4 were within the range of medium disease activity.



Month	DAPSA	C1 (n=11)	C2 (n=395)	C3 (n=29)	C4 (n=104)
0	Median (IQR)	48.3 (34.4–69.9)	34.7 (25.6–43.1)	33.4 (28.6–49.1)	43.2 (36.8–51.7)
12	REM+LDA	8 (72.7%)	360 (91.1%)	14 (48.3%)	55 (52.9%)
	Median (IQR)	10.4 (0.8–27.1)	5.7 (2.6–9.1)	15.0 (5.7–18.7)	13.6 (9.6–19.1)

Figure 25 *Disease activity of PsA patients according to DAPSA at baseline and after one year of treatment; REM remission; LDA low disease activity; MDA medium disease activity; HDA high disease activity; IQR interquartile range*

In **PsA** diagnosis, we could see the best treatment results after 12 months in the group C2 with 91% of patients with REM/LDA compared to 73% of patients in group C1 (p=0.039), 48% of patients in group C3 (p<0.001) and 53% in group C4 (p<0.001). The proportion of patients with REM/LDA was very similar in groups C3 (following T2T strategy) and C4 (not following T2T strategy) after 12 months, with slightly better results in C4 (but not statistically significant). We observed the lowest median value of DAPSA in group C2, and it fell within the level of low disease activity. The median value of DAPSA in group C1 corresponded to low disease activity as well. The median DAPSA value in group C3 fell in the medium disease activity (close to the lower limit), while the median DAPSA value in C4 belonged to the category of low disease activity (close to the upper boundary).



Month	ASDAS	C1 (*n*=25)	C2 (*n*=938)	C3 (*n*=90)	C4 (*n*=404)
0	Median (IQR)	4.5 (3.8–4.9)	4.0 (3.4–4.5)	4.3 (3.7–4.8)	4.2 (3.8–4.8)
12	REM+LDA	7 (28.0%)	804 (85.7%)	27 (30.0%)	153 (37.9%)
	Median (IQR)	2.7 (1.6–3.5)	1.3 (0.9–1.8)	2.5 (2.0–3.2)	2.3 (1.8–3.0)

Figure 26 *Disease activity of axSpA patients according to ASDAS at baseline and after one year of treatment; REM remission; LDA low disease activity; MDA medium disease activity; HDA high disease activity; IQR interquartile range*

In **axSpA** diagnosis, we could see the best treatment results after 12 months in the group C2 (same as in RA and PsA) with almost 86% patients with REM/LDA compared to 28% patients in group C1 (p<0.001), 30% patients in group C3 (p<0.001) and 38% in group C4 (p<0.001). Although there was no statistically significant difference in the proportion of patients with REM/LDA between groups C3 (following T2T strategy) and C4 (not following T2T strategy) after 12 months (p=0.161), we could observe slightly better results in the group C4 (37.9% vs 30.0% with REM/LDA). We observed the lowest median value of ASDAS in group C2, and it fell within the level of low disease activity (low bound). The median value of ASDAS in groups C1, C3 and C4 corresponded to medium disease activity.

7.1.3 Comparison of cohorts C3 and C4 at 6-month and 12-month visit

For **RA** diagnosis, the comparison of disease activity, quality of life and concomitant therapy between C3 and C4 cohorts are presented in **Table 6**. At the 6-month visit, patients from groups C3 and C4 differed in all parameters related to disease activity and quality of life. We observed lower disease activity and better quality of life in C4. Patients from C3 and C4

did not significantly differ in concomitant therapy, but numerically more changes in dosage of GCs and MTX were observed in the C3 cohort within the period M6–M12. At the 12-month visit, patients from both groups did not significantly differ in most of the parameters related to disease activity; they only differed in PtGA (p=0.044) and EQ-5D (p=0.017).

Table 6 *Comparison of parameters related to disease activity, quality of life and concomitant therapy between C3 and C4 cohort at the 6-month and 12-month visit within RA diagnosis*

	6 months			**12 months**		
	C3 (*n*=124)	C4 (*n*=491)	P	C3 (*n*=124)	C4 (*n*=491)	P
DAS28-ESR	5.4 (4.6–6.3)	4.0 (3.5–4.5)	<**0.001**	3.7 (2.6–4.7)	3.7 (3.0–4.4)	0.710
TJC (/28)	9.0 (4.0–14.0)	3.0 (2.0–5.0)	<**0.001**	3.0 (1.0–7.0)	2.0 (1.0–5.0)	0.490
SJC (/28)	6.0 (2.0–9.5)	2.0 (1.0–4.0)	<**0.001**	2.0 (0.0–4.0)	2.0 (0.0–3.0)	0.498
ESR (mm/h)	28.0 (16.5–46.5)	22.0 (13.0–33.0)	<**0.001**	16.5 (6.5–32.0)	19.0 (11.0–30.5)	0.052
CRP (mg/l)	15.0 (7.9–28.9)	5.7 (2.5–13.7)	<**0.001**	4.7 (1.6–17.0)	5.0 (2.3–11.3)	0.766
SDAI	30.2 (19.7–39.5)	13.9 (10.7–18.3)	<**0.001**	13.8 (8.0–20.9)	11.3 (7.7–17.4)	0.093
PtGA	61.0 (50.0–75.0)	40.0 (26.0–50.0)	<**0.001**	36.0 (25.0–60.0)	33.0 (20.0–50.0)	**0.044**
MDGA	58.0 (40.0–70.0)	30.0 (20.0–40.0)	<**0.001**	25.0 (15.0–45.0)	25.0 (15.0–40.0)	0.812
HAQ-DI	1.5 (1.1–1.9)	1.3 (0.9–1.6)	<**0.001**	1.3 (0.9–1.9)	1.3 (0.9–1.6)	0.140
EQ-5D	0.2 (0.1–0.7)	0.7 (0.5–0.7)	<**0.001**	0.6 (0.1–0.7)	0.7 (0.5–0.8)	**0.017**
Concomitant csDMARDs	98 (79.0%)	414 (84.3%)	0.159	94 (75.8%)	407 (82.9%)	0.070
Concomitant MTX	79 (63.7%)	341 (69.5%)	0.220	77 (62.1%)	332 (67.6%)	0.245
Concomitant GCs	95 (76.6%)	374 (76.2%)	0.918	92 (74.2%)	370 (75.4%)	0.789

DAS28-ESR 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *SDAI* Simplified Disease Activity Index; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life*; csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *GCs* glucocorticoids
Continuous variables are described through the median (interquartile range); categorical variables are characterised by n (%).

Regarding the magnitude of changes across the two visits, patients from C3 significantly improved in all parameters related to disease activity and quality of life (see **Table 7**). Patients from C4 did not statistically significantly improve in CRP and HAQ-DI. In the comparison of the size of changes between the two groups, patients from C3 showed better results (i.e., more significant improvements) in all tested parameters (see **Table 7**).

Table 7 *Comparison of differences in parameters from month 6 to 12 between cohort C3 and C4 within RA diagnosis*

	C3 (*n*=124)	p*	C4 (*n*=491)	p*	p†
DAS28-ESR	-1.60 (-2.81; -0.49)	<**0.001**	-0.35 (-1.00; 0.28)	<**0.001**	<**0.001**
TJC (28 joints)	-5.00 (-10.00; -1.00)	<**0.001**	-1.00 (-2.00; 1.00)	<**0.001**	<**0.001**
SJC (28 joints)	-3.00 (-7.00; 0.00)	<**0.001**	0.00 (-1.00; 0.00)	<**0.001**	<**0.001**
ESR (mm/h)	-9.50 (-22.00; 0.00)	<**0.001**	-1.00 (-10.00; 6.00)	**0.015**	<**0.001**

CRP (mg/l)	-7.31 (-16.15; 1.39)	<**0.001**	-0.20 (-3.50; 3.00)	0.052	<**0.001**
SDAI	-15.34 (-25.13; -4.85)	<**0.001**	-2.23 (-5.83; 1.93)	<**0.001**	<**0.001**
PTGA	-16.00 (-41.50; 0.00)	<**0.001**	-5.00 (-15.00; 7.00)	<**0.001**	<**0.001**
MDGA	-26.00 (-45.00; -3.50)	<**0.001**	-3.00 (-15.00; 6.00)	<**0.001**	<**0.001**
HAQ-DI	-0.24 (-0.38; 0.00)	<**0.001**	0.00 (-0.25; 0.13)	0.059	<**0.001**
EQ-5D	0.04 (0.00; 0.53)	<**0.001**	0.00 (-0.05; 0.07)	**0.032**	<**0.001**

Medians of differences between 6-month and 12-month visits with interquartile ranges are presented.
* We were testing the hypothesis that the differences are equal to zero through Wilcoxon paired test.
† We were testing the hypothesis of equality of medians of differences between groups C3 and C4 (Mann-Whitney test).

For **PsA** diagnosis, the comparison of disease activity, quality of life and concomitant therapy between C3 and C4 cohorts are presented in **Table 8**. At the 6-month visit, patients from groups C3 and C4 differed in all tested parameters related to disease activity. We observed statistically significantly lower disease activity according to DAS28-ESR, DAPSA, TJC and SJC in C4. Further, patients from C3 and C4 significantly differed in the general assessment of disease activity both by patient and physician. Cohorts C3 and C4 also differed in the frequency of csDMARDs in concomitant therapy (more frequent in C4). At the 12-month visit, patients from both groups did not significantly differ in any parameters related to disease activity, quality of life and concomitant therapy.

In terms of the magnitude of changes across the two visits, PsA patients from C3 significantly improved in most of the parameters related to disease activity and quality of life (see **Table 9**). They only did not statistically significantly improve in CRP, ESR and EQ-5D. Similarly, patients from C4 did not significantly improve in CRP and ESR but improved in the rest of the parameters. When comparing the size of changes between the two groups, patients from C3 showed better results (i.e., more significant improvements) in most parameters related to disease activity (see **Table 9**). A statistically significant difference was not found between the two groups in CRP, ESR, PtGA, HAQ, and EQ-5D. However, patients from C3 showed numerically better improvements within the studied period.

Table 8 *Comparison of parameters related to disease activity, quality of life and concomitant therapy between C3 and C4 cohort at the 6-month and 12-month visit within PsA diagnosis*

	6 months			**12 months**		
	C3 (*n*=29)	C4 (*n*=104)	P	C3 (*n*=29)	C4 (*n*=104)	P
DAS28-ESR	4.6 (3.6–5.7)	3.9 (3.3–4.5)	**0.005**	2.8 (1.9–4.0)	3.3 (2.6–3.9)	0.293
DAPSA	24.3 (19.8–37.1)	18.3 (15.7–23.9)	<**0.001**	15.0 (5.7–18.7)	13.6 (9.6–19.1)	0.657
TJC (/68)	6.0 (3.0–8.0)	4.0 (2.0–6.0)	**0.005**	0.0 (0.0–4.0)	2.0 (0.5–4.0)	0.141
SJC (/66)	3.0 (1.0–6.0)	2.0 (0.0–4.0)	**0.010**	0.0 (0.0–2.0)	1.0 (0.0–2.0)	0.198
ESR (mm/h)	19.0 (9.0–30.0)	11.0 (7.0–25.0)	0.112	13.0 (5.0–20.0)	12.0 (6.0–18.0)	0.684
CRP (mg/l)	7.0 (2.0–19.0)	3.8 (1.9–8.5)	0.110	4.1 (1.0–13.5)	4.4 (1.9–7.0)	0.779

PtGA	59.0 (45.0–75.0)	50.0 (37.5–65.0)	**0.034**	40.0 (20.0–50.0)	40.0 (25.0–51.5)	0.967
MDGA	55.0 (48.0–70.0)	28.0 (20.0–41.0)	**<0.001**	20.0 (12.0–45.0)	20.5 (15.0–35.0)	0.735
HAQ-DI	1.4 (0.9–1.8)	1.4 (0.9–1.8)	0.607	1.0 (0.4–1.5)	1.1 (0.9–1.5)	0.195
EQ-5D	0.6 (0.1–0.7)	0.6 (0.2–0.7)	0.181	0.7 (0.1–0.7)	0.6 (0.5–0.7)	0.989
Concomitant csDMARDs	17 (58.6%)	82 (78.8%)	**0.027**	18 (62.1%)	82 (78.8%)	0.064
Concomitant MTX	12 (41.4%)	52 (50.0%)	0.411	10 (34.5%)	51 (49.0%)	0.164
Concomitant GCs	8 (27.6%)	44 (42.3%)	0.151	9 (31.0%)	44 (42.3%)	0.273

DAS28-ESR 28-joint disease activity score with ESR; DAPSA Disease Activity index for Psoriatic Arthritis; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *SDAI* Simplified Disease Activity Index; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life*; csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *GCs* glucocorticoids
Continuous variables are described through the median (interquartile range); categorical variables are characterised by n (%).

Table 9 *Comparison of differences in parameters from month 6 to 12 between cohort C3 and C4 within PsA diagnosis*

	C3 (*n*=29)	p*	C4 (*n*=104)	p*	p†
DAS28-ESR	**-1.52** (-2.71; -0.38)	**<0.001**	**-0.58** (-1.33; 0.18)	**<0.001**	**0.004**
DAPSA	**-9.62** (-20.71; -2.54)	**<0.001**	**-5.57** (-9.92; -0.86)	**<0.001**	**0.023**
TJC (68 joints)	**-3.00** (-6.00; -2.00)	**<0.001**	**-1.00** (-3.00; 1.00)	**0.002**	**<0.001**
SJC (66 joints)	**-3.00** (-4.00; 0.00)	**0.001**	**0.00** (-2.00; 0.00)	**<0.001**	**0.001**
ESR (mm/h)	-2.00 (-19.00; 2.00)	0.057	0.00 (-4.00; 4.00)	0.314	0.200
CRP (mg/l)	-0.49 (-14.00; 2.91)	0.304	0.00 (-2.00; 1.61)	0.647	0.423
PtGA	**-15.0** (-35.0; 5.0)	**0.005**	**-10.00** (-20.0; 0.0)	**0.000**	0.316
MDGA	**-37.0** (-45.0; -15.0)	**<0.001**	**-2.50** (-12.5; 2.0)	**<0.001**	**<0.001**
HAQ-DI	**-0.13** (-0.38; 0.00)	**0.004**	**0.00** (-0.38; 0.13)	**0.002**	0.188
EQ-5D	0.00 (0.00; 0.37)	0.170	**0.00** (0.00; 0.14)	**0.018**	0.738

Medians of differences between 6-month and 12-month visits with interquartile ranges are presented.
* We were testing the hypothesis that the differences are equal to zero through Wilcoxon paired test.
† We were testing the hypothesis of equality of medians of differences between groups C3 and C4 (Mann-Whitney test).

For **axSpA** diagnosis, the comparison of disease activity, quality of life and concomitant therapy between C3 and C4 cohorts are presented in **Table 10**. At the 6-month visit, patients from groups C3 and C4 differed in all tested parameters related to disease activity and quality of life (**Table 10**). We observed lower disease activity and better quality of life in C4. Patients from C3 and C4 did not significantly differ in concomitant therapy, but numerically more changes in dosage of glucocorticoids and methotrexate were observed in the C3 cohort compared to the C4 cohort within the period M6–M12. At the 12-month visit, patients from both groups did not significantly differ in most of the parameters related to disease activity; they only differed in PTGA (p=0.044) and EQ-5D (p=0.017).

Table 10 *Comparison of parameters related to disease activity, quality of life and concomitant therapy between C3 and C4 cohort at the 6-month and 12-month visit within axSpA diagnosis*

	6 months			12 months		
	C3 (*n*=90)	C4 (*n*=404)	P	C3 (*n*=90)	C4 (*n*=404)	P
ASDAS	3.5 (3.0–4.2)	2.6 (2.3–3.1)	<**0.001**	2.5 (2.0–3.2)	2.3 (1.8–3.0)	0.070
BASDAI	5.8 (4.5–6.6)	3.9 (2.9–5.2)	<**0.001**	3.6 (2.2–5.1)	3.1 (2.0–4.7)	0.113
SJC (/44)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	<**0.001**	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.910
ESR (mm/h)	22.0 (10.0–40.0)	12.0 (6.0–22.0)	<**0.001**	10.5 (5.0–26.0)	12.0 (5.0–23.0)	0.820
CRP (mg/l)	15.0 (5.4–32.9)	7.4 (4.0–13.4)	<**0.001**	6.0 (2.9–15.0)	6.0 (3.0–13.0)	0.786
BASFI	5.4 (3.7–7.0)	4.0 (2.5–5.7)	<**0.001**	3.8 (2.3–5.8)	3.5 (1.9–5.3)	0.131
MDGA	43.5 (25.0–60.5)	25.0 (12.0–35.0)	<**0.001**	26.5 (15.0–40.0)	20.0 (10.0–30.0)	**0.002**
HAQ-DI	1.1 (0.8–1.6)	1.0 (0.6–1.4)	<**0.001**	1.0 (0.6–1.4)	0.9 (0.5–1.3)	0.237
EQ-5D	0.2 (0.1–0.7)	0.7 (0.5–0.8)	<**0.001**	0.6 (0.6–0.7)	0.7 (0.5–0.8)	0.204
Concomitant csDMARDs	23 (26.1%)	138 (34.3%)	0.139	21 (24.1%)	131 (32.8%)	0.116
Concomitant NSAIDs	38 (43.2%)	123 (30.6%)	**0.023**	18 (20.7%)	107 (26.8%)	0.241
Concomitant GCs	11 (12.5%)	63 (15.7%)	0.452	11 (12.6%)	60 (15.0%)	0.578

ASDAS ankylosing spondylitis disease activity score; BASDAI Bath ankylosing spondylitis disease index; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *BASFI* Bath Ankylosing Spondylitis Functional Index; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life*; csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; NSAIDs nonsteroidal anti-inflammatory drugs; *GCs* glucocorticoids
Continuous variables are described through the median (interquartile range); categorical variables are characterised by n (%).

Regarding the magnitude of changes across the two visits, axSpA patients from both C3 and C4 significantly improved in all parameters related to disease activity and quality of life (see **Table 11**). Comparing the size of changes between the two groups, patients from C3 showed better results (more significant improvements) in all tested parameters (see **Table 11**).

Table 11 *Comparison of differences in parameters from month 6 to 12 between cohort C3 and C4 within axSpA diagnosis*

	C3 (*n*=124)	p*	C4 (*n*=491)	p*	p†
ASDAS	-0.79 (-1.56; -0.27)	<**0.001**	-0.38 (-0.76; 0.08)	<**0.001**	<**0.001**
BASDAI	-1.45 (-2.95; -0.28)	<**0.001**	-0.50 (-1.50; 0.25)	<**0.001**	<**0.001**
BASFI	-0.72 (-2.35; 0.05)	<**0.001**	-0.29 (-1.07; 0.34)	<**0.001**	**0.002**
CRP (mg/l)	-5.33 (-21.01; 0.50)	<**0.001**	-0.90 (-3.80; 2.30)	**0.006**	<**0.001**
MDGA (0–100)	-15.00 (-35.00; 5.00))	<**0.001**	-2.00 (-10.00; 5.00)	<**0.001**	<**0.001**
HAQ-DI (0–3)	-0.13 (-0.50; 0.00)	<**0.001**	0.00 (-0.25; 0.13)	**0.021**	<**0.001**
EQ-5D	0.10 (0.00; 0.53)	<**0.001**	0.00 (-0.04; 0.07)	**0.029**	<**0.001**

ASDAS ankylosing spondylitis disease activity score; BASDAI Bath ankylosing spondylitis disease index; *BASFI* Bath Ankylosing Spondylitis Functional Index; *CRP* C-reactive protein; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life
Medians of differences between 6-month and 12-month visits with interquartile ranges are presented.
* We were testing the hypothesis that the differences are equal to zero through Wilcoxon paired test.
† We were testing the hypothesis of equality of medians of differences between groups C3 and C4 (Mann-Whitney test).

7.1.4 Odds for treatment target in C3 vs C4 at the 12-month visit

We employed propensity score matching to reduce selection bias by adjusting for potential confounding factors at the 6-month visit. We show a description of patients' characteristics at the 6-month visit after using propensity score matching in **Table 12** (RA), **Table 13** (PsA) and **Table 14** (axSpA). Density plots of propensity scores before and after matching are displayed in **Figure 27** (RA), **Figure 28** (PsA) and **Figure 29** (axSpA).

Table 12 *Description of RA patients from C3 and C4 cohort at 6-month visit after applying propensity score matching*

	C3 (*n*=75)	C4 (*n*=75)	P-value
Female*	60 (80.0%)	61 (81.3%)	0.836
Age at diagnosis, years	45.0 (36.0–53.0)	45.0 (37.0–53.0)	0.678
Age at start of 1st line, years*	52.0 (45.0–61.0)	55.0 (44.0–61.0)	0.811
Disease duration, years*	5.0 (2.4–12.7)	5.8 (3.0–13.1)	0.937
RF positive*	60 (80.0%)	54 (72.0%)	0.251
Presence of comorbidities*	54 (72.0%)	55 (73.3%)	0.855
Currently smoking*	21 (28.0%)	21 (28.0%)	1.000
Number of previous csDMARDs*			
0	2 (2.7%)	0 (0.0%)	
1	16 (21.3%)	15 (20.0%)	
2	20 (26.7%)	28 (37.3%)	0.230
3	17 (22.7%)	20 (26.7%)	
4+	20 (26.7%)	12 (16.0%)	
Glucocorticoids in previous history*	67 (89.3%)	66 (88.0%)	0.797
Concomitant csDMARDs*	61 (81.3%)	63 (84.0%)	0.666
Concomitant GCs*	56 (74.7%)	55 (73.3%)	0.852
DAS28-ESR (0–10)	5.0 (4.2–5.9)	5.0 (4.1–5.7)	0.717
TJC (28 joints) *	8.0 (4.0–12.0)	6.0 (3.0–11.0)	0.677
SJC (28 joints) *	4.0 (2.0–8.0)	4.0 (2.0–7.0)	0.973
ESR (mm/h) *	27.0 (15.0–37.0)	25.0 (12.0–41.0)	0.844
CRP (mg/l) *	15.0 (8.0–22.2)	8.4 (3.5–25.7)	0.090
SDAI (0–86)	25.5 (15.6–34.9)	22.7 (16.1–30.9)	0.531
PtGA (0–100) *	60.0 (40.0–71.0)	50.0 (40.0–71.0)	0.519
MDGA (0–100)	55.0 (35.0–70.0)	45.0 (30.0–60.0)	0.059
HAQ-DI (0–3) *	1.50 (1.12–1.88)	1.50 (1.13–1.88)	0.877
EQ-5D (-0.59–1)	0.23 (0.06–0.69)	0.59 (0.06–0.69)	0.290

IQR interquartile range; *RF* rheumatoid factor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; GCs glucocorticoids; *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *SDAI* Simplified Disease Activity Index; *PTGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life
Continuous variables are described through the median (interquartile range); categorical variables are characterised by *n* (%).
* These parameters were included in the propensity score model.

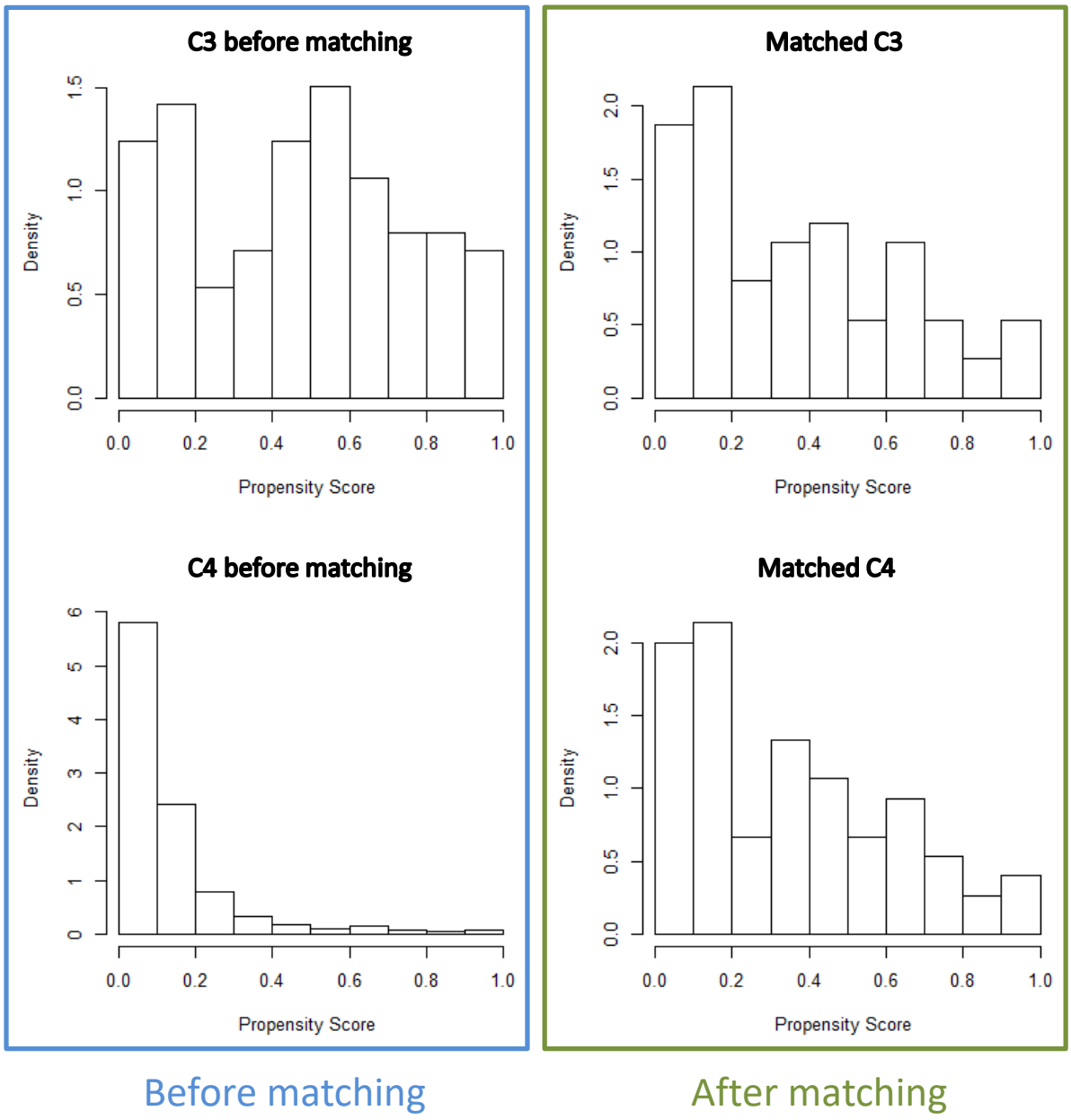


Figure 27 *Propensity score densities of RA cohorts C3 and C4 before and after matching*

Table 13 *Description of PsA patients from C3 and C4 cohort at 6-month visit after applying propensity score matching*

	C3 (*n*=21)	C4 (*n*=35)	P-value
Female*	7 (33.3%)	13 (37.1%)	0.773
Age at diagnosis, years	38.0 (31.0–46.0)	45.0 (31.0–51.0)	0.294
Age at start of 1st line, years*	47.0 (39.0–53.0)	53.0 (39.0–57.0)	0.356
Disease duration, years	1.8 (0.8–10.8)	5.2 (2.3–8.6)	0.134
RF+/ACPA+	4 (19.0%)	6 (17.1%)	1.000
Psoriasis	8 (38.1%)	12 (34.3%)	0.773

Dactylitis	8 (38.1%)	4 (11.4%)	0.152
Enthesitis	8/20 (38.1%)	3 (8.6%)	1.000
Currently smoking	4 (19.0%)	9 (25.7%)	0.747
Presence of comorbidities	16 (76.2%)	26 (74.3%)	0.873
BMI	27.0 (24.8–30.3)	30.7 (28.4–33.0)	**0.006**
HLA-B27 positivity	8/18 (44.4%)	8/27 (29.6%)	0.309
Nail involvement			
No	2 (9.5%)	1/34 (2.9%)	0.599
Mild	13 (61.9%)	18/34 (52.9%)	
Medium	3 (14.3%)	7/34 (20.6%)	
Severe	3 (14.3%)	8/34 (23.5%)	
Previous csDMARDs			
0	0 (0.0%)	0 (0.0%)	
1	6 (28.6%)	14 (40.0%)	0.687
2	8 (38.1%)	11 (31.4%)	
3+	7 (33.3%)	10 (28.6%)	
GCs in previous history*	13 (61.9%)	19 (54.3%)	0.577
Concomitant csDMARDs*	12 (57.1%)	22 (62.9%)	0.780
Concomitant GCs	6 (28.6%)	9 (25.7%)	0.815
DAS28-ESR (0–10)	4.3 (3.4–5.7)	4.1 (3.1–5.0)	0.537
DAPSA*	21.6 (19.4–31.3)	22.1 (17.1–28.5)	0.515
TJC (68 joints)	6.0 (3.0–7.0)	5.0 (3.0–9.0)	0.885
SJC (66 joints)	3.0 (0.0–6.0)	2.0 (0.0–4.0)	0.236
CRP (mg/l)	6.0 (2.6–20.0)	4.0 (1.7–10.2)	0.150
ESR (mm/h)	16.0 (8.0–31.0)	11.0 (6.0–33.0)	0.332
PtGA (0–100)	56.0 (45.0–75.0)	50.0 (41.0–70.0)	0.659
MDGA (0–100)	68.0 (50.0–70.0)	30.0 (23.0–45.0)	<**0.001**
HAQ-DI (0–3)	1.4 (0.8–1.8)	1.4 (1.0–1.8)	0.793
EQ-5D (-0.59–1)	0.6 (0.1–0.7)	0.6 (0.1–0.7)	0.806
PGA of psoriasis			
0–1	10/20 (50.0%)	22 (62.9%)	
2–3	9/20 (45.0%)	13 (37.1%)	0.303
4–5	1/20 (5.0%)	0 (0.0%)	

RF rheumatoid factor; *ACPA* anti-citrullinated protein; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *GCs* glucocorticoids, *DAS28-ESR* 28-joint disease activity score with ESR; DAPSA Disease Activity index for Psoriatic Arthritis; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PGA* Physician global assessment; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented; if the denominator is smaller than the number of patients in given cohorts, n/total (%) are presented.

* These parameters were included in the propensity score model (year of administration not shown here).

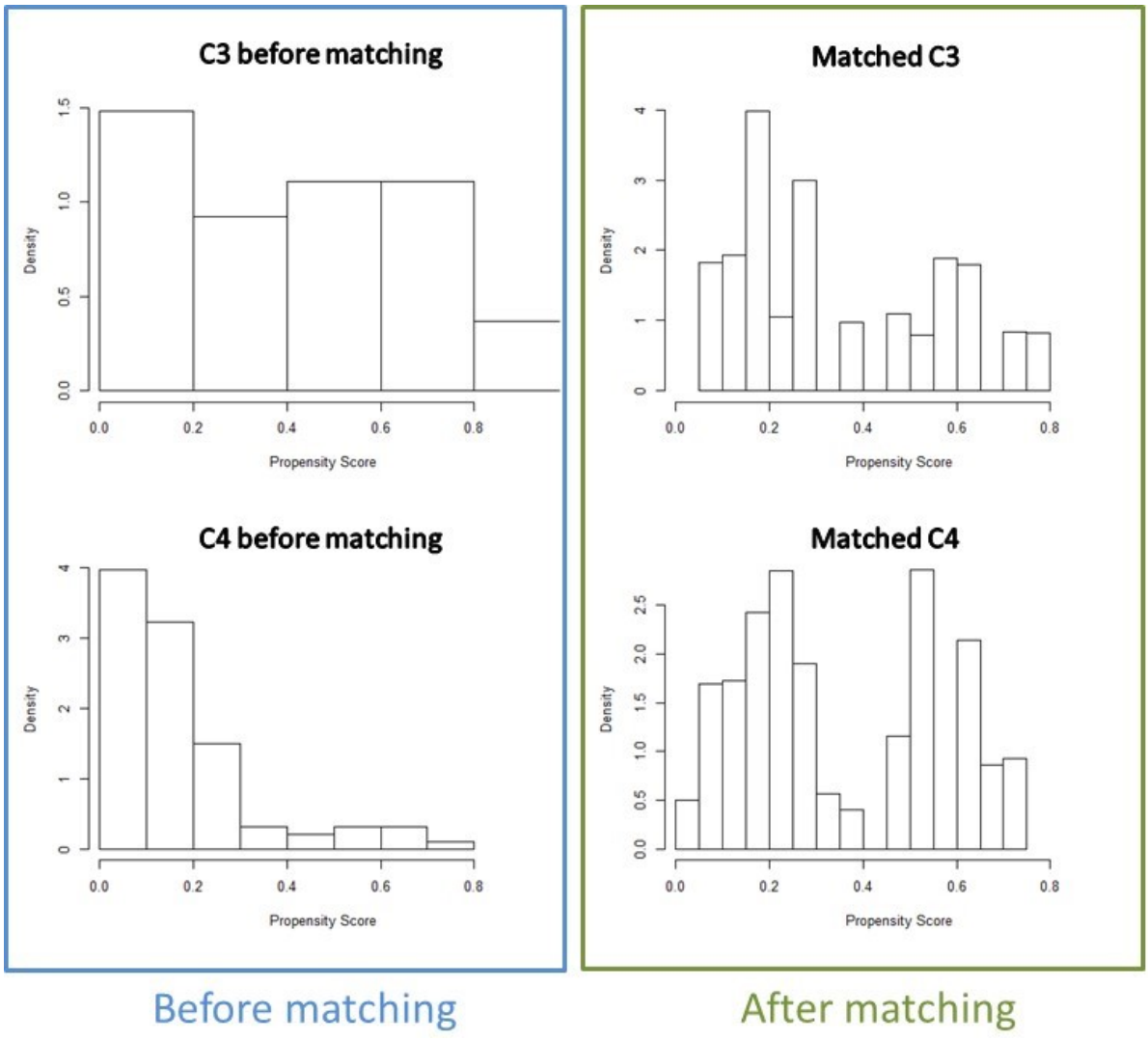


Figure 28 *Propensity score densities of PsA cohorts C3 and C4 before and after matching*

Table 14 *Description of axSpA patients from C3 and C4 cohort at 6-month visit after applying propensity score matching*

	C3 (*n*=60)	C4 (*n*=60)	P value
Female*	22 (36.7%)	24 (40.0%)	0.707
Age at diagnosis, years	35.0 (26.0–45.0)	35.5 (27.5–42.0)	0.823
Age at start of 1st line, years*	45.5 (36.0–51.5)	44.0 (39.0–54.0)	0.480
Disease duration, years	4.4 (0.6–14.3)	6.1 (1.4–12.4)	0.452
Uveitis	16 (26.7%)	11 (18.3%)	0.274
Colitis	3 (5.0%)	5 (8.3%)	0.717
Psoriasis	4 (6.7%)	2 (3.3%)	0.679
Dactylitis	0/59 (0.0%)	2/58 (3.4%)	0.244
Currently smoking*	22 (36.7%)	22 (36.7%)	1.000
Presence of comorbidities*	38 (63.3%)	39 (65.0%)	0.849
BMI	28.3 (25.2–31.3)	28.6 (25.3–32.9)	0.476
HLA-B27 positivity	55 (91.7%)	53 (88.3%)	0.543
Joint involvement			

Axial	21/59 (35.6%)	20 (33.3%)	
Root	13/59 (22.0%)	23 (38.3%)	0.123
Peripheral	25/59 (42.4%)	17 (28.3%)	
Previous csDMARDs*			
0	28 (46.7%)	26 (43.3%)	
1	21 (35.0%)	23 (38.3%)	0.826
2	7 (11.7%)	5 (8.3%)	
3+	4 (6.7%)	6 (10.0%)	
GCs in previous history*	6 (10.0%)	11 (18.3%)	0.705
Concomitant csDMARDs	16 (26.7%)	16 (26.7%)	1.000
Concomitant GCs	6 (10.0%)	11 (18.3%)	0.191
Concomitant NSAIDs*	25 (41.7%)	23 (38.3%)	0.709
ASDAS*	3.2 (2.7–3.9)	3.2 (2.6–3.7)	0.749
BASDAI	5.6 (4.0–6.4)	4.6 (3.6–6.0)	0.154
SJC (44 joints)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.225
CRP (mg/l)	9.8 (3.4–25.2)	11.6 (6.0–21.0)	0.552
ESR (mm/h)	16.0 (8.0–35.0)	20.0 (8.0–35.0)	0.598
BASFI	4.7 (3.2–6.3)	4.9 (4.0–6.9)	0.423
MDGA (0–100) *	35.0 (23.0–60.0)	38.5 (20.0–50.0)	0.939
HAQ-DI (0–3)*	1.1 (0.8–1.6)	1.1 (0.8–1.6)	0.964
EQ-5D (-0.59–1)	0.5 (0.1–0.7)	0.7 (0.1–0.7)	0.200
Sacroiliitis grading			
Pre-radiographic stage	3/57 (5.3%)	2 (3.3%)	
Stage I	2/57 (3.5%)	0 (0.0%)	
Stage II	19/57 (33.3%)	16 (26.7%)	0.589
Stage III	4/57 (7.0%)	7 (11.7%)	
Stage IV	12/57 (21.1%)	13 (21.7%)	
Stage V	17/57 (29.8%)	22 (36.7%)	

BMI body mass index; csDMARDs conventional synthetic disease-modifying anti-rheumatic drugs; *GCs* glucocorticoids, NSAIDs nonsteroidal anti-inflammatory drugs; *ASDAS* ankylosing spondylitis disease activity score; BASDAI Bath ankylosing spondylitis disease index; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *BASFI* Bath Ankylosing Spondylitis Functional Index; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented; if the denominator is smaller than the number of patients in given cohorts, n/total (%) are presented.

* These parameters were included in the propensity score model (presence o biosimilars and year of administration not shown here).

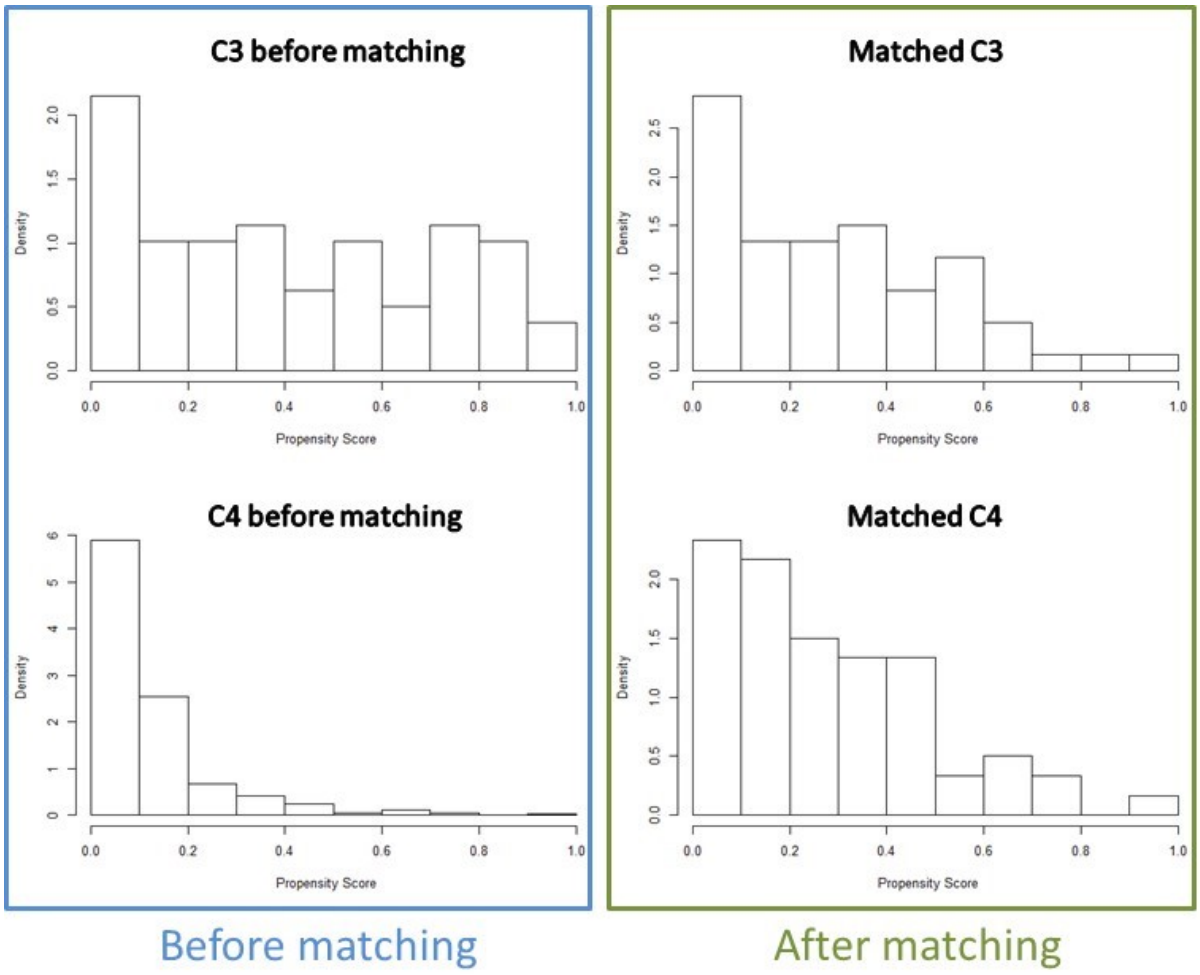


Figure 29 *Propensity score densities of axSpA cohorts C3 and C4 before and after matching*

In **RA** diagnosis, both groups included 75 patients after the matching. The set of covariates selected for the propensity score model included gender, age at the start of 1st line therapy, disease duration, number of previous csDMARDs, glucocorticoids in previous therapy, swollen joint count, tender joint count, PTGA, ESR, CRP, HAQ, RF positivity, presence of comorbidities, smoking, csDMARDs and GCs in concomitant therapy. Patients did not differ anymore in parameters related to disease activity and quality of life (see **Table 12**). The most frequently administered drugs at the 12-mont visit were tocilizumab (27%), certolizumab (17%), abatacept (15%) and etanercept (12%) in C3. Patients from C4 were most frequently treated with adalimumab (35%), etanercept (21%), golimumab (16%) and certolizumab (13%). To compare odds for reaching the treatment target at the 12-month visit in patients following T2T principle at 6-month visit (C3) vs patients staying on the first treatment (C4), we employed a logistic regression model with outcome DAS28-ESR ≤ 3.2. Patients following the T2T principle (C3) showed 2.8 (CI 1.4–5.8) times higher odds for reaching at least LDA at the 12-month visit (p=0.005) compared to patients not following the T2T principle (C4), see **Table**

15. In group C3, 41% of patients achieved at least REM/LDA at the 12-month visit, while in group C4, it was 20%.

Table 15 *Results of univariate logistic regression models with outcome DAS28-ESR ≤ 3.2 (RA), DAPSA ≤ 14 (PsA) and ASDAS < 2.1 (for axSpA), with the covariate C3 vs C4*

Diagnosis	Covariate	OR (95% CI)	P-value	*n*
RA	C3 (vs C4)	**2.82** (1.36–5.84)	**0.005**	150
PsA	C3 (vs C4)	1.04 (0.35–3.07)	0.945	56
axSpA	C3 (vs C4)	1.62 (0.73–3.56)	0.234	120

OR odds ratio; CI confidence interval

In PsA diagnosis, a 1:2 matching ratio was employed, resulting in only 21 patients in C3 and 35 patients in the C4 cohort. The set of covariates selected for the propensity score model included gender, age at the start of 1st line therapy, glucocorticoids in previous therapy, csDMARDs in concomitant therapy, DAPSA and year of administration. Patients did not differ anymore in parameters related to disease activity (except MDGA) and quality of life (see **Table 13**). C3 and C4 cohorts remained statistically significantly different in BMI after the matching. Both matched cohorts included a small number of patients. Absolute values of standardized mean differences were slightly higher than 0.1 but were under 0.2. The most frequently administered drugs at the 12-mont visit were secukinumab (24%), adalimumab (24%), golimumab (19%) and certolizumab (14%) in C3. Patients from C4 were most frequently treated with adalimumab (46%), secukinumab (26%), golimumab (11%) and etanercept (9%). To compare odds for reaching the treatment target at the 12-month visit in patients following the T2T principle at the 6-month visit (C3) vs patients staying on the first treatment (C4), we employed a logistic regression model with outcome DAPSA ≤ 14. Patients following the T2T principle (C3) showed almost the same odds for reaching at least LDA at the 12-month as patients not following the T2T principle (C4), see **Table 15**. In group C3, 52% of patients achieved at least REM/LDA at the 12-month visit; in group C4, it was 51%.

In **axSpA** diagnosis, both groups included 60 patients after the matching. The set of covariates selected for the propensity score model included gender, age at the start of 1st line therapy, number of previous csDMARDs, GCs in the previous history, NSAIDs in concomitant therapy, ASDAS, HAQ, MDGA, presence of comorbidities, smoking, presence of biosimilars and year of administration. Patients did not differ anymore in disease activity and quality of life (see **Table 14**). They did not significantly differ in the year of administration and drug type either. The most frequently administered drugs at the 12-month visit were adalimumab (30%), etanercept (23%), secukinumab (18%) and golimumab (17%) in C3. Patients from C4 were

most frequently treated with adalimumab (30%), etanercept (23%), golimumab (20%), infliximab (12%) and secukinumab (12%). To compare odds for reaching treatment target at the 12-month visit in patients following T2T principle at 6-month visit (C3) vs patients staying on the first treatment (C4), we employed a logistic regression model with outcome ASDAS < 2.1. Patients following the T2T principle (C3) showed 1.6 (CI 0.7–3.6) times higher odds for reaching at least LDA at the 12-month visit compared to patients not following the T2T principle (C4), but the result was not statistically significant (see **Table 15**). In group C3, 35% of patients achieved at least REM/LDA at the 12-month visit, while in group C4, it was 25%.

7.2 Predictive ability of self-perceived general health at TNFi therapy start

7.2.1 Patients‘ characteristics at baseline

Rheumatoid arthritis

In total, we included 2215 patients with **RA** within the primary dataset and 734 patients within the validation dataset (see **Figure 16**). Further, patients were divided into groups based on their response to SF36 questions (Q 11A and Q 11C; **Figure 19**). Only decisive patients were analyzed. Within the primary dataset, baseline characteristics of patients who answered *yes* (*n*=730) and *no* (*n*=580) to Q11C are shown in **Table 16**, while **Table 17** shows a description of patients responding *yes* (*n*=648) and *no* (*n*=792) to Q11A.

Patients answering *yes* to **Q11C** had statistically significantly longer disease duration (median 7.8 vs 6.1 years), a bigger number of previous csDMARDs, worse quality of life - lower EQ-5D (median 0.1 vs 0.2), higher HAQ (median 1.6 vs 1.5) and lower MDGA (median 60 vs 66) compared to patients answering *no*. The most frequently administered drugs in both groups were adalimumab (42.6% in both), etanercept (*yes*: 25.5 %; *no*: 20.7%) and infliximab (*yes*: 20.1%; *no*: 22.4%). The frequency of biosimilars was similar in both studied groups.

There was a statistically significantly higher percentage of women (83% vs 77%), a higher number of previous csDMARDs, more frequent GCs in previous therapy (93% vs 89%) as well as a higher percentage of csDMARDs (85% vs 80%) and GCs (64% vs 57%) in concomitant therapy in patients answering *yes* to **Q11A** compared to patients answering *no*. Further, patients answering *yes* had statistically significantly higher disease activity according to DAS28 (median 6.3 vs 6.2), higher CRP (median 18.9 vs 15.5) and ESR (median 35 vs 32), worse quality of life – lower EQ-5D (median 0.1 vs 0.2), higher HAQ (1.6 vs 1.5), but lower MDGA (median 60 vs 68). There was also a statistical difference in drugs, with etanercept more frequent in patients answering *yes* and infliximab more frequent in patients answering *no*.

Table 16 *Baseline characteristics of RA patients (primary dataset) answering yes/no to Q11C ('I expect my health to get worse')*

	Yes (*n*=730)	*n*	No (*n*=580)	*n*
Female, *n* (%)	577 (79.0%)	730	468 (80.7%)	580
Age at diagnosis, years	42.0 (33.0–50.0)	725	43.0 (32.0–52.0)	578
Age at start of 1st line, years	52.0 (44.0–60.0)	730	52.5 (42.0–60.0)	580
Disease duration, years	7.8 (3.8–13.4)	725	6.1 (2.9–12.5)	578
RF positive	487 (75.0%)	649	374 (73.2%)	511
ACPA positive	405 (68.9%)	588	341 (72.7%)	469
Previous csDMARDs				
0	3 (0.4%)		3 (0.5%)	
1	107 (14.8%)		137 (23.8%)	
2	142 (19.6%)	724	157 (27.3%)	576
3	146 (20.2%)		118 (20.5%)	
4+	326 (45.0%)		161 (28.0%)	
GCs in previous history	669 (92.1%)	726	526 (91.0%)	578
Concomitant csDMARDs	604 (82.7%)	730	463 (79.8%)	580
Concomitant MTX	465 (63.7%)	730	384 (66.2%)	580
Concomitant GCs	459 (62.9%)	730	342 (59.0%)	580
DAS28-ESR (0–10)	6.3 (5.7–6.8)	727	6.3 (5.6–6.9)	579
TJC (28 joints)	13.0 (10.0–17.0)	727	13.0 (9.0–18.0)	579
SJC (28 joints)	10.0 (8.0–14.0)	727	10.0 (7.0–14.0)	579
ESR (mm/h)	35.0 (22.0–48.0)	721	32.0 (22.0–50.0)	566
CRP (mg/l)	17.4 (8.9–33.0)	726	16.9 (7.1–32.5)	570
SDAI (0–86)	36.5 (30.9–43.2)	362	36.6 (30.9–46.5)	296
PtGA (0–100)	70.0 (60.0–80.0)	727	70.0 (60.0–80.0)	579
MDGA (0–100)	60.0 (50.0–75.0)	365	66.0 (52.0–78.0)	305
HAQ-DI (0–3)	1.6 (1.3–2.0)	728	1.5 (1.0–1.9)	578
EQ-5D (-0.59–1)	0.1 (0.0–0.5)	724	0.2 (0.1–0.7)	575
Year of administration: 2001–2011	455 (62.3%)		317 (54.7%)	
Year of administration: 2012	45 (6.2%)		37 (6.4%)	
Year of administration: 2013	52 (7.1%)	730	47 (8.1%)	580
Year of administration: 2014	50 (6.8%)		50 (8.6%)	
Year of administration: 2015	65 (8.9%)		61 (10.5%)	
Year of administration: 2016–2017	63 (8.6%)		68 (11.7%)	
Adalimumab	311 (42.6%)		247 (42.6%)	
Etanercept	186 (25.5%)		120 (20.7%)	
Infliximab	147 (20.1%)	730	130 (22.4%)	580
Certolizumab	35 (4.8%)		40 (6.9%)	
Golimumab	51 (7.0%)		43 (7.4%)	
Bo ADA/ETA/INF	614 (95.3%)	644	469 (94.4%)	497
Bs ADA/ETA/INF	30 (4.7%)		28 (5.6%)	

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

Table 17 *Baseline characteristics of RA patients (validation dataset) answering yes/no to Q11A ('I seem to get sick a little easier than other people')*

	Yes (*n*=648)	*n*	No (*n*=792)	*n*
Female, *n* (%)	539 (83.2%)	648	612 (77.3%)	792
Age at diagnosis, years	43.0 (33.0–51.0)	646	42.0 (33.0–51.0)	785
Age at start of 1st line, years	52.0 (43.0–60.0)	648	52.0 (43.0–59.0)	792
Disease duration, years	7.3 (3.4–12.8)	646	6.8 (3.2–13.1)	785
RF positive	453 (76.1%)	595	499 (72.4%)	689
ACPA positive	377 (68.8%)	548	438 (70.5%)	621
Previous csDMARDs				
0	3 (0.5%)		3 (0.4%)	
1	90 (14.0%)		170 (21.7%)	
2	123 (19.2%)	641	193 (24.6%)	784
3	126 (19.7%)		174 (22.2%)	
4+	299 (46.6%)		244 (31.1%)	
GCs in previous history	601 (93.0%)	646	701 (89.1%)	787
Concomitant csDMARDs	551 (85.0%)	648	633 (79.9%)	792
Concomitant MTX	415 (64.0%)	648	522 (65.9%)	792
Concomitant GCs	417 (64.4%)	648	451 (56.9%)	792
DAS28-ESR (0–10)	6.3 (5.8–6.8)	648	6.2 (5.6–6.8)	788
TJC (28 joints)	13.0 (10.0–18.0)	648	13.0 (9.0–17.0)	788
SJC (28 joints)	10.0 (8.0–14.0)	648	10.0 (7.0–14.0)	788
ESR (mm/h)	35.0 (22.0–50.0)	644	32.0 (21.0–47.0)	775
CRP (mg/l)	18.9 (9.3–34.0)	643	15.5 (6.7–32.6)	779
SDAI (0–86)	37.1 (30.7–45.0)	348	36.5 (31.1–45.0)	382
PtGA (0–100)	70.0 (60.0–80.0)	648	70.0 (59.0–80.0)	788
MDGA (0–100)	60.0 (50.0–75.0)	352	68.0 (52.0–80.0)	392
HAQ-DI (0–3)	1.6 (1.3–2.0)	645	1.5 (1.0–1.9)	790
EQ-5D (-0.59–1)	0.1 (0.0–0.5)	640	0.2 (0.1–0.7)	787
Year of administration: 2001–2011	383 (59.1%)		452 (57.1%)	
Year of administration: 2012	53 (8.2%)		45 (5.7%)	
Year of administration: 2013	52 (8.0%)	648	54 (6.8%)	792
Year of administration: 2014	36 (5.6%)		67 (8.5%)	
Year of administration: 2015	57 (8.8%)		92 (11.6%)	
Year of administration: 2016–2017	67 (10.3%)		82 (10.4%)	
Adalimumab	278 (42.9%)		348 (43.9%)	
Etanercept	186 (28.7%)		162 (20.5%)	
Infliximab	103 (15.9%)	648	175 (22.1%)	792
Certolizumab	33 (5.1%)		52 (6.6%)	
Golimumab	48 (7.4%)		55 (6.9%)	
Bo ADA/ETA/INF	545 (96.1%)	567	646 (94.3%)	685
Bs ADA/ETA/INF	22 (3.9%)		39 (5.7%)	

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

For the **RA validation dataset**, the baseline description of patients answering *yes* (*n*=231/*n*=216) and *no* (*n*=201/*n*=254) to Q11C / Q11A is presented in **Table 18** and **Table 19**.

Patients answering *yes* to **Q11C** had statistically significantly higher disease activity according to DAS28-ESR (median 6.3 vs 6.0), higher TJC (median 14 vs 13) and higher SJC (median 10 vs 8), higher PtGA (median 75 vs 70) and worse quality of life - lower EQ-5D (median 0.1 vs 0.2), higher HAQ (median 1.5 vs 1.4). The most frequently administered drugs in both groups were adalimumab (*yes*: 47.6%; *no*: 39.3%), etanercept (*yes*: 32.5 %; *no*: 30.3%) and golimumab (*yes*: 8.7%; *no*: 12.9%). The frequency of biosimilars was significantly higher in patients answering *yes* than in patients answering *no* to Q11C (52.4% vs 36.4%).

There was a statistically significantly higher number of previous csDMARDs in patients answering *yes* to **Q11A** compared to patients answering *no*. Further, patients answering *yes* had statistically significantly higher disease activity according to DAS28-ESR (median 6.3 vs 6.0), higher TJC (median 14 vs 13), higher ESR (median 34 vs 30), higher PtGA (median 80 vs 70) and worse quality of life – lower EQ-5D (median 0.1 vs 0.2), higher HAQ (1.6 vs 1.5). The most frequently administered drugs in both groups were adalimumab (*yes*: 47.2%; *no*: 40.6%), etanercept (*yes*: 30.6 %; *no*: 35.0%) and certolizumab (*yes*: 11.1%; *no*: 10.6%). The frequency of biosimilars was significantly higher in patients answering *yes* to Q11C (53.9% vs 31.8%).

Table 18 *Baseline characteristics of RA patients (validation dataset) answering yes/no to Q 11C ('I expect my health to get worse')*

	Yes (*n*=231)	*n*	No (*n*=201)	*n*
Female, *n* (%)	181 (78.4%)	231	163 (81.1%)	201
Age at diagnosis, years	47.0 (35.0–55.0)	231	44.0 (35.0–55.0)	201
Age at start of 1st line, years	55.0 (46.0–64.0)	231	53.0 (43.0–63.0)	201
Disease duration, years	5.7 (2.8–11.8)	231	5.7 (2.0–10.4)	201
RF positive	158 (69.3%)	228	133 (66.8%)	199
ACPA positive	155 (69.5%)	223	137 (68.8%)	199
Previous csDMARDs				
0	6 (2.6%)		2 (1.0%)	
1	55 (23.8%)		61 (30.3%)	
2	84 (36.4%)	231	81 (40.3%)	201
3	51 (22.1%)		42 (20.9%)	
4+	35 (15.2%)		15 (7.5%)	
GCs in previous history	205 (88.7%)	231	186 (92.5%)	201
Concomitant csDMARDs	199 (86.1%)	231	183 (91.0%)	201
Concomitant MTX	172 (74.5%)	231	154 (76.6%)	201
Concomitant GCs	151 (65.4%)	231	133 (66.2%)	201
DAS28-ESR (0–10)	6.3 (5.6–6.9)	231	6.0 (5.3–6.5)	200

TJC (28 joints)	14.0 (10.0–18.0)	231	13.0 (9.0–17.0)	201
SJC (28 joints)	10.0 (7.0–13.0)	231	8.0 (5.0–11.0)	201
ESR (mm/h)	30.0 (19.0–45.0)	225	27.0 (15.0–40.0)	186
CRP (mg/l)	14.7 (6.0–25.0)	230	13.2 (6.0–22.7)	200
SDAI (0–86)	38.3 (31.8–45.7)	230	36.5 (29.4–43.1)	200
PtGA (0–100)	75.0 (65.0–85.0)	231	70.0 (60.0–80.0)	201
MDGA (0–100)	68.0 (50.0–80.0)	231	70.0 (60.0–80.0)	201
HAQ-DI (0–3)	1.5 (1.1–2.0)	231	1.4 (1.0–2.0)	201
EQ-5D (-0.59–1)	0.1 (0.0–0.3)	231	0.2 (0.1–0.7)	201
Year of administration: 2018	69 (29.9%)	231	72 (35.8%)	201
Year of administration: 2019	162 (70.1%)		129 (64.2%)	
Adalimumab	110 (47.6%)		79 (39.3%)	
Etanercept	75 (32.5%)		61 (30.3%)	
Infliximab	6 (2.6%)	231	14 (7.0%)	201
Certolizumab	20 (8.7%)		21 (10.4%)	
Golimumab	20 (8.7%)		26 (12.9%)	
Bo ADA/ETA/INF	91 (47.6%)	191	98 (63.6%)	154
Bs ADA/ETA/INF	100 (52.4%)		56 (36.4%)	

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute (relative) frequencies are presented.

Table 19 *Baseline characteristics of RA patients (validation dataset) answering yes/no to Q11A ('I seem to get sick a little easier than other people')*

	Yes (*n*=216)	*n*	No (*n*=254)	*n*
Female, *n* (%)	178 (82.4%)	216	196 (77.2%)	254
Age at diagnosis, years	46.0 (34.0–54.5)	216	46.0 (35.0–55.0)	254
Age at start of 1st line, years	54.5 (43.0–64.0)	216	55.0 (44.0–63.0)	254
Disease duration, years	6.0 (2.8–11.7)	216	6.0 (2.1–10.4)	254
RF positive	147 (68.7%)	214	179 (72.5%)	247
ACPA positive	151 (72.2%)	209	168 (68.3%)	246
Previous csDMARDs				
0	5 (2.3%)		4 (1.6%)	
1	56 (25.9%)		78 (30.7%)	
2	63 (29.2%)	216	99 (39.0%)	254
3	57 (26.4%)		45 (17.7%)	
4+	35 (16.2%)		28 (11.0%)	
GCs in previous history	198 (91.7%)	216	231 (90.9%)	254
Concomitant csDMARDs	188 (87.0%)	216	229 (90.2%)	254
Concomitant MTX	162 (75.0%)	216	191 (75.2%)	254
Concomitant GCs	151 (69.9%)	216	156 (61.4%)	254
DAS28-ESR (0–10)	6.3 (5.7–7.1)	214	6.0 (5.3–6.7)	253
TJC (28 joints)	14.0 (10.0–19.0)	216	13.0 (9.0–17.0)	254
SJC (28 joints)	10.0 (6.0–13.5)	216	9.0 (6.0–12.0)	254
ESR (mm/h)	34.0 (22.0–49.0)	207	30.0 (16.5–43.5)	240
CRP (mg/l)	15.0 (7.0–25.0)	213	13.0 (5.3–25.0)	253

SDAI (0–86)	38.7 (32.1–47.0)	213	37.3 (30.0–45.0)	253
PtGA (0–100)	80.0 (70.0–85.0)	216	70.0 (60.0–85.0)	254
MDGA (0–100)	70.0 (50.0–80.0)	216	70.0 (60.0–80.0)	254
HAQ-DI (0–3)	1.6 (1.3–2.1)	216	1.5 (1.1–2.0)	254
EQ-5D (-0.59–1)	0.1 (0.0–0.2)	216	0.2 (0.1–0.7)	253
Year of administration: 2018	69 (31.9%)	216	93 (36.6%)	254
Year of administration: 2019	147 (68.1%)		161 (63.4%)	
Adalimumab	102 (47.2%)	216	103 (40.6%)	254
Etanercept	66 (30.6%)		89 (35.0%)	
Infliximab	10 (4.6%)		9 (3.5%)	
Certolizumab	24 (11.1%)		27 (10.6%)	
Golimumab	14 (6.5%)		26 (10.2%)	
Bo ADA/ETA/INF	82 (42.1%)	178	137 (68.2%)	201
Bs ADA/ETA/INF	96 (53.9%)		64 (31.8%)	

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

Psoriatic arthritis

In total, we included 315 patients with **PsA** within the primary dataset and 176 patients within the validation dataset (see **Figure 17**). Further, patients were divided into groups based on their response to SF36 questions (Q11A and Q11C; **Figure 20**). Only decisive patients who answered *definitely/mostly yes/no* were analysed. Within the old cohort, baseline characteristics of patients who answered *yes* (*n*=80) and *no* (*n*=94) to Q 11C are shown in **Table 20**, while **Table 21** shows a description of patients responding *yes* (*n*=82) and *no* (*n*=128) to Q11A.

Patients answering *yes* to **Q11C** had statistically significantly higher age at diagnosis (median 41 vs 35), at bDMARD initiation (median 52 vs 42), longer disease duration (9.3 vs 4.8 years), a bigger number of previous csDMARDs, higher frequency of csDMARDs in concomitant therapy (90% vs 70%), worse quality of life - lower EQ-5D (median 0.1 vs 0.2), higher PGA of psoriasis and higher ESR (median 32 vs 23) compared to patients answering *no*. The most frequently administered drugs in both groups were adalimumab (*yes*: 47.5%; *no* 40.4%), golimumab (*yes*: 17%; *no*: 20.2%), etanercept (*yes*: 20.0 %; *no*: 10.6%) and infliximab (*yes*: 11.3%; *no*: 19.1%). Only seven patients from the group responding *yes*, and nine patients from the group responding *no* had biosimilars (infliximab).

Patients answering *yes* to **Q11A** had statistically significantly higher age at diagnosis (median 41 vs 37), at bDMARD initiation (median 51 vs 46), longer disease duration (7.8 vs 5.0 years), a bigger number of previous csDMARDs, worse quality of life - lower EQ-5D (median 0.1 vs 0.2), lower MDGA (median 60 vs 65), higher ESR (median 34 vs 23) and higher

frequency of dactylitis (51.9% vs 32.5%) compared to patients answering *no*. The most frequently administered drugs in both groups were adalimumab (*yes*: 43.9%; *no* 48.4%), golimumab (*yes*: 23.2%; *no*: 18.0%), etanercept (*yes*: 14.6 %; *no*: 11.7%) and infliximab (*yes*: 11.0%; *no*: 18.0%). Only seven patients from the group responding positively, and thirteen patients from the group responding negatively had biosimilars (infliximab).

Table 20 *Baseline characteristics of PsA patients (primary dataset) answering yes/no to Q11C ('I expect my health to get worse')*

	Yes (*n*=80)	*n*	No (*n*=94)	*n*
Female, *n* (%)	36 (45.0%)	80	42 (44.7%)	94
Age at diagnosis, years	40.5 (31.0–51.0)	80	35.0 (29.0–43.0)	94
Age at start of 1st line, years	52.0 (45.0–59.0)	80	42.0 (37.0–52.0)	94
Disease duration, years	9.3 (3.9–15.7)	80	4.8 (1.7–10.0)	94
RF+/ACPA+	5 (6.3%)	79	8 (8.5%)	94
Psoriasis	60 (90.9%)	66	62 (89.9%)	69
Dactylitis	37 (47.4%)	78	33 (35.9%)	92
Enthesitis	10 (15.4%)	65	12 (15.0%)	80
HLA-B27 positivity	14 (20.9%)	67	12 (17.1%)	70
Nail involvement				
No	27 (40.9%)		37 (46.3%)	
Mild	13 (19.7%)	66	20 (25.0%)	80
Medium	23 (34.8%)		23 (28.8%)	
Severe	3 (3.8%)		0 (0.0%)	
Previous csDMARDs				
0	0 (0.0%)		5 (5.6%)	
1	21 (26.3%)		34 (38.2%)	
2	20 (25.0%)	80	37 (41.6%)	89
3	27 (33.8%)		11 (12.4%)	
4+	12 (15.0%)		2 (2.2%)	
GCs in previous history	47 (60.3%)	78	50 (53.8%)	93
Concomitant csDMARDs	72 (90.0%)	80	66 (70.2%)	94
Concomitant MTX	54 (67.5%)	80	50 (53.2%)	94
Concomitant GCs	29 (36.3%)	80	31 (33.0%)	94
DAS28-ESR (0–10)	5.6 (4.9–6.1)	77	5.3 (4.6–6.1)	93
DAPSA	35.0 (28.2–41.4)	64	36.6 (23.9–47.8)	79
TJC (68 joints)	12.0 (7.0–18.0)	79	12.5 (6.0–18.0)	92
SJC (66 joints)	8.0 (5.0–11.0)	79	9.5 (5.0–14.0)	92
CRP (mg/l)	15.0 (7.4–29.3)	80	12.0 (5.5–26.2)	94
ESR (mm/h)	31.5 (16.0–49.0)	80	23.0 (12.0–37.0)	94
PtGA (0–100)	68.5 (53.5–80.0)	80	70.0 (55.0–78.0)	94
MDGA (0–100)	60.0 (50.0–75.0)	80	60.5 (50.0–70.0)	94
HAQ-DI (0–3)	1.3 (1.0–1.6)	80	1.1 (0.8–1.8)	94

EQ-5D (-0.59–1)	0.1 (0.0–0.6)	79	0.2 (0.1–0.7)	94
PGA of psoriasis				
0–1	15 (19.0%)		31 (33.7%)	
2–3	47 (59.5%)	79	52 (56.5%)	92
4–5	17 (21.5%)		9 (9.8%)	
Year of administration: ≤2011	15 (18.8%)		8 (8.5%)	
Year of administration: 2012	13 (16.3%)		15 (16.0%)	
Year of administration: 2013	7 (8.8%)	80	7 (7.4%)	94
Year of administration: 2014	11 (13.8%)		16 (17.0%)	
Year of administration: 2015	18 (22.5%)		28 (29.8%)	
Year of administration: 2016–2017	16 (20.0%)		20 (21.3%)	
Adalimumab	38 (47.5%)		38 (40.4%)	
Etanercept	16 (20.0%)		10 (10.6%)	
Infliximab	9 (11.3%)	80	18 (19.1%)	94
Certolizumab	3 (3.8%)		9 (9.6%)	
Golimumab	14 (17.5%)		19 (20.2%)	

RF rheumatoid factor; *ACPA* anti-citrullinated protein; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *GCs* glucocorticoids, *DAS28-ESR* 28-joint disease activity score with ESR; DAPSA Disease Activity index for Psoriatic Arthritis; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PGA* Physician global assessment; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

Table 21 *Baseline characteristics of PsA patients (primary dataset) answering yes/no to Q11A ('I seem to get sick a little easier than other people')*

	Yes (*n*=82)	*n*	No (*n*=128)	*n*
Female, *n* (%)	43 (52.4%)	82	47 (36.7%)	128
Age at diagnosis, years	41.0 (32.0–51.0)	82	37.0 (30.0–46.0)	128
Age at start of 1st line, years	51.0 (42.0–58.0)	82	46.0 (36.0–53.0)	128
Disease duration, years	7.8 (2.4–14.4)	82	5.0 (2.0–10.0)	128
RF+/ACPA+	9 (11.1%)	81	11 (8.6%)	128
Psoriasis	70 (97.2%)	72	95 (91.3%)	104
Dactylitis	42 (51.9%)	81	41 (32.5%)	126
Enthesitis	14 (20.3%)	69	15 (13.3%)	113
HLA-B27 positivity	14 (20.9%)	67	19 (19.2%)	99
Nail involvement				
No	22 (31.4%)		49 (43.8%)	
Mild	23 (32.9%)	70	29 (25.9%)	112
Medium	21 (30.0%)		29 (25.9%)	
Severe	4 (5.7%)		5 (4.5%)	
Previous csDMARDs				
0	1 (1.3%)		4 (3.2%)	
1	18 (22.5%)	80	52 (41.3%)	126
2	26 (32.5%)		47 (37.3%)	
3	24 (30.0%)		21 (16.7%)	

4+	11 (13.8%)		2 (1.6%)	
GCs in previous history	50 (61.7%)	81	67 (52.8%)	127
Concomitant csDMARDs	70 (85.4%)	82	95 (74.2%)	128
Concomitant MTX	49 (59.8%)	82	71 (55.5%)	128
Concomitant GCs	33 (40.2%)	82	44 (34.4%)	128
DAS28-ESR (0–10)	5.8 (5.1–6.4)	81	5.3 (4.4–6.0)	126
DAPSA	36.8 (30.7–45.7)	69	36.1 (25.5–43.1)	111
TJC (68 joints)	12.0 (9.0–19.0)	82	11.0 (6.0–18.0)	127
SJC (66 joints)	9.0 (6.0–12.0)	82	8.0 (5.0–12.0)	127
CRP (mg/l)	15.0 (9.5–28.0)	81	15.0 (4.9–26.3)	128
ESR (mm/h)	33.5 (18.0–49.0)	82	23.0 (12.0–40.0)	128
PtGA (0–100)	70.0 (55.0–80.0)	82	66.5 (55.0–80.0)	128
MDGA (0–100)	60.0 (50.0–75.0)	82	65.0 (55.5–80.0)	128
HAQ-DI (0–3)	1.4 (1.0–1.9)	82	1.3 (0.9–1.6)	128
EQ-5D (-0.59–1)	0.1 (0.0–0.5)	81	0.2 (0.1–0.7)	128
PGA of psoriasis				
0–1	14 (17.3%)		31 (24.6%)	
2–3	46 (56.8%)	81	69 (54.8%)	126
4–5	21 (25.9%)		26 (20.6%)	
Year of administration: ≤2011	12 (14.6%)		11 (8.6%)	
Year of administration: 2012	11 (13.4%)		20 (15.6%)	
Year of administration: 2013	8 (9.8%)	82	14 (10.9%)	128
Year of administration: 2014	16 (19.5%)		20 (15.6%)	
Year of administration: 2015	21 (25.6%)		34 (26.6%)	
Year of administration: 2016–2017	14 (17.1%)		29 (22.7%)	
Adalimumab	36 (43.9%)		62 (48.4%)	
Etanercept	12 (14.6%)		15 (11.7%)	
Infliximab	9 (11.0%)	82	23 (18.0%)	128
Certolizumab	6 (7.3%)		5 (3.9%)	
Golimumab	19 (23.2%)		23 (18.0%)	

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

For the PsA validation dataset, the baseline description of patients answering *yes* (*n*=55/*n*=43) and *no* (*n*=49/*n*=60) to Q11C / Q11A is presented in **Table 22** and **Table 23**.

Patients answering *yes* to Q11C had statistically significantly lower EQ-5D (median 0.2 vs 0.3) and worse nail involvement. The most frequently administered drugs in both groups were adalimumab (*yes* 60.0%; *no*: 51.0%), certolizumab (*yes*: 10.9%; *no*: 16.3%) and etanercept (*yes*: 10.9%; *no*: 14.3%). The frequency of biosimilars was higher in patients answering *yes* than in patients answering no to Q11C, but it was not statistically significant (52.2% vs 40.0%).

There was a statistically significantly higher frequency of GCs in patients answering *yes* to Q11A compared to patients answering *no* (42% vs 22%). Further, patients answering yes had

statistically significantly lower EQ-5D (median 0.1 vs 0.2), worse PGA of psoriasis and higher frequency of biosimilars (*yes*: 62.2%; *no*: 36.4%). The most frequently administered drug in both groups was adalimumab (yes: 60.5%; no: 53.3%). Patients answering *yes* to Q11A had a higher frequency of infliximab (18.6% vs 5.%), while patients answering *no* had a higher frequency of etanercept (7.0% vs 15.0%).

Table 22 *Baseline characteristics of PsA patients (validation dataset) answering yes/no to Q11C ('I expect my health to get worse')*

	Yes (*n*=55)	*n*	No (*n*=49)	*n*
Female, *n* (%)	30 (54.5%)	55	29 (59.2%)	49
Age at diagnosis, years	41.0 (33.0–49.0)	55	42.0 (34.0–50.0)	49
Age at start of 1st line, years	50.0 (44.0–60.0)	55	48.0 (41.0–57.0)	49
Disease duration, years	4.5 (1.9–15.8)	55	3.5 (1.5–8.1)	49
RF+/ACPA+	5 (9.1%)	55	3 (6.1%)	49
Psoriasis	37 (97.4%)	38	34 (89.5%)	38
Dactylitis	20 (37.0%)	54	22 (46.8%)	47
Enthesitis	7 (12.7%)	55	9 (18.4%)	49
HLA-B27 positivity	16 (34.0%)	47	12 (33.3%)	36
Nail involvement				
No	12 (21.8%)	55	28 (59.6%)	47
Mild	19 (34.5%)		7 (14.9%)	
Medium	20 (36.4%)		8 (17.0%)	
Severe	4 (7.3%)		4 (8.5%)	
Previous csDMARDs				
0	2 (3.6%)	55	2 (4.1%)	49
1	14 (25.5%)		21 (42.9%)	
2	15 (27.3%)		12 (24.5%)	
3	21 (38.2%)		11 (22.4%)	
4+	3 (5.5%)		3 (6.1%)	
GCs in previous history	32 (58.2%)	55	25 (51.0%)	49
Concomitant csDMARDs	44 (80.0%)	55	35 (71.4%)	49
Concomitant MTX	35 (63.6%)	55	30 (61.2%)	49
Concomitant GCs	19 (34.5%)	55	14 (28.6%)	49
DAS28-ESR (0–10)	5.5 (5.0–6.3)	55	5.3 (4.3–5.9)	49
DAPSA	35.6 (28.7–48.1)	55	35.5 (27.8–45.9)	49
TJC (68 joints)	12.0 (8.0–22.0)	55	12.0 (9.0–16.0)	49
SJC (66 joints)	8.0 (4.0–11.0)	55	8.0 (5.0–13.0)	49
CRP (mg/l)	11.5 (4.9–30.0)	55	12.0 (4.0–23.6)	49
ESR (mm/h)	32.0 (19.0–41.0)	53	23.0 (10.0–41.0)	46
PtGA (0–100)	75.0 (50.0–85.0)	55	70.0 (60.0–80.0)	49
MDGA (0–100)	65.0 (8.0–80.0)	55	70.0 (59.0–80.0)	49
HAQ-DI (0–3)	1.3 (0.8–1.6)	55	1.3 (0.6–1.8)	49

EQ-5D (-0.59–1)	0.2 (0.1–0.5)	55	0.3 (0.1–0.7)	49
PGA of psoriasis				
0–1	11 (22.0%)		15 (33.3%)	
2–3	30 (60.0%)	50	27 (60.0%)	45
4–5	9 (18.0%)		3 (6.7%)	
Year of administration: 2018	20 (36.4%)	55	13 (26.5%)	49
Year of administration: 2019	35 (63.6%)		36 (73.5%)	
Adalimumab	33 (60.0%)		25 (51.0%)	
Etanercept	6 (10.9%)		7 (14.3%)	
Infliximab	7 (12.7%)	55	3 (6.1%)	35
Certolizumab	6 (10.9%)		8 (16.3%)	
Golimumab	3 (5.5%)		6 (12.2%)	
Biosimilars (vs bio-originals)	24 (52.2%)	46	14 (40.0%)	35

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

Table 23 *Baseline characteristics of PsA patients (validation dataset) answering yes/no to Q11A ('I seem to get sick a little easier than other people')*

	Yes (*n*=43)	*n*	No (*n*=60)	*n*
Female, *n* (%)	26 (60.5%)	43	33 (55.0%)	60
Age at diagnosis, years	39.0 (31.0–45.0)	43	42.5 (34.0–51.0)	60
Age at start of 1st line, years	48.0 (43.0–58.0)	43	51.0 (41.0–58.0)	60
Disease duration, years	4.8 (2.2–18.1)	43	3.8 (1.6–8.9)	60
RF+/ACPA+	4 (9.3%)	43	3 (5.0%)	60
Psoriasis	33 (94.3%)	35	38 (88.4%)	43
Dactylitis	16 (38.1%)	42	22 (37.9%)	58
Enthesitis	10 (23.3%)	43	9 (15.0%)	60
HLA-B27 positivity	12 (30.0%)	40	13 (26.0%)	50
Nail involvement				
No	10 (23.3%)		24 (40.7%)	
Mild	14 (32.6%)	43	15 (25.4%)	59
Medium	16 (37.2%)		17 (28.8%)	
Severe	3 (7.0%)		3 (5.1%)	
Previous csDMARDs				
0	0 (0.0%)		3 (5.0%)	
1	20 (46.5%)		26 (43.3%)	
2	7 (16.3%)	43	19 (31.7%)	60
3	14 (32.6%)		10 (16.7%)	
4+	2 (4.7%)		2 (3.3%)	
GCs in previous history	24 (55.8%)	43	29 (48.3%)	60
Concomitant csDMARDs	38 (88.4%)	43	44 (73.3%)	60
Concomitant MTX	33 (76.7%)	43	37 (61.7%)	60
Concomitant GCs	18 (41.9%)	43	13 (21.7%)	60
DAS28-ESR (0–10)	5.9 (5.0–6.3)	43	5.2 (4.3–6.1)	60
DAPSA	34.6 (27.5–52.5)	43	37.9 (25.7–46.3)	60

TJC (68 joints)	12.0 (8.0–22.0)	43	11.0 (8.5–19.0)	60
SJC (66 joints)	8.0 (5.0–12.0)	43	9.0 (4.5–13.0)	60
CRP (mg/l)	15.0 (9.0–33.0)	43	10.4 (4.0–21.7)	60
ESR (mm/h)	36.0 (25.0–49.0)	43	20.5 (9.0–33.0)	58
PtGA (0–100)	75.0 (50.0–85.0)	43	72.5 (60.0–82.5)	60
MDGA (0–100)	67.0 (6.0–80.0)	43	70.0 (58.0–80.0)	60
HAQ-DI (0–3)	1.3 (0.9–1.6)	43	1.2 (0.8–1.8)	60
EQ-5D (-0.59–1)	0.1 (0.1–0.5)	43	0.2 (0.1–0.7)	60
PGA of psoriasis				
0–1	4 (10.3%)		17 (31.5%)	
2–3	26 (66.7%)	39	32 (59.3%)	54
4–5	9 (23.1%)		5 (9.3%)	
Year of administration: 2018	16 (37.2%)	43	20 (33.3%)	60
Year of administration: 2019	27 (62.8%)		40 (66.7%)	
Adalimumab	26 (60.5%)		32 (53.3%)	
Etanercept	3 (7.0%)		9 (15.0%)	
Infliximab	8 (18.6%)	43	3 (5.0%)	60
Certolizumab	4 (9.3%)		7 (11.7%)	
Golimumab	2 (4.7%)		9 (15.0%)	
Biosimilars (vs bio-originals)	23 (62.2%)	37	16 (36.4%)	44

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

Axial spondyloarthritis

In total, we included 769 patients with **axSpA** within the primary dataset and 475 patients within the secondary dataset (see **Figure 18**). Further, patients were divided into groups based on their responses to SF36 questions (Q 11A and Q 11C; **Figure 21**). Only decisive patients were analyzed. Within the validation dataset, baseline characteristics of patients who answered *yes* (*n*=251) and *no* (*n*=168) to Q 11C are shown in **Table 24**, while **Table 25** shows a description of patients responding *yes* (*n*=143) and *no* (*n*=356) to Q 11A.

Patients answering *yes* to **Q11C** had statistically significantly higher age at bDMARD initiation (median 40.0 vs 37.5), longer disease duration (6.4 vs 3.0 years), higher frequency of NSAIDs in concomitant therapy (61.4% vs 50.6%), worse quality of life - lower EQ-5D (median 0.2 vs 0.3), higher HAQ (median 1.1 vs 1.0), higher BASFI (median 5.5 vs 4.8) and higher BASDAI (median 6.3 vs 5.9) compared to patients answering *no*. The most frequently administered drugs in both groups were adalimumab (*yes*: 41.0%; *no* 42.9%), golimumab (*yes*: 24.7%; *no*: 26.8%), infliximab (*yes*: 19.5 %; *no*: 14.3%) and etanercept (*yes*: 11.6%; *no*: 10.1%). Biosimilars were administered at similar frequencies in both groups (16% and 14.2%).

Patients answering *yes* to **Q11A** had statistically significantly higher frequency of women (37.8% vs 22.2%), longer disease duration (7.0 vs 4.6 years), a bigger number of previous csDMARDs, higher frequency of csDMARDs (50.3% vs 37.1%) and GGs (23.8% vs 13.8%) in concomitant therapy, worse quality of life - lower EQ-5D (median 0.1 vs 0.2), higher HAQ (median 1.1 vs 1.0), higher BASDAI (median 6.6 vs 6), higher frequency of uveitis (28.7% vs 20.2%) and colitis (8.4% vs 2.6%) and lower frequency of HLA-B27 positivity (88.7% vs 95.4%) compared to patients answering *no*. Patients also differed in sacroiliitis grading. The most frequently administered drugs in both groups were adalimumab (*yes*: 49.0%; *no* 40.4%), golimumab (*yes*: 17.5%; *no*: 25.6%), infliximab (*yes*: 21.0 %; *no*: 15.7%) and etanercept (*yes*: 10.5%; *no*: 11.8%). Biosimilars were administered at similar frequencies in both groups (17% and 15%).

Table 24 *Baseline characteristics of axSpA patients (primary dataset) answering yes/no to Q11C ('I expect my health to get worse')*

	Yes (*n*=251)	*n*	No (*n*=168)	*n*
Female, *n* (%)	63 (25.1%)	251	43 (25.6%)	168
Age at diagnosis, years	32.5 (25.0–40.0)	250	32.0 (26.0–40.0)	165
Age at start of 1st line, years	40.0 (34.0–50.0)	251	37.5 (31.0–46.5)	168
Disease duration, years	6.4 (2.5–11.3)	250	3.0 (0.9–7.7)	165
Uveitis	64 (25.8%)	248	38 (23.0%)	165
Colitis	12 (4.8%)	248	7 (4.2%)	165
Psoriasis	11 (4.4%)	249	8 (4.8%)	166
Dactylitis	6 (2.5%)	237	9 (5.5%)	164
HLA-B27 positivity	221 (91.7%)	241	154 (93.9%)	164
Joint involvement				
Axial	98 (39.5%)		66 (39.5%)	
Root	67 (27.0%)	248	36 (21.6%)	167
Peripheral	83 (33.5%)		65 (38.9%)	
Previous csDMARDs				
0	86 (34.4%)		72 (43.9%)	
1	104 (41.6%)	250	61 (37.2%)	164
2	44 (17.6%)		23 (14.0%)	
3+	16 (6.4%)		8 (4.9%)	
GCs in previous history	74 (29.5%)	251	60 (35.7%)	168
Concomitant csDMARDs	94 (37.5%)	251	63 (37.5%)	168
Concomitant MTX	39 (15.5%)	251	27 (16.1%)	168
Concomitant GCs	38 (15.1%)	251	29 (17.3%)	168
Concomitant NSAIDs	153 (61.4%)	249	85 (50.6%)	168
ASDAS	4.1 (3.6–4.6)	251	4.0 (3.3–4.4)	168
BASDAI	6.3 (5.2–7.5)	251	5.9 (4.8–7.0)	168
SJC (44 joints)	0.0 (0.0–1.0)	250	0.0 (0.0–1.0)	168
CRP (mg/l)	19.1 (12.4–28.7)	250	19.4 (10.9–36.7)	164

ESR (mm/h)	30.0 (18.0–40.0)	248	30.0 (17.0–43.0)	167
BASFI	5.5 (3.7–7.2)	250	4.8 (2.9–6.7)	167
MDGA (0–100)	65.0 (50.0–78.0)	238	64.5 (50.0–78.0)	164
HAQ-DI (0–3)	1.1 (0.8–1.5)	251	1.0 (0.6–1.5)	168
EQ-5D (-0.59–1)	0.2 (0.1–0.6)	251	0.3 (0.1–0.7)	167
Sacroiliitis grading				
Pre-radiographic stage	2 (0.8%)	248	8 (4.8%)	166
Stage I	8 (3.2%)		5 (3.0%)	
Stage II	76 (30.6%)		62 (37.3%)	
Stage III	33 (13.3%)		18 (10.8%)	
Stage IV	55 (22.2%)		31 (18.7%)	
Stage V	74 (29.8%)		42 (25.3%)	
Year of administration: ≤2012	37 (14.7%)	251	14 (8.3%)	168
Year of administration: 2013	58 (23.1%)		28 (16.7%)	
Year of administration: 2014	58 (23.1%)		44 (26.2%)	
Year of administration: 2015	60 (23.9%)		43 (25.6%)	
Year of administration: 2016–2017	38 (15.1%)		39 (23.2%)	
Adalimumab	103 (41.0%)	251	72 (42.9%)	168
Etanercept	29 (11.6%)		17 (10.1%)	
Infliximab	49 (19.5%)		24 (14.3%)	
Certolizumab	8 (3.2%)		10 (6.0%)	
Golimumab	62 (24.7%)		45 (26.8%)	
Biosimilars (bs bio-originals)	29 (16.0%)	181	16 (14.2%)	113

BMI body mass index; csDMARDs conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *GCs* glucocorticoids, NSAIDs nonsteroidal anti-inflammatory drugs; *ASDAS* ankylosing spondylitis disease activity score; BASDAI Bath ankylosing spondylitis disease index; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *SDAI* Simplified Disease Activity Index; *BASFI* Bath Ankylosing Spondylitis Functional Index; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

Table 25 *Baseline characteristics of axSpA patients (primary dataset) answering yes/no to Q11A ('I seem to get sick a little easier than other people')*

	Yes (*n*=143)	*n*	No (*n*=356)	*n*
Female, *n* (%)	54 (37.8%)	143	79 (22.2%)	356
Age at diagnosis, years	32.0 (24.0–39.0)	143	31.0 (25.0–38.0)	351
Age at start of 1st line, years	40.0 (33.0–48.0)	143	38.0 (32.0–47.0)	356
Disease duration, years	7.0 (1.8–13.0)	143	4.6 (1.3–9.1)	351
Uveitis	41 (28.7%)	143	71 (20.2%)	351
Colitis	12 (8.4%)	143	9 (2.6%)	351
Psoriasis	8 (5.6%)	143	11 (3.1%)	353
Dactylitis	2 (1.4%)	140	15 (4.4%)	344
HLA-B27 positivity	125 (88.7%)	141	330 (95.4%)	346
Joint involvement				
Axial	46 (32.9%)	140	137 (39.0%)	351
Root	33 (23.6%)		100 (28.5%)	
Peripheral	61 (43.6%)		114 (32.5%)	

Previous csDMARDs				
0	39 (27.3%)	143	137 (39.0%)	351
1	50 (35.0%)		155 (44.2%)	
2	38 (26.6%)		48 (13.7%)	
3+	16 (11.2%)		11 (3.2%)	
GCs in previous history	51 (35.7%)	143	111 (31.2%)	356
Concomitant csDMARDs	72 (50.3%)	143	132 (37.1%)	356
Concomitant MTX	33 (23.1%)	143	50 (14.0%)	356
Concomitant GCs	34 (23.8%)	143	49 (13.8%)	356
Concomitant NSAIDs	87 (61.3%)	142	215 (60.6%)	355
ASDAS	4.0 (3.5–4.6)	143	4.0 (3.4–4.5)	356
BASDAI	6.6 (5.5–7.7)	143	6.0 (4.9–7.1)	356
SJC (44 joints)	0.0 (0.0–1.0)	141	0.0 (0.0–1.0)	355
CRP (mg/l)	18.6 (10.8–28.7)	141	20.0 (12.1–32.0)	351
ESR (mm/h)	29.5 (17.0–43.0)	140	30.0 (18.0–40.0)	353
BASFI	5.5 (3.6–7.2)	143	5.0 (3.4–6.8)	354
MDGA (0–100)	63.5 (46.0–75.0)	138	65.0 (50.0–79.5)	344
HAQ-DI (0–3)	1.1 (0.8–1.6)	143	1.0 (0.8–1.4)	356
EQ-5D (-0.59–1)	0.1 (0.1–0.6)	143	0.2 (0.1–0.7)	354
Sacroiliitis grading				
Pre-radiographic stage	2 (1.4%)	141	10 (2.8%)	351
Stage I	2 (1.4%)		11 (3.1%)	
Stage II	57 (40.7%)		117 (33.3%)	
Stage III	27 (19.3%)		32 (9.1%)	
Stage IV	24 (17.1%)		82 (23.4%)	
Stage V	28 (20.0%)		99 (28.2%)	
Year of administration: ≤2012	14 (9.8%)	143	52 (14.6%)	356
Year of administration: 2013	35 (24.5%)		68 (19.1%)	
Year of administration: 2014	33 (23.1%)		86 (24.2%)	
Year of administration: 2015	30 (21.0%)		88 (24.7%)	
Year of administration: 2016–2017	31 (21.7%)		62 (17.4%)	
Adalimumab	70 (49.0%)	143	144 (40.4%)	356
Etanercept	15 (10.5%)		42 (11.8%)	
Infliximab	30 (21.0%)		56 (15.7%)	
Certolizumab	3 (2.1%)		23 (6.5%)	
Golimumab	25 (17.5%)		91 (25.6%)	
Biosimilars (bs bio-originals)	20 (17.4%)	115	36 (14.9%)	242

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

For the axSpA validation dataset, the baseline description of patients answering *yes* (*n*=143/*n*=110) and *no* (*n*=118/*n*=193) to Q11C / Q11A is presented in **Table 26** and **Table 27**.

Patients answering *yes* to Q11C had statistically significantly higher BASDAI (median 6.9 vs 6.3), lower frequency of HLA-B27 positivity (85% vs 95%) and lower frequency of GCs in the previous history (19.6% vs 31.4%). The most frequently administered drugs in both

groups were adalimumab (*yes* 56.6%; *no*: 50.8%), etanercept (*yes*: 20.3%; *no*: 18.6%) and golimumab (*yes*: 11.2%; *no*: 16.9%). The frequency of biosimilars was higher in patients answering *yes* to Q11C, but it was not statistically significant (55.9% vs 44.3%).

There was a statistically significantly higher frequency of women in patients answering *yes* to Q11A compared to patients answering *no* (47.3% vs 33.2%). Further, patients answering *yes* had statistically significantly lower MDGA (median 60 vs 68), lower EQ-5D (median 0.1 vs 0.2), different joint involvement, a higher number of previous csDMARDs, higher frequency of csDMARDs (38.2% vs 24.9%) and GCs (19.1% vs 9.8%) in concomitant therapy. The most frequently administered drug in both groups was adalimumab (yes: 62.7%; no: 50.8%). Both groups had a similar frequency of biosimilars.

Table 26 *Baseline characteristics of axSpA patients (validation dataset) answering yes/no to Q11C ('I expect my health to get worse')*

	Yes (*n*=143)	*n*	No (*n*=118)	*n*
Female, *n* (%)	55 (38.5%)	143	46 (39.0%)	118
Age at diagnosis, years	33.0 (27.0–42.0)	131	33.0 (25.0–40.0)	113
Age at start of 1st line, years	41.0 (31.0–51.0)	143	39.5 (32.0–47.0)	118
Disease duration, years	4.1 (1.3–8.3)	131	3.9 (0.8–9.5)	113
Uveitis	28 (20.1%)	139	25 (21.4%)	117
Colitis	7 (5.0%)	139	5 (4.3%)	117
Psoriasis	9 (6.3%)	143	5 (4.2%)	118
Dactylitis	5 (3.9%)	129	7 (6.3%)	111
HLA-B27 positivity	6 (7.1%)	84	5 (6.5%)	77
Joint involvement				
Axial	65 (47.4%)		47 (41.2%)	
Root	27 (19.7%)	137	25 (21.9%)	114
Peripheral	45 (32.8%)		42 (36.8%)	
Previous csDMARDs				
0	70 (49.0%)		54 (45.8%)	
1	47 (32.9%)		48 (40.7%)	
2	21 (14.7%)		13 (11.0%)	
3+	5 (3.5%)		3 (2.5%)	
GCs in previous history	28 (19.6%)	143	37 (31.4%)	118
Concomitant csDMARDs	43 (30.1%)	143	42 (35.6%)	118
Concomitant MTX	9 (6.3%)	143	12 (10.2%)	118
Concomitant GCs	14 (9.8%)	143	18 (15.3%)	118
Concomitant NSAIDs	99 (70.7%)	140	76 (66.1%)	115
ASDAS	4.2 (3.6–4.7)	143	4.0 (3.6–4.5)	118
BASDAI	6.9 (5.6–7.9)	143	6.3 (5.2–7.4)	118
SJC (44 joints)	0 (0–0)	143	0 (0–1)	118
CRP (mg/l)	26.0 (16.0–40.0)	140	26.0 (15.0–37.0)	117
ESR (mm/h)	26.0 (16.0–40.0)	140	26.0 (15.0–37.0)	117

BASFI	5.6 (3.4–7.5)	136	5.3 (3.5–7.2)	115
MDGA (0–100)	61.0 (50.0–75.0)	139	65.0 (51.0–80.0)	116
HAQ-DI (0–3)	1.1 (0.8–1.6)	143	1.1 (0.8–1.5)	118
EQ-5D (-0.59–1)	0.2 (0.1–0.6)	143	0.2 (0.1–0.7)	117
Sacroiliitis grading				
Pre-radiographic stage	12 (8.8%)		12 (10.5%)	
Stage I	4 (2.9%)		3 (2.6%)	
Stage II	55 (40.1%)	137	43 (37.7%)	114
Stage III	11 (8.0%)		14 (12.3%)	
Stage IV	26 (19.0%)		12 (10.5%)	
Stage V	29 (21.2%)		30 (26.3%)	
Year of administration: 2018	54 (37.8%)	143	41 (34.7%)	118
Year of administration: 2019	89 (62.2%)		77 (65.3%)	
Adalimumab	81 (56.6%)		60 (50.8%)	
Etanercept	29 (20.3%)		22 (18.6%)	
Infliximab	8 (5.6%)	143	6 (5.1%)	118
Certolizumab	9 (6.3%)		10 (8.5%)	
Golimumab	16 (11.2%)		20 (16.9%)	
Biosimilars (bs bio-originals)	66 (55.9%)	118	39 (44.3%)	88

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

Table 27 *Baseline characteristics of axSpA patients (validation dataset) answering yes/no to Q11A ('I seem to get sick a little easier than other people')*

	Yes (*n*=110)	*n*	No (*n*=193)	*n*
Female, *n* (%)	52 (47.3%)	110	64 (33.2%)	193
Age at diagnosis, years	33.0 (27.0–42.0)	107	33.0 (26.0–42.0)	181
Age at start of 1st line, years	36.5 (31.0–47.0)	110	40.0 (32.0–47.0)	193
Disease duration, years	2.1 (0.7–5.6)	107	3.4 (0.9–8.2)	181
Uveitis	23 (21.1%)	109	43 (22.9%)	188
Colitis	7 (6.4%)	109	7 (3.7%)	188
Psoriasis	7 (6.4%)	110	5 (2.6%)	193
Dactylitis	2 (2.0%)	100	4 (2.2%)	179
HLA-B27 positivity	4 (5.9%)	68	7 (5.9%)	119
Joint involvement				
Axial	39 (36.1%)		93 (50.3%)	
Root	29 (26.9%)	108	33 (17.8%)	185
Peripheral	40 (37.0%)		59 (31.9%)	
Previous csDMARDs				
0	44 (40.0%)		110 (57.0%)	
1	47 (42.7%)	110	59 (30.6%)	193
2	15 (13.6%)		22 (11.4%)	
3+	4 (3.6%)		2 (1%)	
GCs in previous history	36 (32.7%)	110	46 (23.8%)	193
Concomitant csDMARDs	42 (38.2%)	110	48 (24.9%)	193
Concomitant MTX	10 (9.1%)	110	14 (7.3%)	193

Concomitant GCs	21 (19.1%)	110	19 (9.8%)	193
Concomitant NSAIDs	79 (73.1%)	108	123 (65.1%)	189
ASDAS	4.3 (3.7–4.7)	110	4.1 (3.5–4.7)	193
BASDAI	7.0 (5.9–8.2)	110	6.5 (5.2–7.6)	193
SJC (44 joints)	0 (0–0)	109	0 (0–0)	193
CRP (mg/l)	16.3 (11.6–26.0)	110	18.0 (11.6–38.0)	193
ESR (mm/h)	27.0 (14.0–39.0)	106	28.0 (15.0–42.0)	191
BASFI	5.6 (3.7–7.8)	104	5.2 (3.0–7.1)	188
MDGA (0–100)	60.0 (50.0–70.0)	108	68.0 (55.0–80.0)	189
HAQ-DI (0–3)	1.3 (0.6–1.6)	110	1.0 (0.8–1.5)	193
EQ-5D (-0.59–1)	0.1 (0.1–0.6)	110	0.2 (0.1–0.7)	193
Sacroiliitis grading				
Pre-radiographic stage	16 (14.8%)	108	17 (9.2%)	185
Stage I	1 (0.9%)		2 (1.1%)	
Stage II	44 (40.7%)		64 (34.6%)	
Stage III	11 (10.2%)		21 (11.4%)	
Stage IV	19 (17.6%)		33 (17.8%)	
Stage V	17 (15.7%)		48 (25.9%)	
Year of administration: 2018	42 (38.2%)	110	72 (37.3%)	193
Year of administration: 2019	68 (61.8%)		121 (62.7%)	
Adalimumab	69 (62.7%)	110	98 (50.8%)	193
Etanercept	22 (20.0%)		32 (16.6%)	
Infliximab	5 (4.5%)		10 (5.2%)	
Certolizumab	4 (3.6%)		19 (9.8%)	
Golimumab	10 (9.1%)		34 (17.6%)	
Biosimilars (bs bio-originals)	46 (47.9%)	96	64 (45.7%)	140

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented.

7.2.2 Comparison of treatment responses within the first year of TNFi treatment

Rheumatoid arthritis

Comparison of remission rates according to the DAS28-ESR score after 3, 6 and 12 months of TNFi treatment between patients answering *yes* and *on* to questions Q11C and Q11A within the primary and validation dataset is illustrated in **Figure 30**, **Figure 31**, **Figure 32** and **Figure 33**.

Within the **primary dataset**, patients who expected their health to get worse at the treatment initiation achieved remission after 3, 6 and 12 months statistically significantly more often than patients who did not expect their health to get worse (see **Figure 30**). Similarly, remission was achieved statistically significantly more often after 3, 6 and 12 months in patients who seemed to get sick a little easier than other people at the treatment initiation than in patients who did not think that (see **Figure 31**). Remission rates remained significantly different even

when computed within patients staying on the treatment through the Lundex index (Kristensen et al. 2006). The crude odds ratios for reaching remission at 6- and 12-month are shown in **Table 28**. Patients answering *yes* to Q11C had 1.7 (1.4) × higher odds for remission at the 6-month (12-month) visit than patients answering *no*. Patients answering *yes* to Q11A had almost 1.5 × higher odds for remission both at the 6- and 12-month visit than patients answering *no*. The odds ratios adjusted for potential confounders (HAQ and DAS28-ESR) at treatment initiation are shown in **Table 29**. Even after accounting for baseline disease activity and functional status, the odds for remission at the 6- and 12-month visits remained significantly higher in patients answering *yes* to both questions.

Within the **validation dataset**, patients answering *yes* to Q11C achieved remission after 12 months statistically significantly more often than patients answering *no* (see **Figure 32**). Even though the remission rates did not statistically significantly differ at 3- and 6-month visits, there were also tendencies for the more frequent occurrence of remission in patients answering *yes* to Q11C. Similarly, remission was achieved statistically significantly more often after 6 and 12 months in patients answering *yes* to Q11A than in patients answering *no* (see **Figure 33**). At the 3-month visit, the difference was not statistically significant; however, patients answering *yes* achieved remission a little bit more often than patients answering *no*. Similar results were also obtained when computed through the Lundex index. The crude odds ratios of achieving remission at six and twelve-month visits for the two studied groups are shown in **Table 30**. Both patients answering *yes* to Q11C and Q11A had significantly higher odds (1.6 and 1.7 times) of reaching remission at the 12-month visit than patients answering *no* to these questions. After accounting for baseline disease activity and functional status (see **Table 31**.), the odds for remission at the 6- and 12-month visits were significantly higher in patients answering *yes*.

Table 28 *Univariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – RA primary dataset*

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	**1.70** (1.33; 2.18)	<**0.001**	**1.42** (1.12; 1.80)	**0.003**
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	**1.46** (1.16; 1.83)	**0.001**	**1.47** (1.18; 1.83)	<**0.001**

OR – odds ratio; CI – confidence interval

Table 29 *Multivariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – RA primary dataset*

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	**1.91** (1.47; 2.47)	<**0.001**	**1.53** (1.20; 1.95)	<**0.001**
HAQ	**0.59** (0.49; 0.70)	<**0.001**	**0.65** (0.55; 0.77)	<**0.001**
DAS28-ESR	**0.57** (0.50; 0.65)	<**0.001**	**0.64** (0.57; 0.72)	<**0.001**
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	**1.82** (1.43; 2.33)	<**0.001**	**1.75** (1.39; 2.21)	<**0.001**
HAQ	**0.58** (0.48; 0.69)	<**0.001**	**0.63** (0.53; 0.74)	<**0.001**
DAS28-ESR	**0.57** (0.50; 0.64)	<**0.001**	**0.64** (0.56; 0.72)	<**0.001**

OR – odds ratio; CI – confidence interval

Table 30 *Univariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – RA validation dataset*

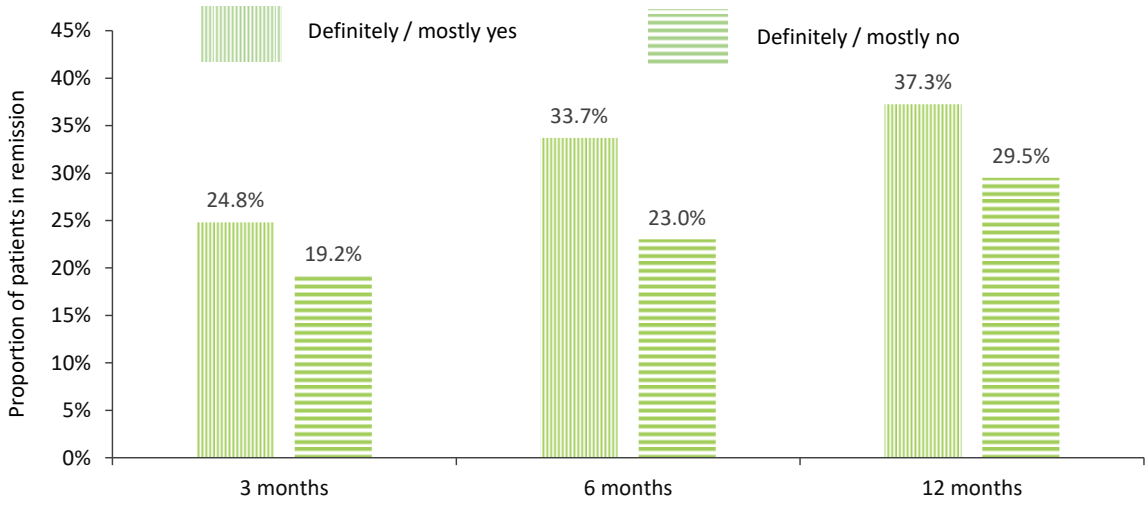
	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	1.27 (0.86; 1.87)	0.230	**1.66** (1.13; 2.45)	**0.010**
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.30 (0.89; 1.90)	0.171	**1.74** (1.20; 2.52)	**0.004**

OR – odds ratio; CI – confidence interval

Table 31 *Multivariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – RA validation dataset*

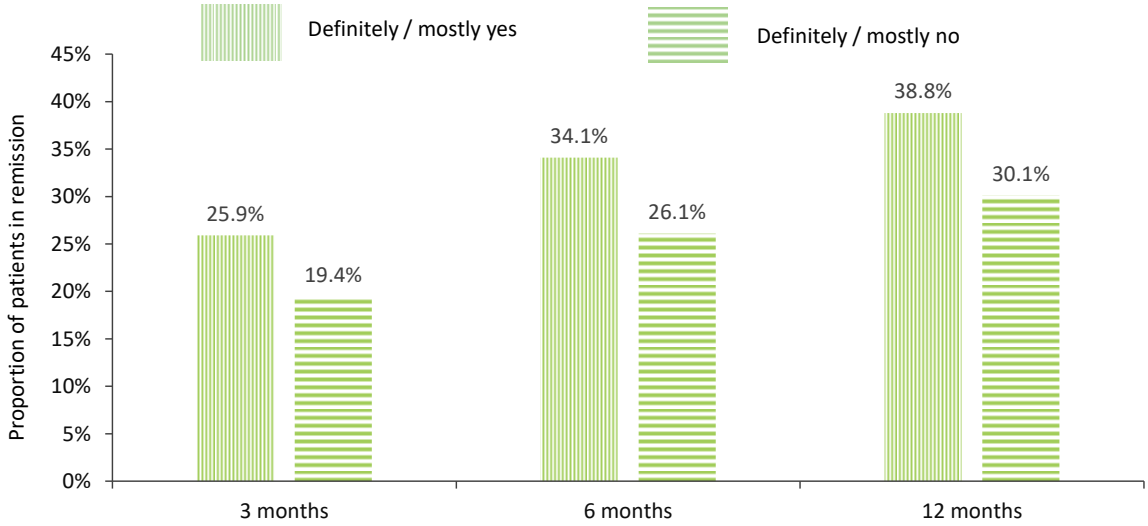
	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	**1.57** (1.04; 2.38)	**0.033**	**1.91** (1.26; 2.88)	**0.002**
HAQ	**0.52** (0.39; 0.71)	<**0.001**	**0.46** (0.34; 0.62)	<**0.001**
DAS28-ESR	**0.77** (0.65; 0.91)	**0.002**	0.91 (0.77; 1.06)	0.232
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	**1.57** (1.05; 2.35)	**0.029**	**2.04** (1.37; 3.03)	<**0.001**
HAQ	**0.52** (0.38; 0.71)	<**0.001**	**0.45** (0.33; 0.62)	<**0.001**
DAS28-ESR	**0.77** (0.65; 0.91)	**0.002**	0.89 (0.76; 1.05)	0.165

OR – odds ratio; CI – confidence interval



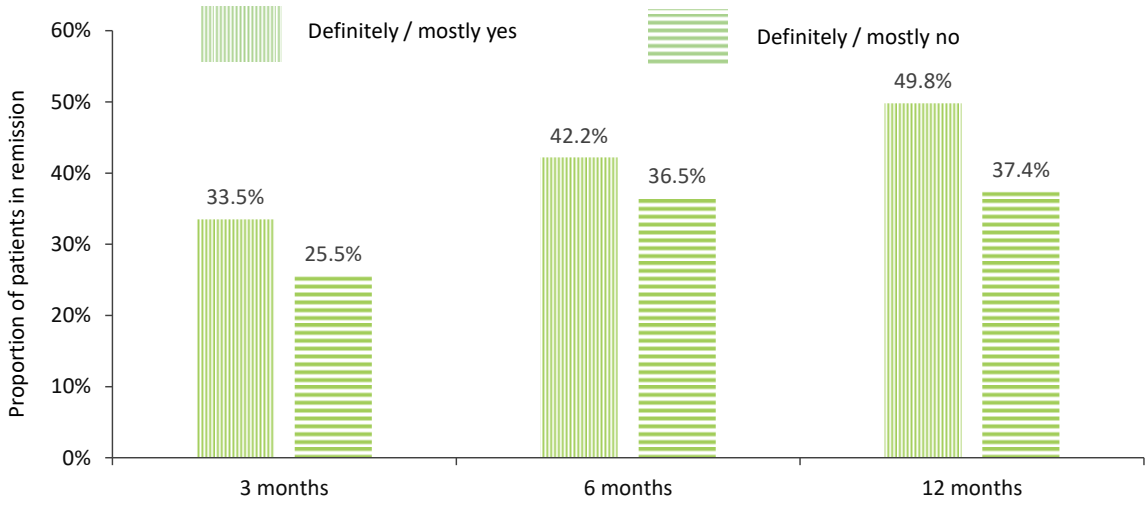
Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=1239)	168 (24.8%)	677	108 (19.2%)	562	**0.018**
6-month visit (*n*=1305)	245 (33.7%)	727	133 (23.0%)	578	**<0.001**
12-month visit (*n*=1287)	266 (37.3%)	714	169 (29.5%)	573	**<0.001**

Figure 30 *Remission rates (DAS28-ESR<2.6) after 3, 6 and 12 months of TNFi treatment in RA patients answering yes/no to Q11C ('I expect my health to get worse') within the primary dataset*



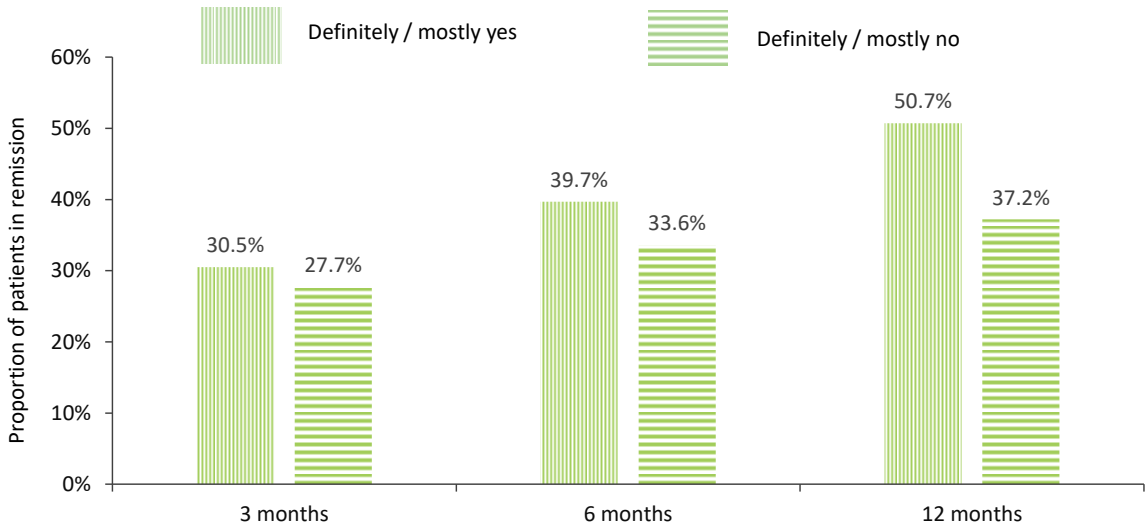
Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=1372)	156 (25.9%)	602	149 (19.4%)	770	**<0.001**
6-month visit (*n*=1434)	220 (34.1%)	646	206 (26.1%)	788	**<0.001**
12-month visit (*n*=1420)	247 (38.8%)	637	236 (30.1%)	783	**<0.001**

Figure 31 *Remission rates (DAS28-ESR<2.6) after 3, 6 and 12 months of TNFi treatment in RA patients answering yes/no to Q11A 'I seem to get sick a little easier than other people') within the primary dataset*



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=393)	66 (33.5%)	197	50 (25.5%)	196	0.082
6-month visit (*n*=430)	97 (42.2%)	230	73 (36.5%)	200	0.280
12-month visit (*n*=427)	114 (49.8%)	229	74 (37.4%)	198	**0.010**

Figure 32 *Remission rates (DAS28-ESR<2.6) after 3, 6 and 12 months of TNFi treatment in RA patients answering yes/no to Q11C ('I expect my health to get worse') within the validation dataset*



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=429)	57 (30.5%)	187	67 (27.7%)	242	0.303
6-month visit (*n*=467)	85 (39.7%)	214	85 (33.6%)	253	**0.041**
12-month visit (*n*=463)	108 (50.7%)	213	93 (37.2%)	250	**<0.001**

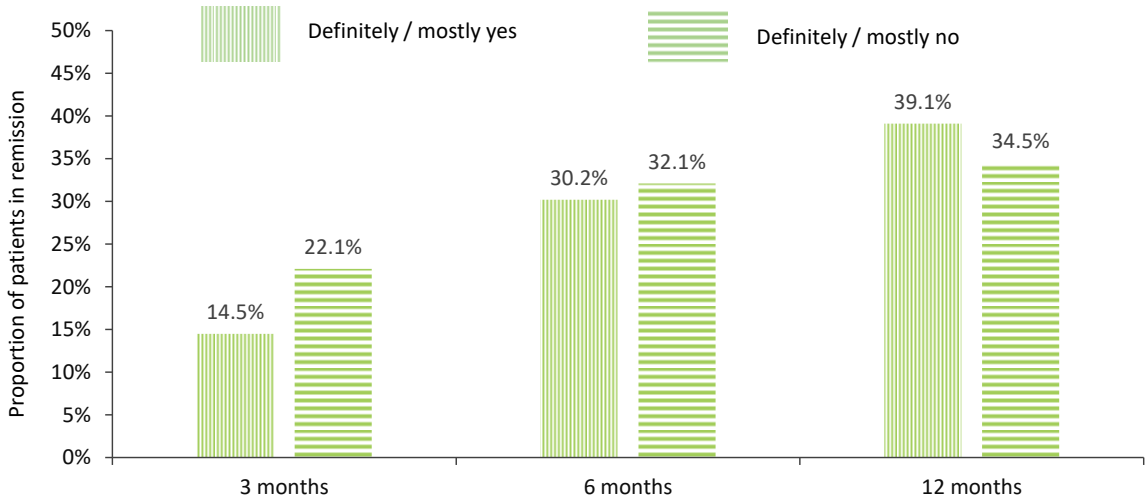
Figure 33 *Remission rates (DAS28-ESR<2.6) after 3, 6 and 12 months of TNFi treatment in RA patients answering yes/no to Q11A 'I seem to get sick a little easier than other people') within the validation dataset*

Psoriatic arthritis

Comparison of remission rates according to the DAPSA score after 3, 6 and 12 months of TNFi treatment between patients answering yes and on to questions Q11C and Q11A within the primary and validation datasets is illustrated in **Figure 34**, **Figure 35**, **Figure 36** and **Figure 37**.

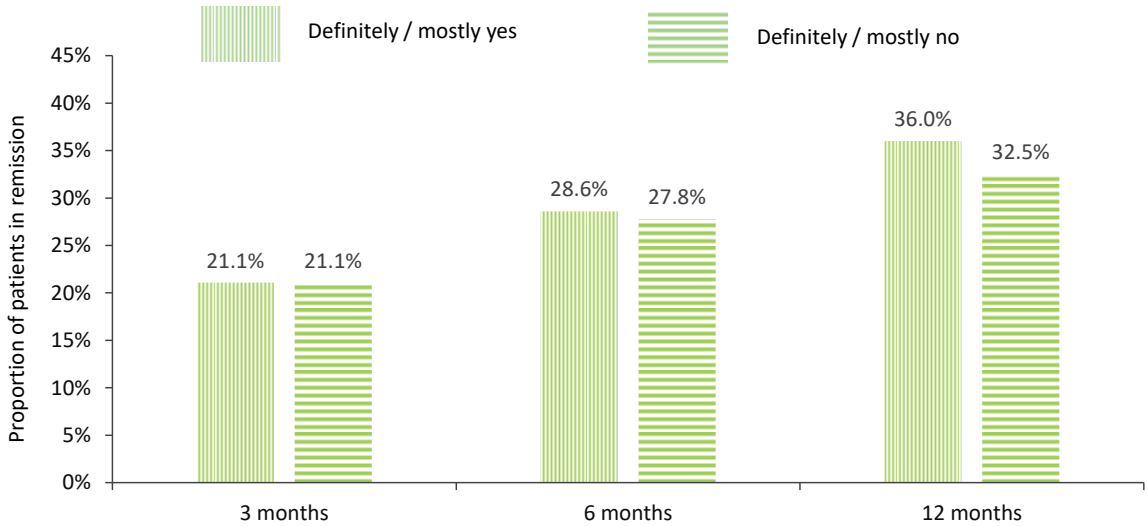
Within the **PsA primary dataset**, there was no statistically significant difference in remission rates after 3, 6 and 12 months between patients who expected and did not expect their health to get worse at treatment initiation (see **Figure 34**). Similarly, there was no statistically significant difference after 3, 6 and 12 months in patients who seemed to get sick a little easier than other people at the treatment initiation and patients who did not think that (see **Figure 35**). Remission rates were also similar when computed within patients staying on the treatment through the Lundex index. The crude odds ratios for reaching remission at 6- and 12-month are shown in **Table 32**. Patients answering *yes* to Q11C had 1.8 × higher odds for remission at the 12-month visit than patients answering *no*, but it was not statistically significant. The odds ratios adjusted for potential confounders (HAQ and DAS28-ESR) at treatment initiation are shown in **Table 33**. Even after accounting for baseline disease activity and functional status, the odds for remission at the 6- and 12-month visits remained not statistically significant.

Within the **PsA validation dataset**, patients answering *yes* to Q11C achieved remission after 12 months more often than patients answering *no*, but the result was not statistically significant (see **Figure 36**). Similarly, remission was achieved more often after 12 months in patients answering *yes* to Q11A than in patients answering *no,* but again the result was not statistically significant (see **Figure 37**). Remission rates were higher in patients answering *yes* when computed through the Lundex index as well. The crude odds ratios of achieving remission at six and twelve-month visits for the two studied groups are shown in **Table 34**. Both patients answering *yes* to Q11C and Q11A had higher odds (1.8 and 2.2 times) of reaching remission at the 12-month visit than patients answering *no* to these questions, but the results were not statistically significant. The results remained not statistically significant even after accounting for baseline disease activity and functional status (see **Table 35**).



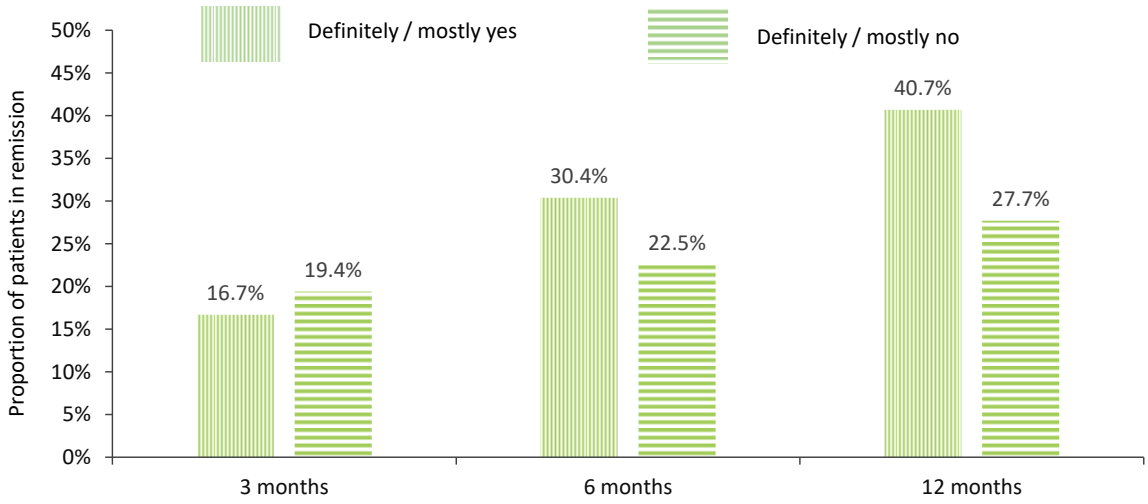
Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=132)	8 (14.5%)	55	17 (22.1%)	77	0.276
6-month visit (*n*=147)	19 (30.2%)	63	27 (32.1%)	84	0.797
12-month visit (*n*=156)	27 (39.1%)	69	30 (34.5%)	87	0.549

Figure 34 *Remission rates (DAPSA ≤ 4) after 3, 6 and 12 months of TNFi treatment in PsA patients answering yes/no to Q11C ('I expect my health to get worse') within the primary dataset*



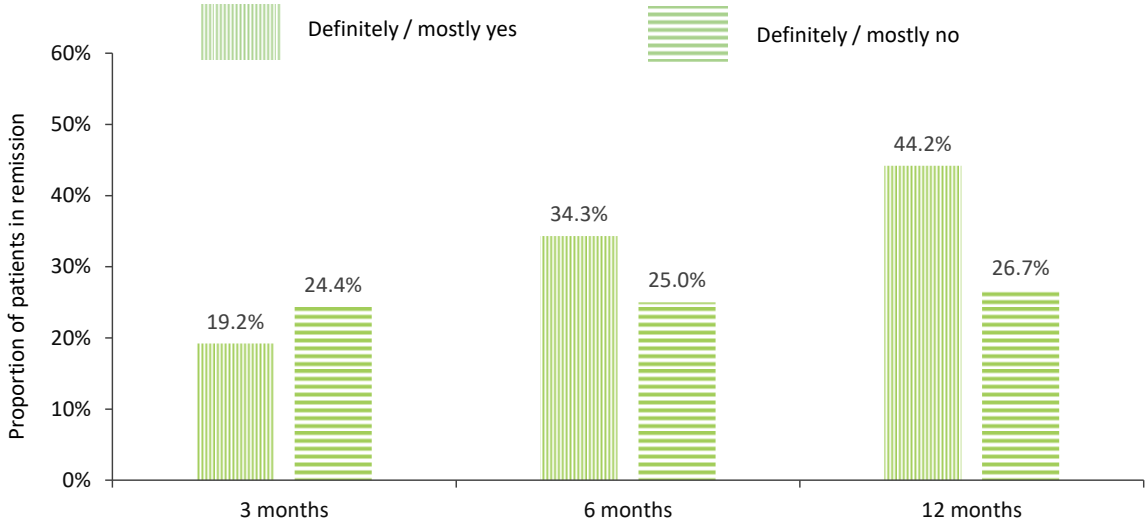
Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=166)	12 (21.1%)	57	23 (21.1%)	109	0.994
6-month visit (*n*=185)	20 (28.6%)	70	32 (27.8%)	115	0.913
12-month visit (*n*=192)	27 (36.0%)	75	38 (32.5%)	117	0.615

Figure 35 *Remission rates (DAPSA ≤ 4) after 3, 6 and 12 months of TNFi treatment in PsA patients answering yes/no to Q11A 'I seem to get sick a little easier than other people') within the primary dataset*



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=72)	6 (16.7%)	36	7 (19.4%)	36	0.759
6-month visit (*n*=86)	14 (30.4%)	46	9 (22.5%)	40	0.407
12-month visit (*n*=101)	22 (40.7%)	54	13 (27.7%)	47	0.168

Figure 36 *Remission rates (DAPSA ≤ 4) after 3, 6 and 12 months of TNFi treatment in PsA patients answering yes/no to Q11C ('I expect my health to get worse') within the validation dataset*



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=71)	5 (19.2%)	26	11 (24.4%)	45	0.612
6-month visit (*n*=87)	12 (34.3%)	35	13 (25.0%)	52	0.348
12-month visit (*n*=103)	19 (44.2%)	43	16 (26.7%)	60	0.064

Figure 37 *Remission rates (DAPSA ≤ 4) after 3, 6 and 12 months of TNFi treatment in PsA patients answering yes/no to Q11A 'I seem to get sick a little easier than other people') within the validation dataset*

Table 32 *Univariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – PsA primary dataset*

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	0.91 (0.45; 1.85)	0.797	1.80 (0.78; 4.16)	0.170
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.04 (0.54; 2.01)	0.913	1.17 (0.64; 2.15)	0.615

OR – odds ratio; CI – confidence interval

Table 33 *Multivariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – PsA primary dataset*

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	1.30 (0.60; 2.84)	0.505	1.38 (0.67; 2.83)	0.381
HAQ	**0.35** (0.19; 0.67)	**0.001**	**0.42** (0.23; 0.74)	**0.003**
DAS28-ESR	0.98 (0.96; 1.00)	0.081	0.98 (0.96; 1.00)	0.094
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.71 (0.82; 3.57)	0.154	1.42 (0.72; 2.81)	0.317
HAQ	**0.34** (0.18; 0.64)	**0.001**	**0.41** (0.23; 0.72)	**0.002**
DAS28-ESR	**0.98** (0.95; 1.00)	**0.046**	0.98 (0.96; 1.00)	0.054

OR – odds ratio; CI – confidence interval

Table 34 *Univariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – PsA validation dataset*

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	1.51 (0.57; 3.98)	0.408	1.80 (0.78; 4.16)	0.170
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.57 (0.61; 4.00)	0.350	2.18 (0.95; 4.99)	0.066

OR – odds ratio; CI – confidence interval

Table 35 *Multivariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – PsA validation dataset*

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	1.78 (0.62; 5.14)	0.285	1.56 (0.57; 4.29)	0.386
HAQ	0.57 (0.24; 1.34)	0.200	0.56 (0.24; 1.28)	0.166
DAS28-ESR	1.00 (0.98; 1.03)	0.756	1.01 (0.99; 1.04)	0.350
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.32 (0.46; 3.75)	0.603	1.14 (0.41; 3.17)	0.799
HAQ	0.68 (0.31; 1.50)	0.344	0.58 (0.25; 1.31)	0.188
DAS28-ESR	1.00 (0.98; 1.03)	0.848	1.01 (0.99; 1.04)	0.371

OR – odds ratio; CI – confidence interval

Axial spondyloarthritis

Comparison of remission rates according to the ASDAS score after 3, 6 and 12 months of TNFi treatment between patients answering yes and on to questions Q11C and Q11A within the primary and validation datasets is illustrated in **Figure 38**, **Figure 39**, **Figure 40** and **Figure 41**.

Within the **axSpA primary dataset**, there was no statistically significant difference in remission rates after 3, 6 and 12 months between patients who expected and did not expect their health to get worse at treatment initiation (see **Figure 38**). However, we can observe a slightly higher frequency of remission in patients answering *no*, which is the opposite result compared to RA and PsA cohorts. Similarly, there was no statistically significant difference after 3, 6 and 12 months in patients who seemed to get sick a little easier than other people at the treatment initiation and patients who did not think that (see **Figure 39**). Remission rates within patients staying on the treatment through the Lundex index gave similar results. The crude odds ratios for reaching remission at 6- and 12-month are shown in **Table 36**. Odds ratios for remission were not statistically significantly different between patients answering *yes*/*no* to Q11C and Q11A. The odds ratios adjusted for potential confounders (HAQ and DAS28-ESR) at treatment initiation are shown in **Table 37**.

Within the **axSpA validation dataset**, patients answering *no* to Q11C achieved remission after three months statistically significantly more often than patients answering *yes* (see **Figure 40**). At 6- and 12-month visits, the results were not statistically significant. Remission was achieved more often after 12 months in patients answering *no* to Q11A than

patients answering *yes,* but the result was not statistically significant (see **Figure 41**). Remission rates computed through the Lundex index gave similar results. The crude odds ratios of achieving remission at six and twelve-month visits for the two studied groups are shown in **Table 38**, and odds ratios adjusted for baseline disease activity and functional status are presented in **Table 39**. Odds ratios were not statistically significantly different between patients answering *yes*/*no* to Q11C and Q11A.

Table 36 *Univariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – axSpA primary dataset*

	Remission after 6 months		**Remission after 12 months**	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	0.74 (0.50; 1.11)	0.147	0.85 (0.57; 1.27)	0.430
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.22 (0.82; 1.82)	0.324	0.80 (0.53; 1.20)	0.281

OR – odds ratio; CI – confidence interval

Table 37 *Multivariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – axSpA primary dataset*

	Remission after 6 months		**Remission after 12 months**	
Parameter	OR (95% CI)	*p*	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	0.80 (0.53; 1.21)	0.294	0.93 (0.61; 1.40)	0.721
HAQ	**0.53** (0.38; 0.73)	<**0.001**	**0.44** (0.32; 0.62)	<**0.001**
DAS28-ESR	0.86 (0.69; 1.06)	0.160	0.93 (0.75; 1.15)	0.491
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.38 (0.92; 2.08)	0.121	0.90 (0.59; 1.36)	0.616
HAQ	**0.52** (0.38; 0.72)	<**0.001**	**0.46** (0.33; 0.64)	<**0.001**
DAS28-ESR	0.85 (0.68; 1.05)	0.124	0.92 (0.74; 1.14)	0.446

OR – odds ratio; CI – confidence interval

Table 38 *Univariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – axSpA validation dataset*

	Remission after 6 months		**Remission after 12 months**	
Parameter	OR (95% CI)	*p*	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	0.74 (0.44; 1.22)	0.236	0.76 (0.46; 1.25)	0.277

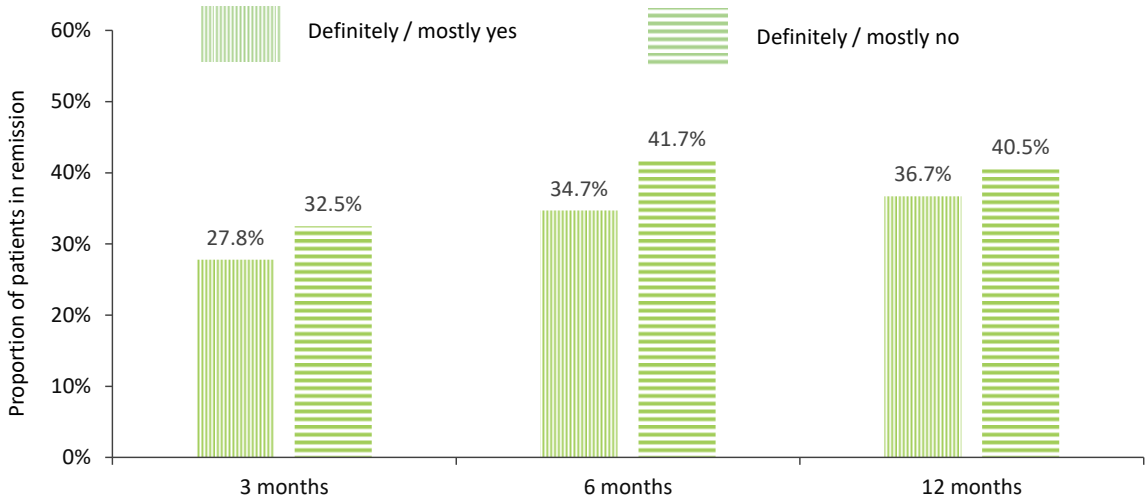
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.00 (0.62; 1.62)	0.995	0.70 (0.43; 1.15)	0.158

OR – odds ratio; CI – confidence interval

Table 39 *Multivariable logistic regression models for reaching remission (1 – yes; 0 – no) based on answers to Q11C and Q11A at treatment initiation – validation axSpA cohort*

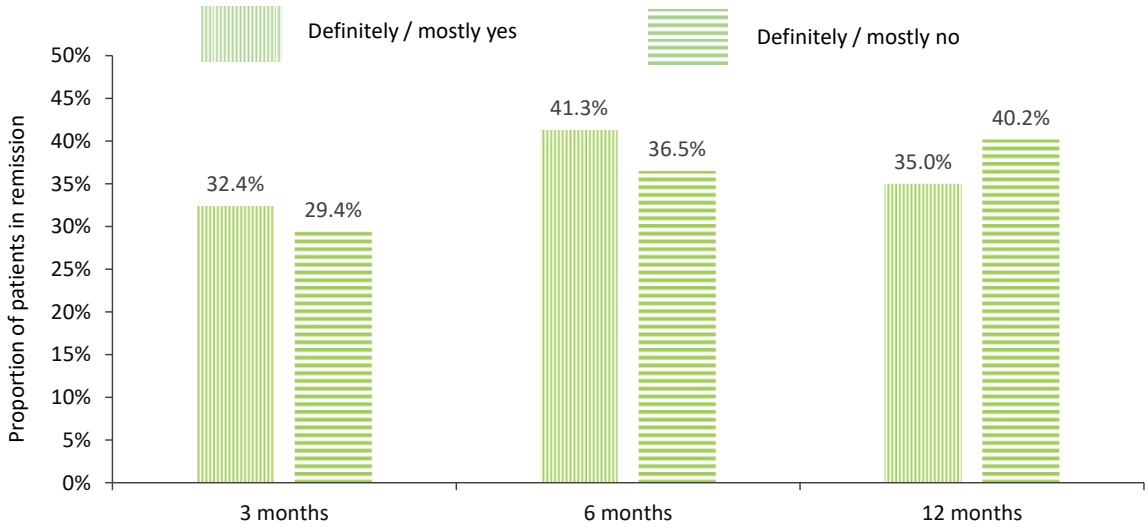
	Remission after 6 months		**Remission after 12 months**	
Parameter	OR (95% CI)	*p*	OR (95% CI)	*p*
Q11C: '*I expect my health to get worse*'				
Yes vs no	0.77 (0.46; 1.29)	0.320	0.78 (0.47; 1.30)	0.345
HAQ	**0.63** (0.43; 0.93)	**0.021**	**0.58** (0.40; 0.86)	**0.006**
DAS28-ESR	0.78 (0.59; 1.02)	0.070	0.86 (0.66; 1.13)	0.279
Q11A: '*I seem to get sick a little easier than other people*'				
Yes vs no	1.07 (0.65; 1.75)	0.785	0.74 (0.45; 1.22)	0.240
HAQ	**0.64** (0.43; 0.94)	**0.024**	**0.60** (0.40; 0.88)	**0.009**
DAS28-ESR	0.77 (0.58; 1.00)	0.052	0.85 (0.65; 1.11)	0.242

OR – odds ratio; CI – confidence interval



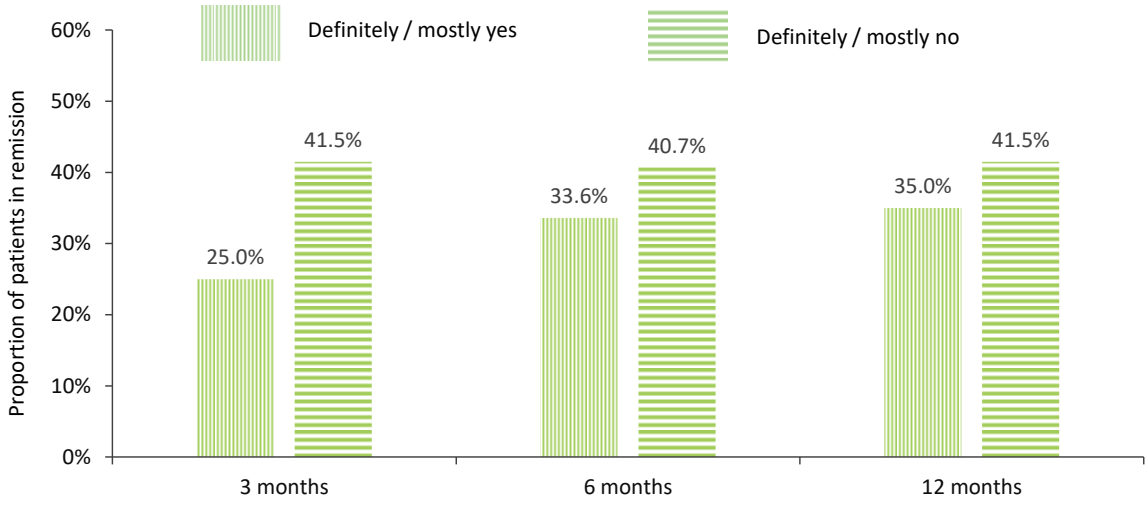
Remission rate	**Definitely / mostly yes**	*n*	**Definitely / mostly no**	*n*	**P-value**
3-month visit (*n*=408)	68 (27.8%)	245	53 (32.5%)	163	0.302
6-month visit (*n*=419)	87 (34.7%)	251	70 (41.7%)	168	0.147
12-month visit (*n*=419)	92 (36.7%)	251	68 (40.5%)	168	0.430

Figure 38 *Remission rates (ASDAS < 1.3) after 3, 6 and 12 months of TNFi treatment in axSpA patients answering yes/no to Q11C ('I expect my health to get worse') within the primary dataset*



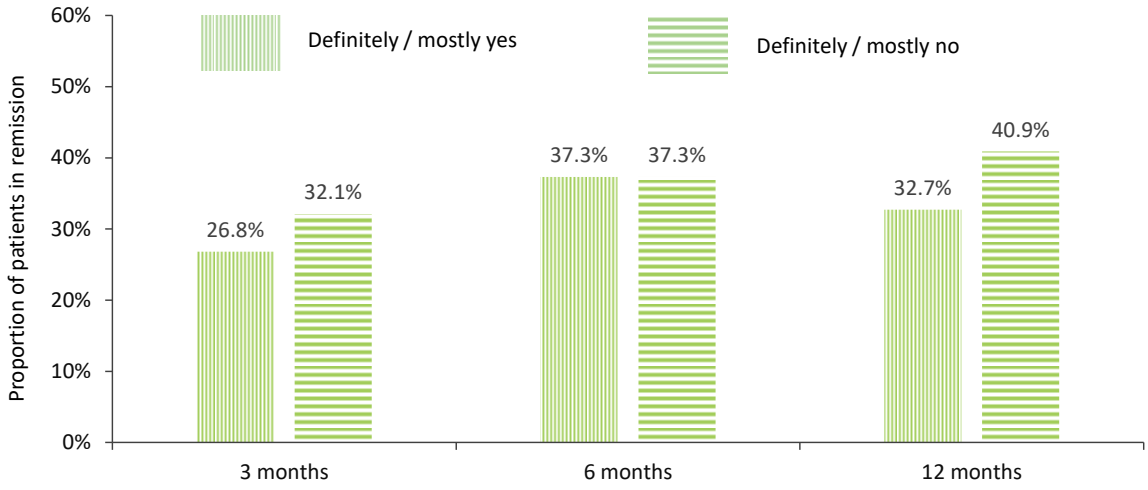
Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=479)	44 (32.4%)	136	101 (29.4%)	343	0.532
6-month visit (*n*=499)	59 (41.3%)	143	130 (36.5%)	356	0.323
12-month visit (*n*=499)	50 (35.0%)	143	143 (40.2%)	356	0.281

Figure 39 *Remission rates (ASDAS < 1.3) after 3, 6 and 12 months of TNFi treatment in axSpA patients answering yes/no to Q11A 'I seem to get sick a little easier than other people') within the primary dataset*



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=250)	33 (25.0%)	132	49 (41.5%)	118	**0.005**
6-month visit (*n*=261)	48 (33.6%)	143	48 (40.7%)	118	0.236
12-month visit (*n*=261)	50 (35.0%)	143	49 (41.5%)	118	0.277

Figure 40 *Remission rates (ASDAS < 1.3) after 3, 6 and 12 months of TNFi treatment in axSpA patients answering yes/no to Q11C ('I expect my health to get worse') within the validation dataset*



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=290)	26 (26.8%)	97	62 (32.1%)	193	0.352
6-month visit (*n*=303)	41 (37.3%)	110	72 (37.3%)	193	0.995
12-month visit (*n*=303)	36 (32.7%)	110	79 (40.9%)	193	0.157

Figure 41 *Remission rates (ASDAS < 1.) after 3, 6 and 12 months of TNFi treatment in axSpA patients answering yes/no to Q11A 'I seem to get sick a little easier than other people') within the validation dataset*

7.2.3 Drug retention

For the **RA primary dataset**, there was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse (see **Figure 42**). The estimated 1-year retention rate was 83.8% (95% CI 81.2–86.5) in the '*yes*' group and 81.9% (95% CI 78.8–85.1) in the '*no*' group. The estimated 2-year retention rate was also very similar, with 70.1% (95% CI 66.8–73.5) and 67.6% (95% CI 63.9–71.6) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 40**. There was no statistically significant difference in median follow-up time between the groups (69 and 62 months). The most frequent reason for the discontinuation was a loss of effect (*yes*: 30.1%; *no*: 31.5%) and inefficacy (*yes*: 17.7%; *no*: 23.5%).

There was found a statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that (see **Figure 43**). Patients answering *yes* had a 1.3 times higher risk of treatment discontinuation than patients answering *no*. Even after adjustment for baseline DAS28-ESR and HAQ, the risk remained 1.3 times higher in the *yes* group. The estimated 1-year retention rate was 83.2% (95% CI 80.4–86.1) in the '*yes'* group

and 86.4% (95% CI 84.0–88.8) in the '*no*' group. The estimated 2-year retention rate was 67.8% (95% CI 64.2–71.5) and 73.3% (95% CI 70.2–76.5) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 40**. The median length of follow-up in the *yes* group was 61 months, and in the *no* group, it was 68 months. The most frequent reason for discontinuation was a loss of effect and inefficacy.

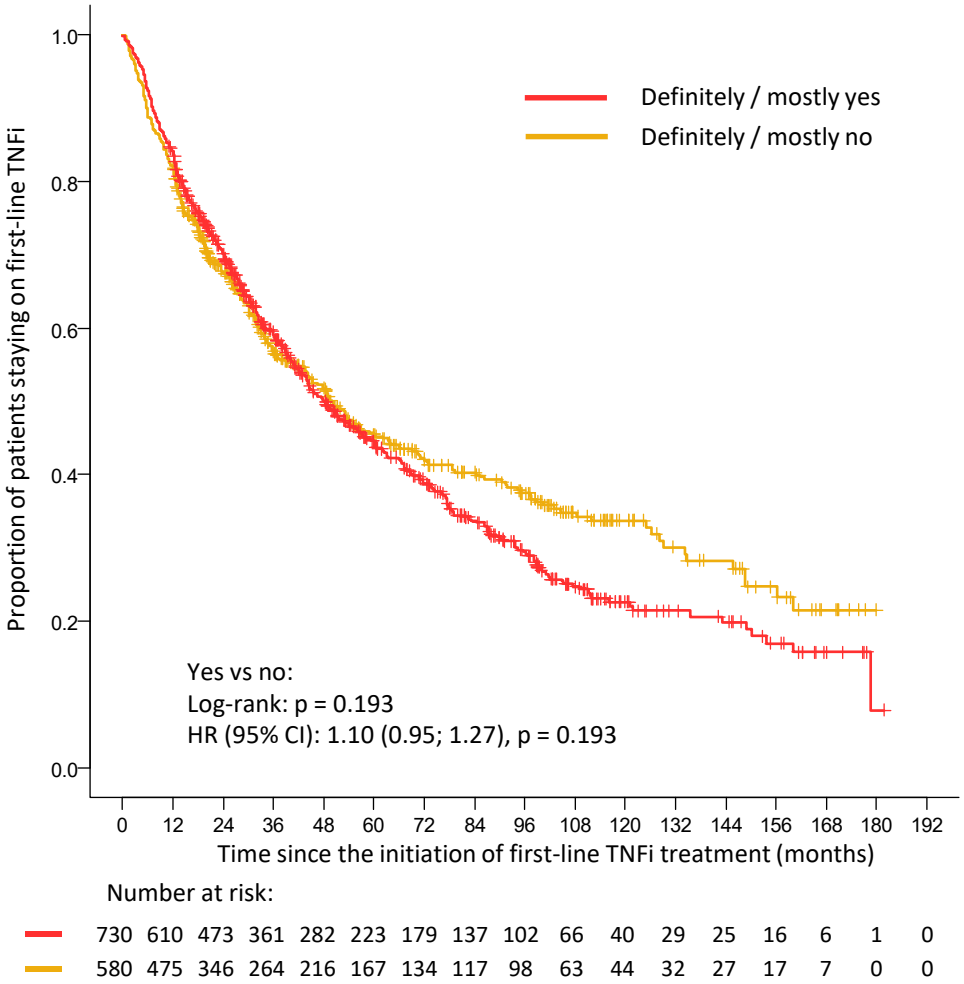


Figure 42 *Kaplan-Meier survival plot showing drug retention in RA patients (primary dataset) answering yes (red) and no (yellow) to Q11C; HR – hazard ratio; CI – confidence interval*

Table 40 *Number of TNFi discontinuation and median survival time within RA primary dataset*

Group	**Discontinuations**, *n* (%)	**Median survival time** in months (95% CI)
Q11C		
Definitely / mostly yes (*n*=730)	462 (63.3%)	48.1 (41.6; 54.6)
Definitely / mostly no (*n*=580)	327 (56.4%)	49.9 (40.6; 59.2)
Q11A		
Definitely / mostly yes (*n*=648)	417 (64.4%)	42.8 (37.4; 48.2)
Definitely / mostly no (*n*=792)	420 (53.0%)	66.0 (54.6; 77.4)

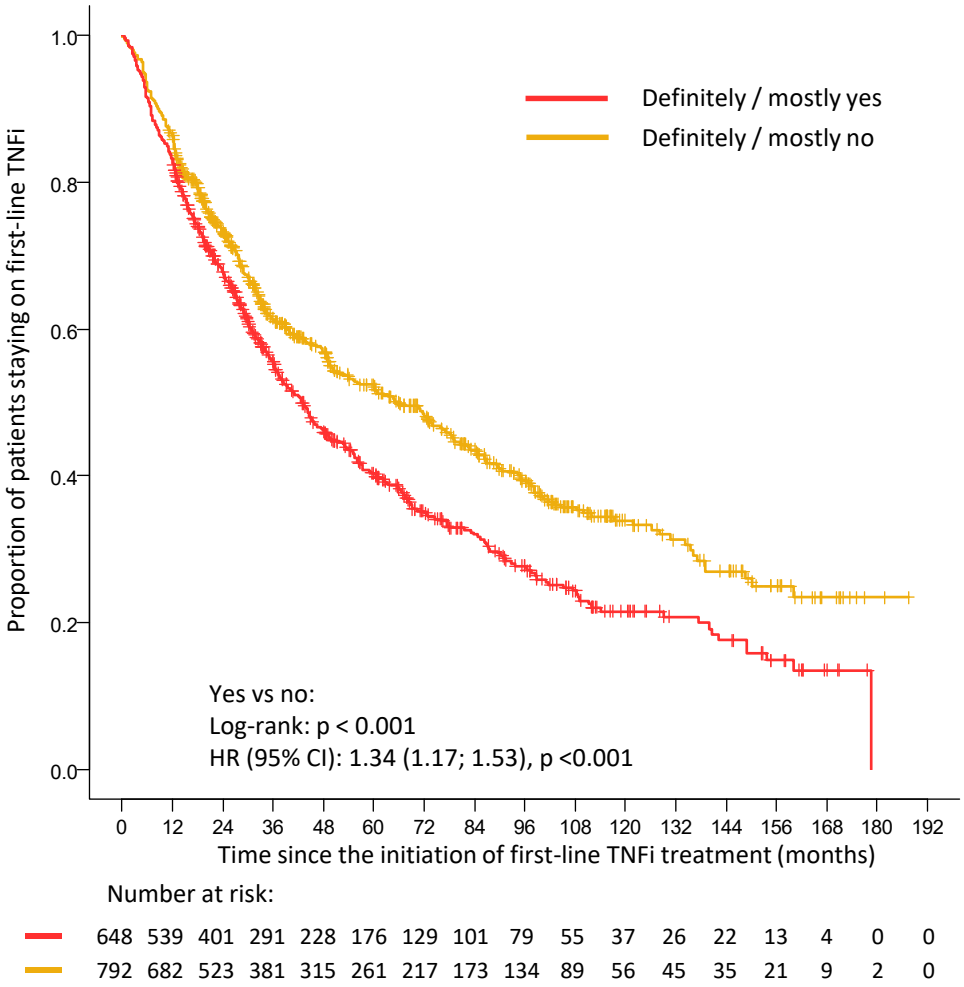


Figure 43 *Kaplan-Meier survival plot showing drug retention in RA patients (primary dataset) answering yes (red) and no (yellow) to Q11A; HR – hazard ratio; CI – confidence interval*

For the **RA validation dataset**, proportions of patients staying on the first-line TNFi based on the answers to questions Q11C and Q11A are displayed in **Figure 44** and **Figure 45**.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse (see **Figure 44**). The estimated 1-year retention rate was 74.0% (95% CI 68.6–79.9) in the '*yes*' group and 73.6% (95% CI 67.8–80.0) in the '*no*' group. The estimated 2-year retention rate was quite similar, too, with 68.0% (95% CI 62.1–74.5) and 62.2% (95% CI 55.5–69.6) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 41**. There was no statistically significant difference in median follow-up time between the groups (22.1 and 22.6 months). The most frequent reason for the discontinuation was a loss of effect (*yes*: 30.9%; *no*: 34.2%) and inefficacy (*yes*: 21.0%; *no*: 28.9%).

There was found no statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that (see **Figure 45**). The estimated 1-year retention rate was 73.6% (95% CI 68.0–79.7) in the '*yes'* group and 72.8% (95% CI 67.5–78.5) in the '*no'* group. The estimated 2-year retention rate was 61.8% (95% CI 55.5–69.0) and 60.2% (95% CI 54.1–66.9) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 41**. The median length of follow-up in the *yes* group was 22.8 months, and in the *no* group, it was 22.6 months. The most frequent reason for discontinuation was a loss of effect (31.7% in both) and inefficacy (*yes*: 24.4%; *no*: 29.7%).

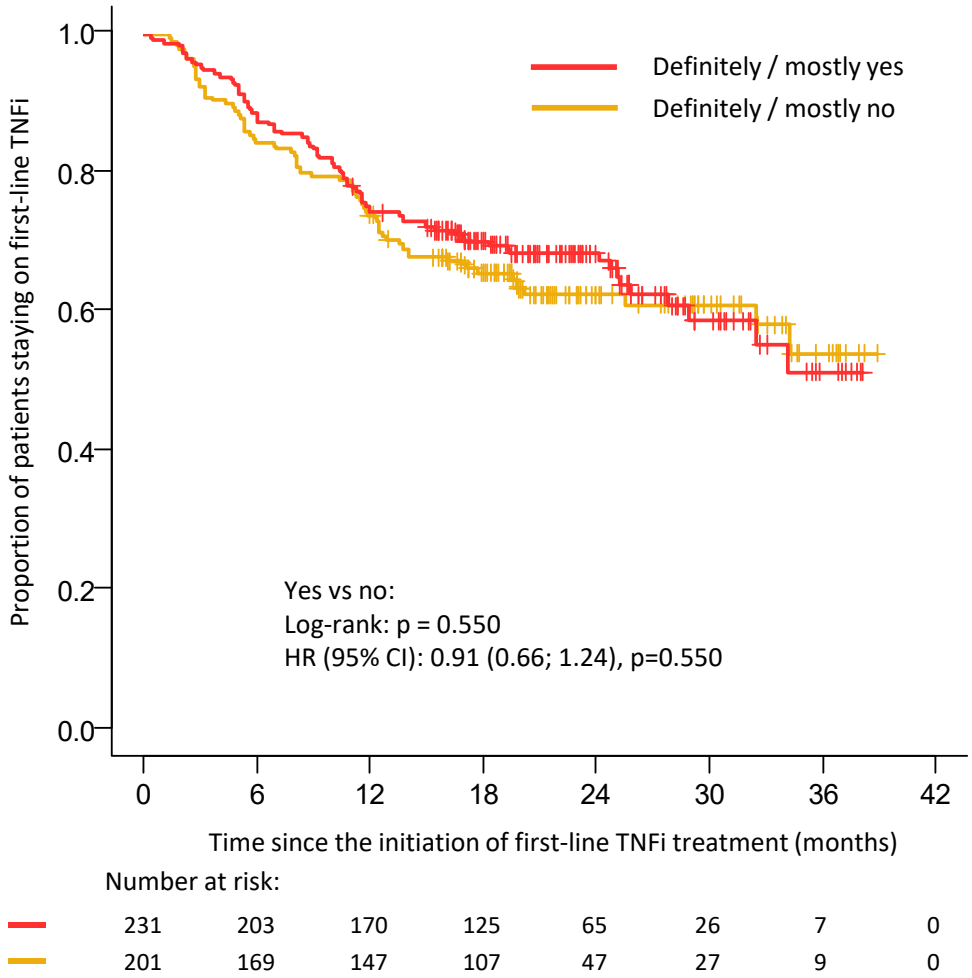


Figure 44 *Kaplan-Meier survival plot showing drug retention in RA patients (validation dataset) answering yes (red) and no (yellow) to Q11C; HR – hazard ratio; CI – confidence interval*

Table 41 *Number of TNFi discontinuation and median survival time in RA patients within the validation dataset*

Group	**Discontinuations**, *n* (%)	**Median survival time** in months (95% CI)
Q11C		
Definitely / mostly yes (*n*=231)	81 (35.1%)	Not reached
Definitely / mostly no (*n*=201)	76 (37.8%)	Not reached
Q11A		
Definitely / mostly yes (*n*=216)	82 (38.0%)	Not reached
Definitely / mostly no (*n*=254)	101 (39.8%)	34.3 (–)

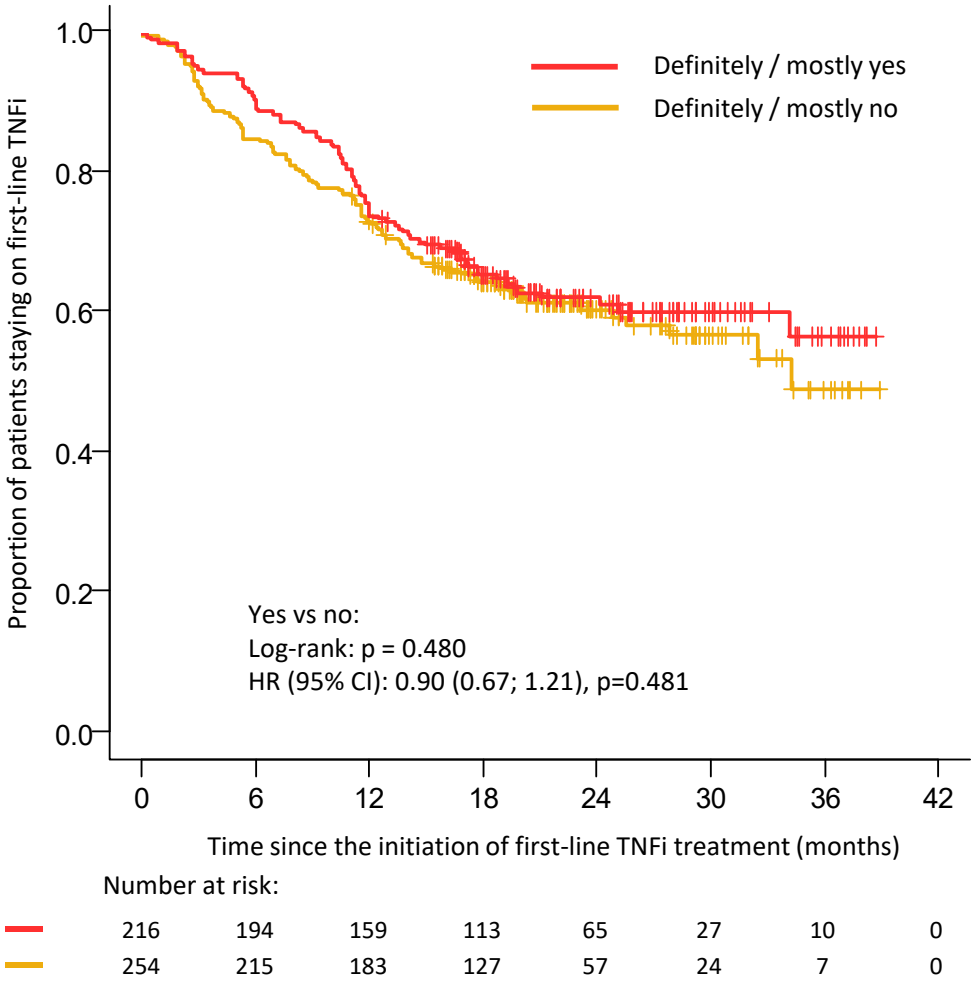


Figure 45 *Kaplan-Meier survival plot showing drug retention in RA patients (validation dataset) answering yes (red) and no (yellow) to Q11A; HR – hazard ratio; CI – confidence interval*

For the **PsA primary dataset**, proportions of patients staying on the first-line TNFi based on the answers to questions Q11C and Q11A are displayed in **Figure 46** and **Figure 47**.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse (see **Figure 46**). Though, patients answering *yes* had a tendency for more frequent treatment discontinuation. The estimated 1-year retention rate was 82.5% (95% CI 74.6–91.3) in the '*yes*' group and 89.4% (95% CI 83.3–95.8) in the '*no*' group. The estimated 2-year retention rate was also very similar, with 76.8% (95% CI 68.0–86.9) and 80.0% (95% CI 72.2–88.8) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 42**. There was not found a statistically significant difference in median follow-up time between the groups (36 and 35 months). The most frequent reason for the discontinuation was a loss of effect (*yes*: 32.1%; *no*: 36.4%) and inefficacy (*yes*: 28.6%; *no*: 18.2%).

There was not found a statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that (see **Figure 47**). The estimated 1-year retention rate was 81.7% (95% CI 73.8–90.5) in the '*yes'* group and 89.1% (95% CI 83.8–94.6) in the '*no'* group. The estimated 2-year retention rate was 73.7% (95% CI 64.5–84.0) and 78.6% (95% CI 71.6–86.3) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 42**. The median length of follow-up in the *yes* group was 36 months, and in the *no* group, it was 33 months. The most frequent reason for treatment discontinuation was a loss of effect (*yes*: 35.7%; *no*: 44.7%) and side effects / adverse events (*yes*: 17.9%; *no*: 18.4%).

Table 42 *Number of TNFi discontinuation and median survival time in PsA patients within the primary dataset*

Group	**Discontinuations**, *n* (%)	**Median survival time** in months (95% CI)
Q11C		
Definitely / mostly yes (*n*=80)	28 (35.0%)	Not reached
Definitely / mostly no (*n*=194)	22 (23.4%)	Not reached
Q11A		
Definitely / mostly yes (*n*=82)	28 (34.1%)	63.0 (–)
Definitely / mostly no (*n*=128)	38 (29.7%)	Not reached

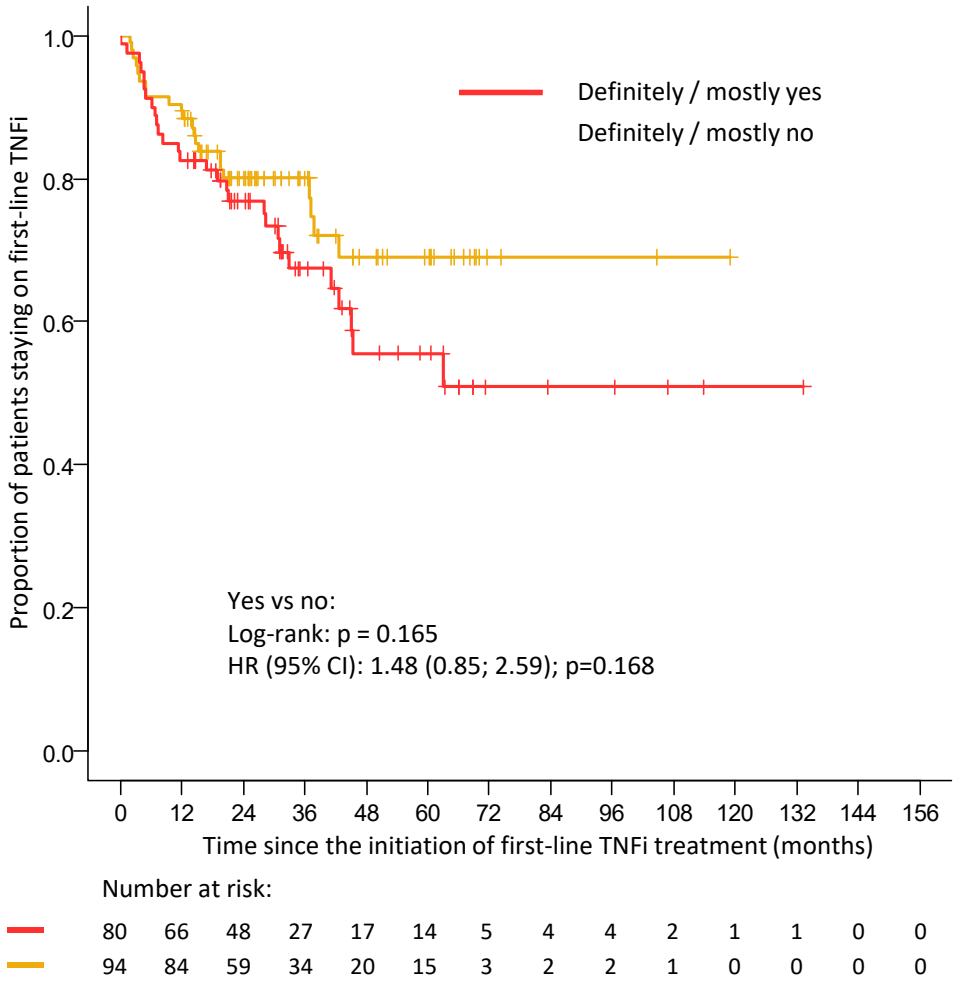


Figure 46 *Kaplan-Meier survival plot showing drug retention in PsA patients (primary dataset) answering yes (red) and no (yellow) to Q11C; HR – hazard ratio; CI – confidence interval*

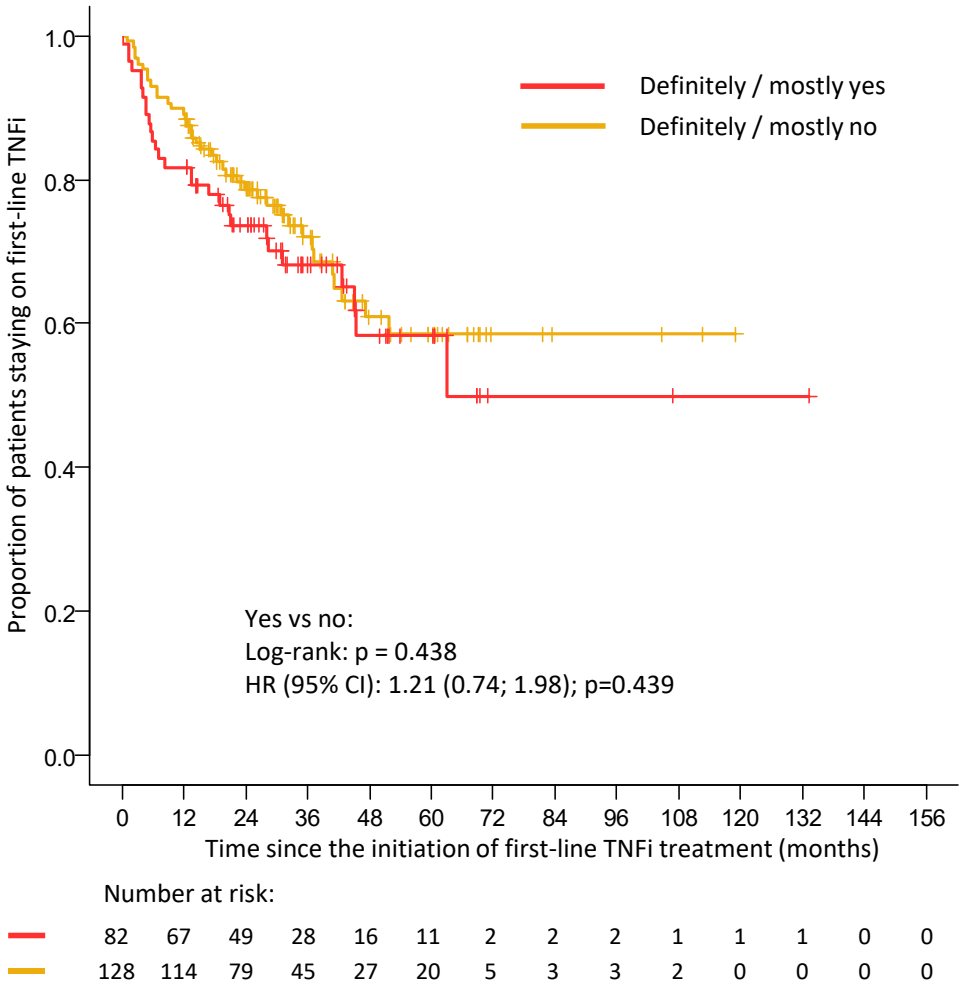


Figure 47 *Kaplan-Meier survival plot showing drug retention in PsA patients (primary dataset) answering yes (red) and no (yellow) to Q11A; HR – hazard ratio; CI – confidence interval*

For the **PsA validation dataset**, proportions of patients staying on the first-line TNFi based on the answers to questions Q11C and Q11A are displayed in **Figure 48** and **Figure 49**.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse (see **Figure 48**). The estimated 1-year retention rate was 81.8% (95% CI 72.2–92.7) in the '*yes*' group and 73.5% (95% CI 62.1–86.9) in the '*no*' group. The estimated 2-year retention rate was quite similar, too, with 59.6% (95% CI 46.9–75.7) and 67.3% (95% CI 55.4–81.8) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 43**. The median length of follow-up in the *yes* group was 24 months, and in the *no* group, it was 20 months. The most frequent reason for treatment discontinuation was a loss of effect (*yes*: 25.0%; *no*: 37.5%) and side effects / adverse events (*yes*: 15.0%; *no*: 25.0%).

There was found no statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that (see **Figure 49**). However, patients answering *yes* had a tendency for more frequent treatment discontinuation (almost 1.8× increased risk, not statistically significant). The estimated 1-year retention rate was 74.4% (95% CI 62.5–88.7) in the '*yes'* group and 83.3% (95% CI 74.4–93.3) in the '*no'* group. The estimated 2-year retention rate was 54.4% (95% CI 40.4–73.3) and 74.6% (95% CI 64.3–86.6) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 43**. The median length of follow-up in the *yes* group was 22 months, and in the *no* group, it was 21 months. The most frequent reason for treatment discontinuation was a loss of effect (*yes*: 22.2%; *no*: 33.3%) and side effects / adverse events (*yes*: 16.7%; *no*: 26.7%).

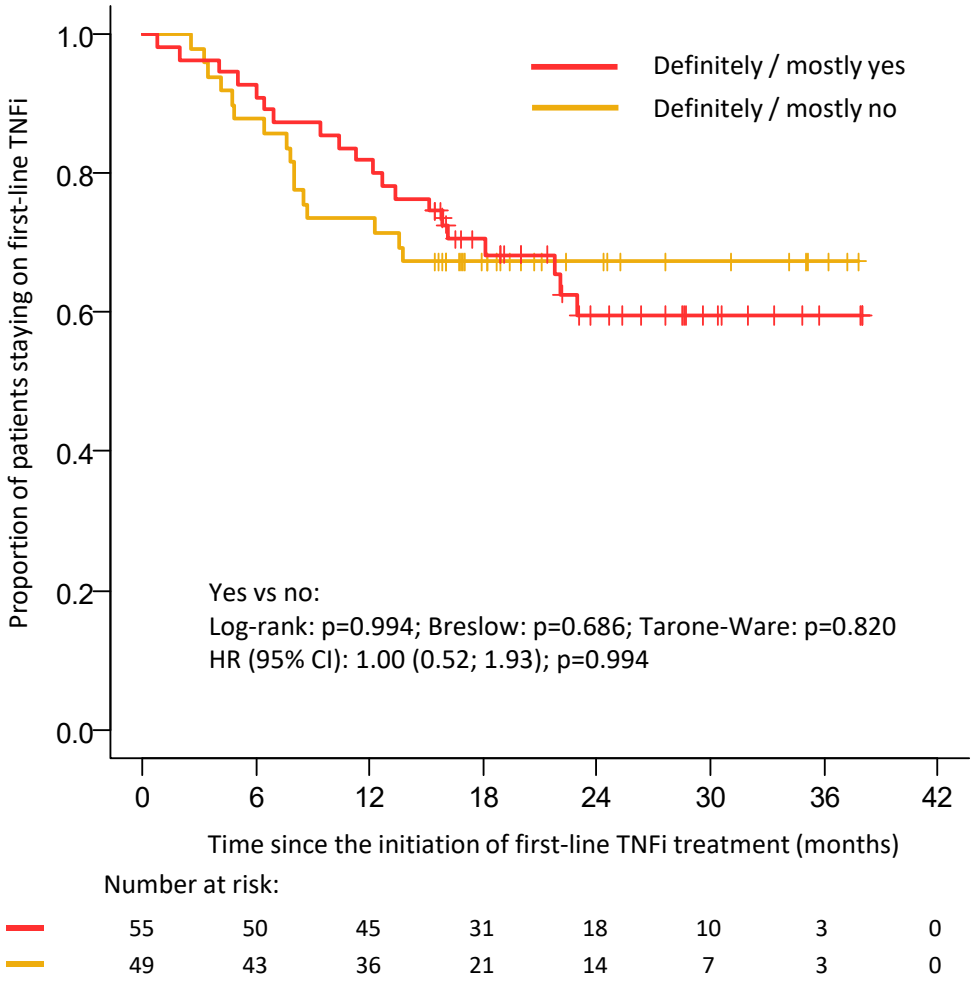


Figure 48 *Kaplan-Meier survival plot showing drug retention in PsA patients (validation dataset) answering yes (red) / no (yellow) to Q11C; HR – hazard ratio; CI – confidence interval*

Table 43 *Number of TNFi discontinuation and median survival time in PsA patients within the validation dataset*

Group	**Discontinuations**, *n* (%)	**Median survival time** in months (95% CI)
Q11C		
Definitely / mostly yes (*n*=55)	20 (36.4%)	Not reached
Definitely / mostly yes (*n*=49)	16 (32.7%)	Not reached
Q11A		
Definitely / mostly yes (*n*=43)	18 (41.9%)	Not reached
Definitely / mostly yes (*n*=60)	15 (25.0%)	Not reached

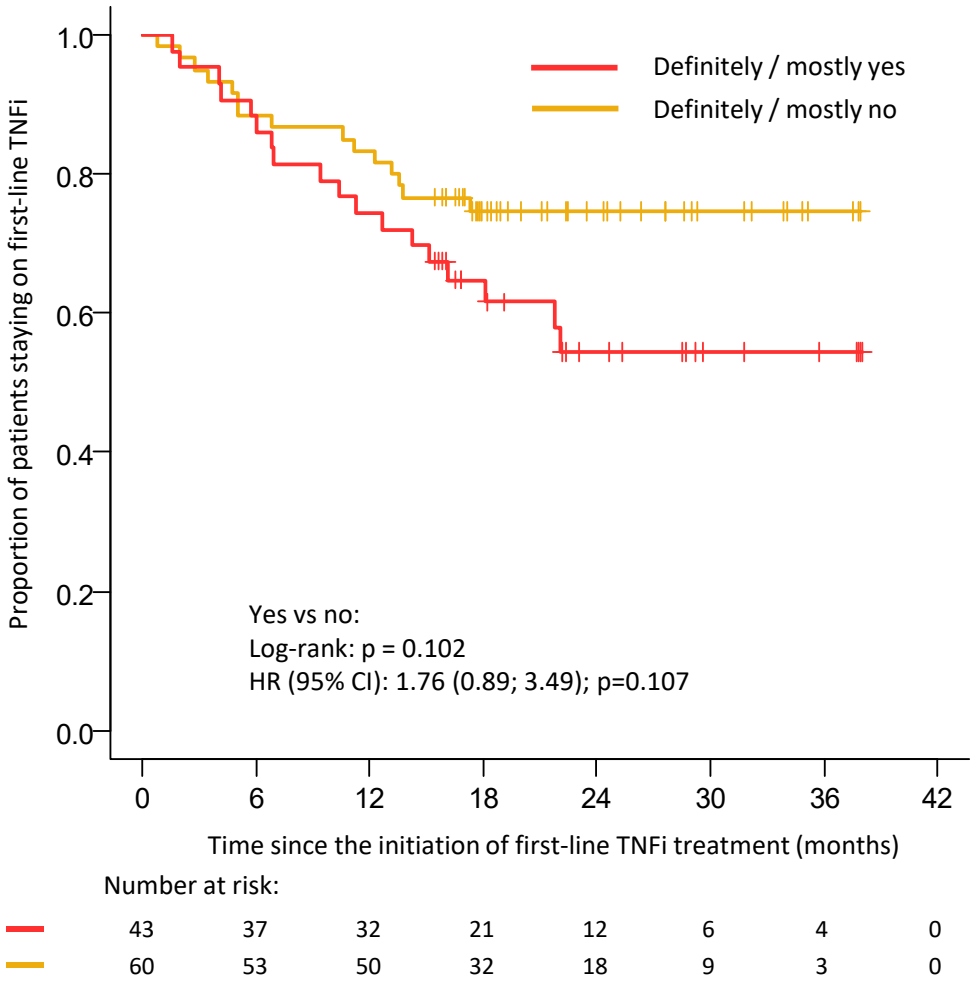


Figure 49 *Kaplan-Meier survival plot showing drug retention in PsA patients (validation dataset) answering yes (red) and no (yellow) to Q11A; HR – hazard ratio; CI – confidence interval*

For the **axSpA primary dataset**, proportions of patients staying on the first-line TNFi based on the answers to questions Q11C and Q11A are displayed in **Figure 50** and **Figure 51**.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse (see **Figure 50**). The estimated 1-year retention rate was very similar in both groups, with 84.6% (95% CI 78.9–90.7) in the '*yes*' group and 83.9% (95% CI 77.5–90.8) in the '*no*' group. The estimated 2-year retention rate was also very similar as well, with 76.1% (95% CI 69.2–83.7) and 77.0% (95% CI 69.5–85.4) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 44**. The median follow-up time was 39 months in *yes* group and 36 months in *no* group. The most frequent reason for the discontinuation was a loss of effect (*yes*: 38.8%; *no*: 35.6%) and side effects / adverse events (*yes*: 16.4%; *no*: 24.4%).

There was found a statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that (see **Figure 51**). Patients answering *yes* had almost 1.6 times higher risk of treatment discontinuation than patients answering *no*. Even after adjustment for baseline ASDAS and HAQ, the risk remained statistically significantly higher in the *yes* group. The estimated 1-year retention rate was 86.7% (95% CI 81.3–92.5) in the '*yes'* group and 91.3% (95% CI 88.4–94.3) in the '*no'* group. The estimated 2-year retention rate was 79.6% (95% CI 73.1–86.7) and 86.0% (95% CI 82.4–89.8) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 44**. The median length of follow-up in the *yes* group was 37 months in both groups. The most frequent reason for treatment discontinuation was a loss of effect (*yes*: 35.6%; *no*: 36.9%), side effects (*yes*: 15.6%; *no*: 21.4%) and inefficacy (*yes*: 22.2%; *no*: 7.1%)

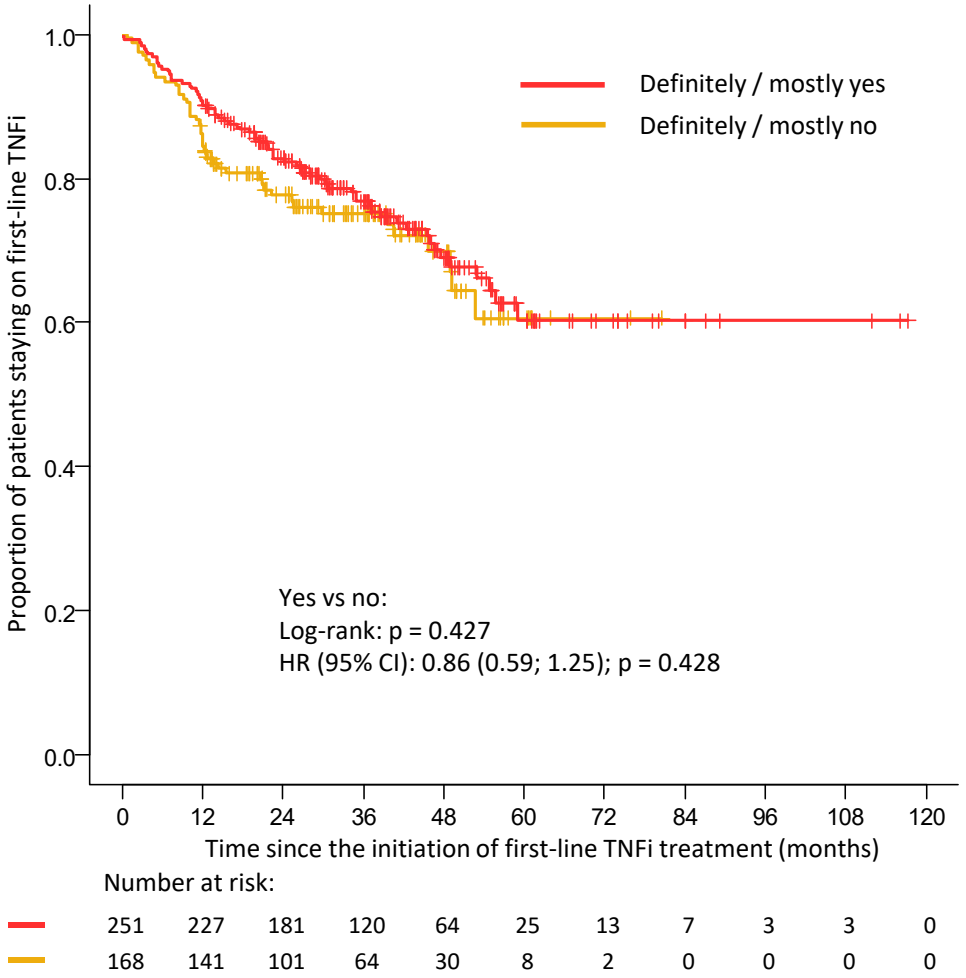


Figure 50 *Kaplan-Meier survival plot showing drug retention in axSpA patients (primary dataset) answering yes (red) and no (yellow) to Q11C; HR – hazard ratio; CI – confidence interval*

Table 44 *Number of TNFi discontinuation and median survival time in axSpA patients within the primary dataset*

Group	**Discontinuations**, *n* (%)	**Median survival time** in months (95% CI)
Q11C		
Definitely / mostly yes (*n*=251)	67 (26.7%)	Not reached
Definitely / mostly yes (*n*=168)	45 (26.8%)	Not reached
Q11A		
Definitely / mostly yes (*n*=143)	45 (31.5%)	Not reached
Definitely / mostly yes (*n*=356)	84 (23.6%)	Not reached

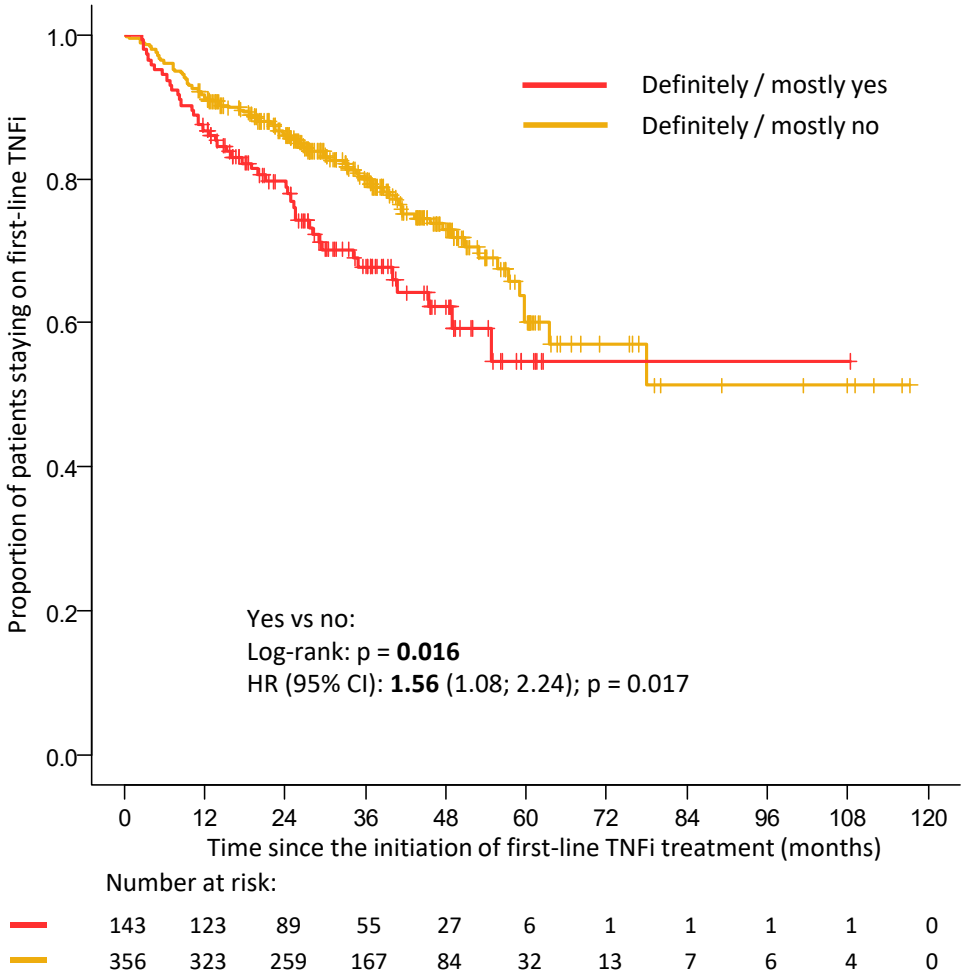


Figure 51 *Kaplan-Meier survival plot showing drug retention in axSpA patients (primary dataset) answering yes (red) / no (yellow) to Q11A; HR – hazard ratio; CI – confidence interval*

For the **axSpA validation dataset**, proportions of patients staying on the first-line TNFi based on the answers to questions Q11C and Q11A are displayed in **Figure 52** and **Figure 53**.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse (see **Figure 52**). The estimated 1-year retention rate was 84.6% (95% CI 78.9–90.7) in the '*yes*' group and 83.9% (95% CI 77.5–90.8) in the '*no*' group. The estimated 2-year retention rate was quite similar, too, with 76.1% (95% CI 69.2–83.7) and 77.0% (95% CI 69.5–85.4) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 45**. There was no statistically significant difference in median follow-up time between the groups (23.3 and 22.7 months). The most frequent reason for the discontinuation was a loss of effect (*yes*: 28.2%; *no*: 38.7%), inefficacy (*yes*: 25.6%; *no*: 12.9%) and pharmacoeconomic reasons (*yes*: 15.4%; no: 16.1%).

There was no statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that (see **Figure 53**). The estimated 1-year retention rate was 83.6% (95% CI 77.0–90.8) in the '*yes'* group and 81.9% (95% CI 76.6–87.5) in the '*no'* group. The estimated 2-year retention rate was 72.9% (95% CI 64.9–81.9) and 75.3% (95% CI 69.2–82.0) in patients answering *yes* and *no*. The numbers of discontinuations and median survival times are presented in **Table 45**. The median length of follow-up in the *yes* group was 24.9 months, and in the *no* group, it was 23.9 months. The most frequent reason for the discontinuation was a loss of effect (*yes*: 31.4%; *no*: 29.8%), pharmacoeconomic reasons (*yes*: 14.3%; *no*: 27.7%) and inefficacy (*yes*: 25.7%; no: 10.6%).

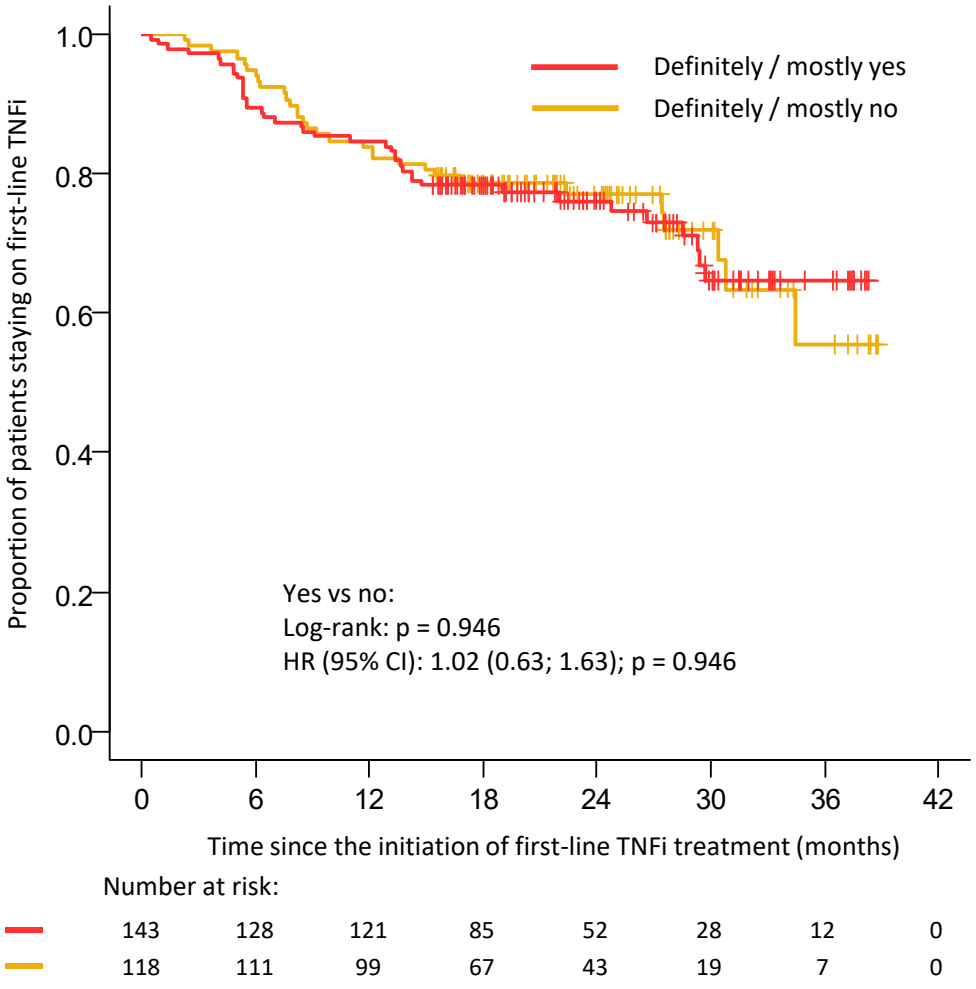


Figure 52 *Kaplan-Meier survival plot showing drug retention in axSpA patients (validation dataset) answering yes (red) and no (yellow) to Q11C; HR – hazard ratio; CI – confidence interval*

Table 45 *Number of TNFi discontinuation and median survival time in axSpA patients within the validation dataset*

Group	**Discontinuations**, *n* (%)	**Median survival time** in months (95% CI)
Q11C		
Definitely / mostly yes (*n*=143)	39 (27.3%)	Not reached
Definitely / mostly yes (*n*=118)	31 (26.3%)	Not reached
Q11A		
Definitely / mostly yes (*n*=110)	35 (31.8%)	Not reached
Definitely / mostly yes (*n*=193)	47 (24.4%)	Not reached

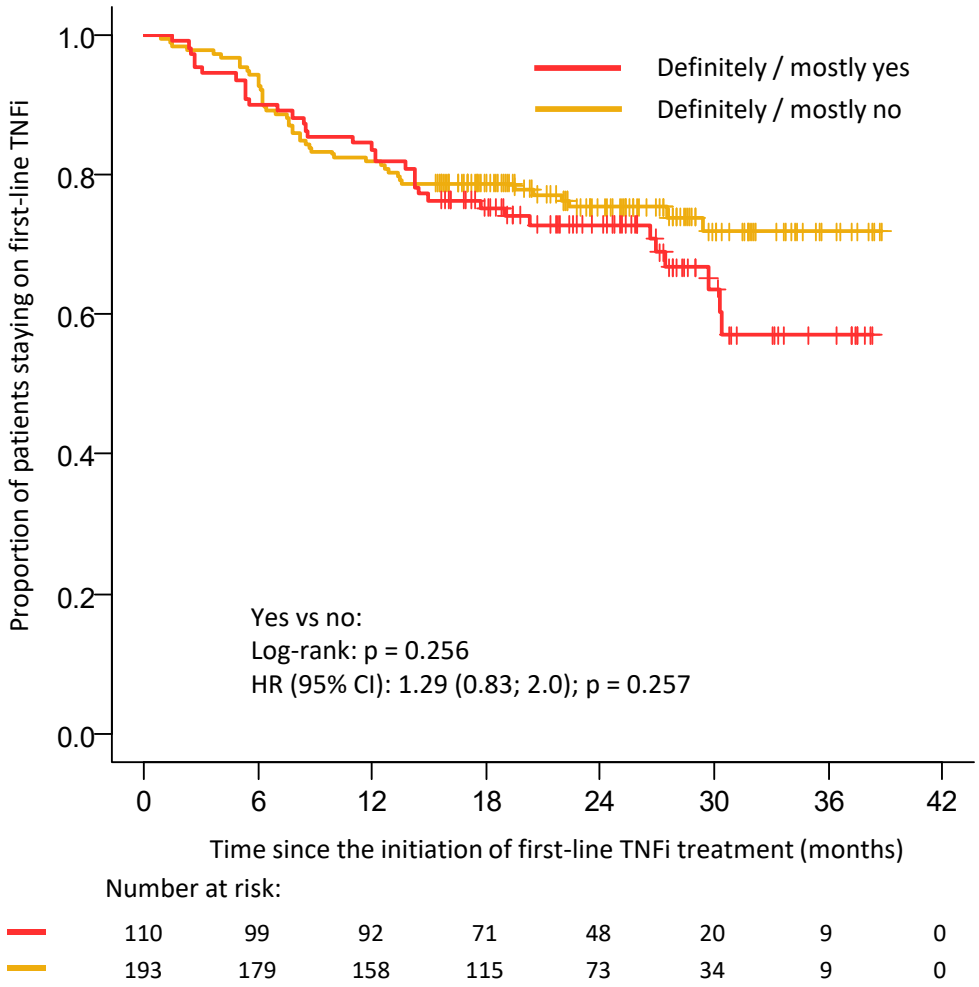


Figure 53 *Kaplan-Meier survival plot showing drug retention in axSpA patients (validation dataset) answering yes (red) and no (yellow) to Q11A; HR – hazard ratio; CI – confidence interval*

7.2.4 Propensity score-matched analysis

In the next step (as part of the validation), we repeated the whole analysis on propensity score-matched datasets. We employed propensity score matching to reduce selection bias by adjusting for potential confounding factors at baseline.

Rheumatoid arthritis

Within the **primary dataset**, for patients‘ groups based on answers to **Q11C**, the set of covariates selected for the PS model included gender, disease duration, baseline DAS28-ESR, number of previous csDMARDs, GCs in concomitant therapy, year of administration and drug type. Out of 730 patients answering *yes* to the Q11C question, 721 patients had all values of covariates available. Out of 580 patients answering *no* to the question, 574 had all values of covariates available. Together 550 from the group *yes* and 550 from the group *no* were matched based on the computed PS. Patients did not statistically significantly differ anymore in disease duration and number of previous csDMARDs. They only differed in parameters related to the quality of life (*yes* vs *no*: median HAQ 1.6 vs 1.5; median EQ-5D 0.1 vs 0.2; median MDGA 60 vs 69). We did not include these parameters in the propensity score model as they correlated with the SF-36 questionnaire (and thus with our studied groups). For patients answering *yes*/*no* to **Q11A**, the covariates selected for the PS model included gender, disease duration, baseline DAS28-ES, number of csDMARDs in previous therapy, csDMARDs and GCs in concomitant therapy, year of administration and drug type. Out of 648 patients answering *yes*, 641 patients had all values of covariates available; out of 792 patients answering *no*, 778 had all values of covariates available. Together 574 from the group answering *yes* and 574 from the group answering *no* were matched based on the computed PS. Patients did not statistically significantly differ anymore in gender, disease activity, previous and concomitant therapy, year of administration or drug type. They only differed in parameters related to the quality of life (*yes* vs *no*: median HAQ 1.6 vs 1.5; median EQ-5D 0.1 vs 0.2; median MDGA 60 vs 68).

Patients who expected their health to get worse at the treatment initiation achieved remission more often after three months (23.1% vs 19.7%; p=0.176), six months (32.5% vs 23.0%; p<0.001) and twelve months (36.6% vs 29.7%; p=0.015) than patients who did not expect their health to get worse. Similarly, remission was achieved more often after three months (24.2% vs 17.6%; p=0.007), six months (31.4% vs 24.2%; p=0.007) and twelve months (36.3% vs 28.5%; p=0.005) in patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. Patients answering *yes* to Q11C had 1.6 (1.4) × higher odds for remission at the 6-months (12-month) visit than patients

answering *no*. Patients answering *yes* to Q11A had 1.4 × higher odds for remission at both 6- and 12-month visits than patients answering *no*.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse. The estimated 1-year retention rate was 83.8% (95% CI 80.8–87.0) and 82.2% (95% CI 79.0–85.4) in patients answering *yes* and *no*. The estimated 2-year retention rate was 71.5% (95% CI 67.8–75.4) and 67.6% (95% CI 63.8–71.7) in patients answering *yes* and *no*. The median survival was 52.9 months in patients answering *yes* and 50.4 months in patients answering no. The frequency of treatment discontinuation was 59% and 57% in the studied groups. The most frequent reason for the discontinuation was a loss of effect (yes: 31.9%; no: 31.4%) and inefficacy (yes: 16.3%; no: 23.4%).

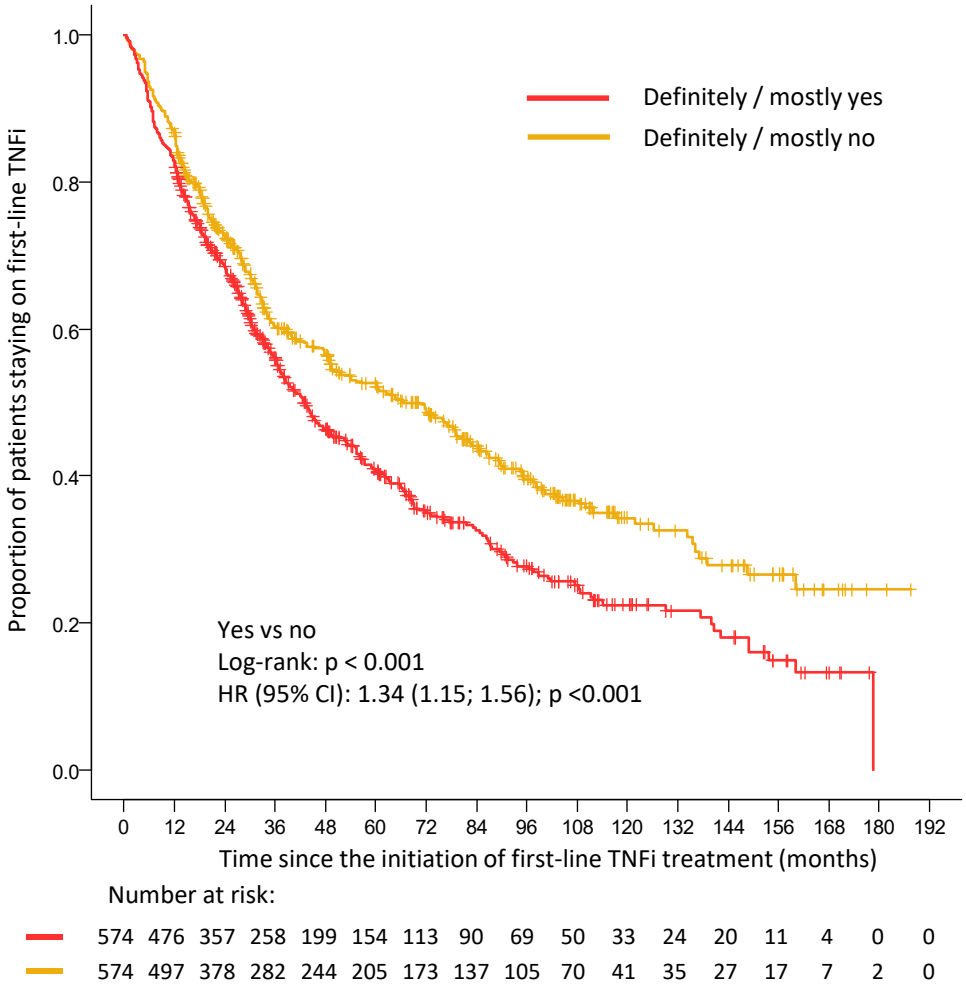


Figure 54 *Kaplan-Meier survival plot showing drug retention in RA patients (primary dataset – propensity score-matched data) answering yes (red) and no (yellow) to Q11A*

There was a statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment

initiation than patients who did not think that (see **Figure 54**). The estimated 1-year retention rate was 82.9% (95% CI 79.9–96.1) in the '*yes'* group and 86.8% (95% CI 84.0–89.6) in the '*no'* group. The estimated 2-year retention rate was 68.4% (95% CI 64.7–72.4) and 72.6% (95% CI 69.0–76.4) in patients answering *yes* and *no*. The median survival was 42.8 (36.0–49.6) months in patients answering *yes* and 66.4 (52.7–80.2) months in patients answering *no*. The frequency of treatment discontinuation was 64% and 54% in the studied groups. The most frequent reason for treatment discontinuation was a loss of effect (*yes*: 31.5%; *no*: 33.2%) and inefficacy (*yes*: 21.1%; *no*: 24.5%).

Within the **RA validation dataset**, for patients' groups based on answers to **Q11C**, the set of covariates selected for the PS model included gender, age at treatment initiation, baseline DAS28-ESR, RF+, GCs and MTX in concomitant therapy, year of administration and drug type. All 231 patients answering *yes* to the Q11C question had available values of these covariates. Out of 201 patients answering *no* to the question, 200 had all values of covariates available. Both groups included 169 patients after the matching. Patients did not statistically significantly differ anymore in disease duration, disease activity and frequency of biosimilars. They only differed in EQ-5D (*yes* vs *no*: median 0.1 vs 0.2). We did not include this parameter in the propensity score model as it correlated with the SF-36 questionnaire (and thus with our studied groups). For patients answering *yes*/*no* to **Q11A**, the covariates selected for the PS model were the same as for Q11C. Out of 216 patients answering *yes*, 214 patients had all values of covariates available; out of 254 patients answering *no*, 252 had all values of covariates available. Both groups included 185 patients after the PS matching. Patients did not statistically significantly differ anymore in disease activity, previous therapy or frequency of biosimilars. They only differed in EQ-5D (*yes* vs *no*: median 0.1 vs 0.2).

Patients who expected their health to get worse at the treatment initiation achieved remission more often after three months (34.2% vs 25.6%), six months (40.5% vs 35.7%) and twelve months (46.7% vs 36.7%) than patients who did not expect their health to get worse. However, the results were not statistically significant. Similarly, remission was achieved more often after three months (31.0% vs 22.3%), six months (36.1% vs 30.8%) and twelve months (47.8% vs 35.0%) in patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. The difference was statistically significant only at the 12-month visit. Patients answering *yes* to Q11C had 1.5 × higher odds for remission at the 12-month visit than patients answering *no,* but the result was only close to statistical signficance (p=0.066). Patients answering *yes* to Q11A had 1.7 × higher odds for remission at the 12-month visit than patients answering *no* (p=0.013).

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse. The estimated 1-year retention rate was 72.2% in both groups. The estimated 2-year retention rate was 68.1% (95% CI 61.3–75.6) and 60.1% (95% CI 52.7–68.6) in patients answering *yes* and *no*. The median survival was 34 months in both groups, and patients answering *yes* and *no* discontinued the treatment in 36% and 40% of cases. The most frequent reason for the discontinuation was a loss of effect (*yes*: 37.7%; *no*: 34.3%) and inefficacy (*yes*: 18.0%; *no*: 28.4%).

There was no statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation and patients who did not think that. The estimated 1-year retention rate was 73.0% (95% CI 66.8–79.7) in the '*yes'* group and 69.7% (95% CI 63.4–76.7) in the '*no'* group. The estimated 2-year retention rate was 59.5% (95% CI 52.6–67.3) and 57.7% (95% CI 50.7–65.8) in patients answering *yes* and *no*. The median survival was reached in patients answering *no* with 32.5 months. Patients answering *yes* and *no* discontinued the treatment in 41% and 43% of cases. The most frequent reason for treatment discontinuation was a loss of effect (*yes*: 33.3%; *no*: 32.9%) and inefficacy (*yes*: 24.0%; *no*: 31.6%).

Psoriatic arthritis

Within the **primary dataset**, for patients' groups based on answers to **Q11C**, the set of covariates selected for the PS model included gender, disease duration, age at diagnosis, baseline DAS28-ESR, nail involvement, PGA of psoriasis, csDMARDs in concomitant therapy, year of administration and drug type. Out of 80 patients answering *yes* to the Q11C question, 77 patients had all values of covariates available. Out of 94 patients answering *no* to the question, 90 had all values of covariates available. Together 47 from the group *yes* and 47 from the group *no* were matched based on the computed PS. Patients did not statistically significantly differ anymore in disease duration, age, ESR, PGA of psoriasis and number of previous. They only differed in EQ-5D (*yes* vs *no*: median 0.1 vs 0.6). However, the number of patients in each cohort was relatively small (47 in each). We did not include this parameter in the PS model as it correlated with the SF-36 questionnaire (and thus with our studied groups). For patients answering *yes*/*no* to **Q11A**, the covariates selected for the PS model included gender, disease duration, age at diagnosis, baseline DAS28-ESR, MDGA, csDMARDs and GCs in concomitant therapy, year of administration and drug type. Out of 82 patients answering *yes*, 81 patients had all values of covariates available; out of 128 patients answering *no*, 125 had all values of covariates available. Together 58 from the group answering *yes,* and 58 from the group answering *no* were matched

based on the computed PS. Patients did not statistically significantly differ anymore in gender, age, disease duration, ESR, MDGA and dactylitis. They only differed in EQ-5D (*yes* vs *no*: median 0.1 vs 0.2) and the number of previous csDMARDs (p=0.041).

There was no statistically significant difference in remission achievements during the first year between patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse. At the 12-month visit, remission was reached in a higher proportion of patients answering *yes* than *no*, but the difference was not statistically significant (37.8% vs 30.2%; p=0.455). Similarly, there was no statistically significant difference in remission achievements during the first year in patients who seemed to get sick a little easier than other people at the treatment initiation and patients who did not think that. At the 12-month visit, remission was reached in a bigger proportion of patients answering *no* than *yes*, but the difference was not statistically significant (*yes* vs *no*: 25.0% vs 32.1%; p=0.413).

There was a statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse (see **Figure 55**). The estimated 1-year retention rate was 76.6% (95% CI 65.4–89.7) and 95.7% (95% CI 90.1–100.0) in patients answering *yes* and *no*. The estimated 2-year retention rate was 68.8% (95% CI 56.3–84.0) and 86.2% (95% CI 76.4–97.1) in patients answering *yes* and *no*. The median survival was 45.5 months in patients answering *yes,* and in patients answering *no*, it was not reached. The frequency of treatment discontinuation was 43% and 19% in the studied groups. Patients answering *yes* to Q11C had 2.9 × higher risk of treatment discontinuation than patients answering *no* (p=0.006). The most frequent reason for the discontinuation was a loss of effect (yes: 35.0%; no: 33.3%) and side effects (yes: 20.0%; no: 22.2%).

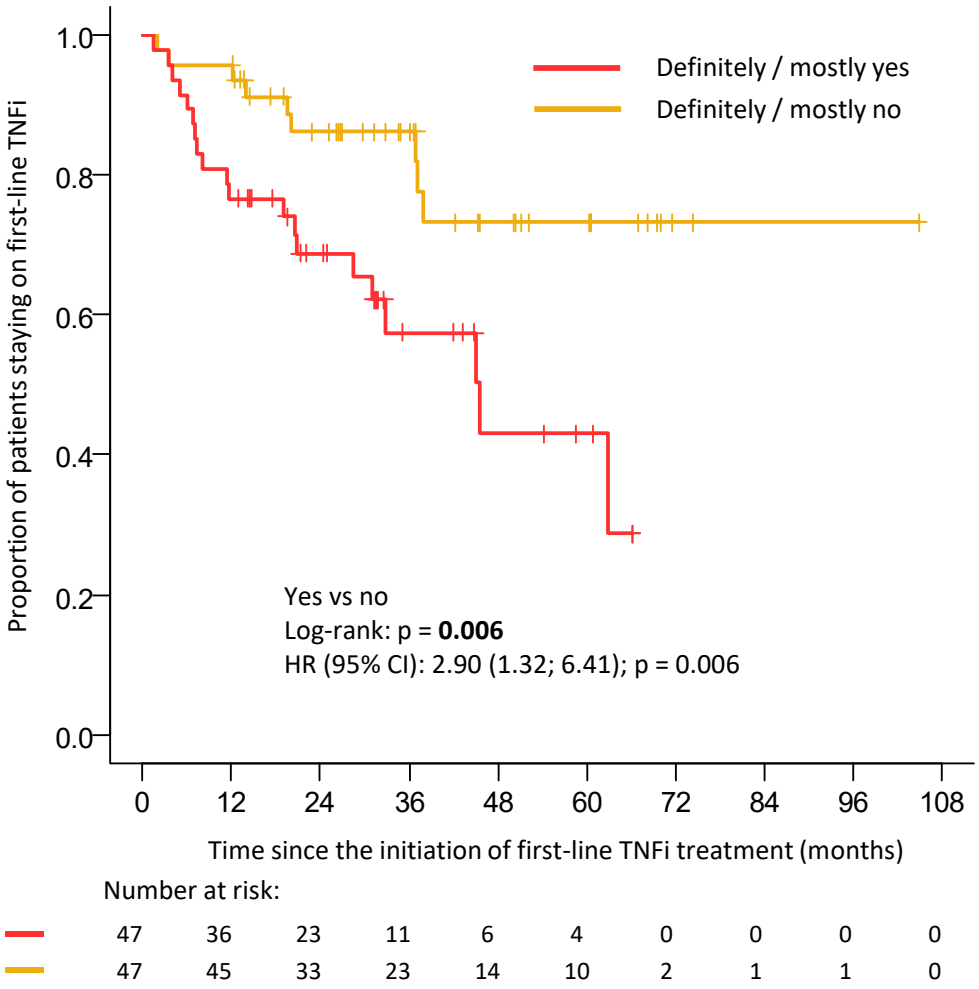


Figure 55 *Kaplan-Meier survival plot showing drug retention in PsA patients (primary dataset – propensity score-matched data) answering yes (red) and no (yellow) to Q11C*

There was no statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation and patients who did not think that. The estimated 1-year retention rate was 82.8% (95% CI 73.6–93.1) in the '*yes'* group and 91.4% (95% CI 84.4–98.9) in the '*no'* group. The estimated 2-year retention rate was 75.2% (95% CI 64.7–87.4) and 79.9% (95% CI 70.0–91.4) in patients answering *yes* and *no*. The median survival was not reached in either of the groups. The frequency of treatment discontinuation was 26% and 28% in the studied groups. The most frequent reason for treatment discontinuation was a loss of effect (yes: 33.3%; no: 37.5%) and inefficacy (yes: 13.3%; no: 25.0%).

Within the **PsA validation dataset**, for patients' groups based on answers to **Q11C**, the set of covariates selected for the PS model included gender, disease duration, baseline DAPSA, nail involvement, MDGA, GCs and csDMARDs in concomitant therapy, year of administration and drug type. All 55 patients answering *yes* to the Q11C question had available values of these

covariates. Out of 49 patients answering *no* to the question, 47 had all values of covariates available. Both groups included only 30 patients after the matching. Patients did not statistically significantly differ anymore in any parameter. For patients answering *yes*/*no* to **Q11A**, the covariates selected for the PS model were the same as for Q11C. All 43 patients answering *yes* had all values of covariates available; out of 60 patients answering *no*, 59 had all values of covariates available. Both groups included only 24 patients after the PS matching. Patients did not statistically significantly differ anymore in EQ-5D, PGA of psoriasis, concomitant GCs and frequency of biosimilars. However, the groups statistically significantly differed in age at diagnosis (*yes* vs *no*: median 40 vs 46 years), age at the start of 1st line (*yes* vs *no*: median 46 vs 56 years) and ESR. Unfortunately, the PS model was not very successful. It was probably due to the small number of patients not allowing to find enough matching patients.

Patients who expected their health to get worse at the treatment initiation achieved remission less often after three months (8.7% vs 27.3%), six months (21.4% vs 29.2%) and twelve months (27.6% vs 37.9%) than patients who did not expect their health to get worse. However, the results were not statistically significant. Similarly, remission was achieved less often after six months (23.8% vs 28.6%) and twelve months (29.2% vs 33.3%) in patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. None of the results was statistically significant, though.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse. The estimated 1-year retention rate was 76.7% (95% CI 62.9–93.4) and 80.0% (95% CI 66.9–95.7) in patients answering *yes* and *no*. The estimated 2-year retention rate was 62.9% (95% CI 46.4–85.2) and 76.7% (95% CI 62.9–93.4) in patients answering *yes* and *no*. The median survival was not reached in any of the groups. Treatment was discontinued in 33% and 23% of cases in patients answering *yes* and *no* to Q11C. The most frequent reason for the discontinuation was an inefficacy (*yes*: 40.0%; *no*: 14.3%) and loss of effect (*yes*: 30.0%; *no*: 28.6%).

There was no statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation and patients who did not think that (p=0.069). However, patients answering *yes* had a higher tendency to discontinue the treatment. The estimated 1-year retention rate was 66.7% (95% CI 50.2–88.5) in the '*yes'* group and 87.5% (95% CI 75.2–100.0) in the '*no'* group. The estimated 2-year retention rate was 56.8% (95% CI 39.6–81.6) and 83.3% (95% CI 67.9–99.7) in patients answering *yes* and *no*. The median survival was not reached. Patients answering *yes*

and *no* discontinued the treatment in 42% and 17% of cases. The most frequent reason for treatment discontinuation was an inefficacy (*yes*: 30.0%; *no*: 25.0%).

Axial spondyloarthritis

Within the **primary dataset**, for patients‘ groups based on answers to **Q11C**, the set of covariates selected for the PS model included gender, age at treatment initiation, disease duration, baseline BASDAI, NSAIDs in concomitant therapy, year of administration and drug type. Out of 251 patients answering *yes* to the Q11C question, 248 patients had all values of covariates available. Out of 168 patients answering *no* to the question, 165 had all values of covariates available. Together 153 from the group *yes* and 153 from the group *no* were matched based on the computed PS. Patients did not statistically significantly differ anymore in age, disease duration baseline BASDAI, BASFI, HAQ, EQ-5D, NSAIDs in concomitant therapy and year of administration. They only differed in frequency of GC in the previous history (*yes*: 25%; *no*: 36%). For patients answering *yes*/*no* to **Q11A**, the covariates selected for the PS model included gender, disease duration, baseline BASDAI, csDMARDs and GCs in concomitant therapy, uveitis, sacroiliitis grading, HLA-B27, year of administration and drug type. Out of 143 patients answering *yes*, 139 patients had all values of covariates available; out of 356 patients answering *no*, 339 had all values of covariates available. Together 126 from the group answering *yes* and 126 from the group answering *no* were matched based on the computed PS. Patients did not statistically significantly differ anymore in gender, disease duration, disease activity, quality of life, uveitis, colitis, HLA-B27 presence, sacroiliitis grading, previous and concomitant therapy or drug type. They only differed in EQ-5D (*yes* vs *no*: median 0.1 vs 0.2). We did not include this parameter in the propensity score model as it correlates with the SF-36 questionnaire (and thus with our studied groups).

Patients who expected their health to get worse at the treatment initiation achieved remission almost equally as patients who did not expect their health to get worse. The remission rates were 33.3% vs 34.7% at the 3-month visit, 40.5% vs 42.5% a 6-month visit and 41.8% vs 41.8% at 12-month visit for patients answering *yes* vs *no*. Similarly, there was not found a significant difference in remission achievements after three months (33.3% vs 31.1%), six months (41.3% vs 38.9) and twelve months (36.5% vs 41.3%) in patients who seemed to get sick a little easier than other people at the treatment initiation and patients who did not.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse. The estimated 1-year retention rate was

91.5% (95% CI 87.2–96.0) and 85.6% (95% CI 80.2–91.4) in patients answering *yes* and *no*. The estimated 2-year retention rate was 84.4% (95% CI 78.8–90.5) and 78.8% (95% CI 72.4–85.8) in patients answering *yes* and *no*. The median survival was not reached in either of the groups. The frequency of treatment discontinuation was 29% and 26% in the studied groups. The most frequent reason for the discontinuation was a loss of effect (*yes*: 43.2%; *no*: 32.5%) and side effects / adverse events (*yes*: 15.9%; *no*: 27.5%).

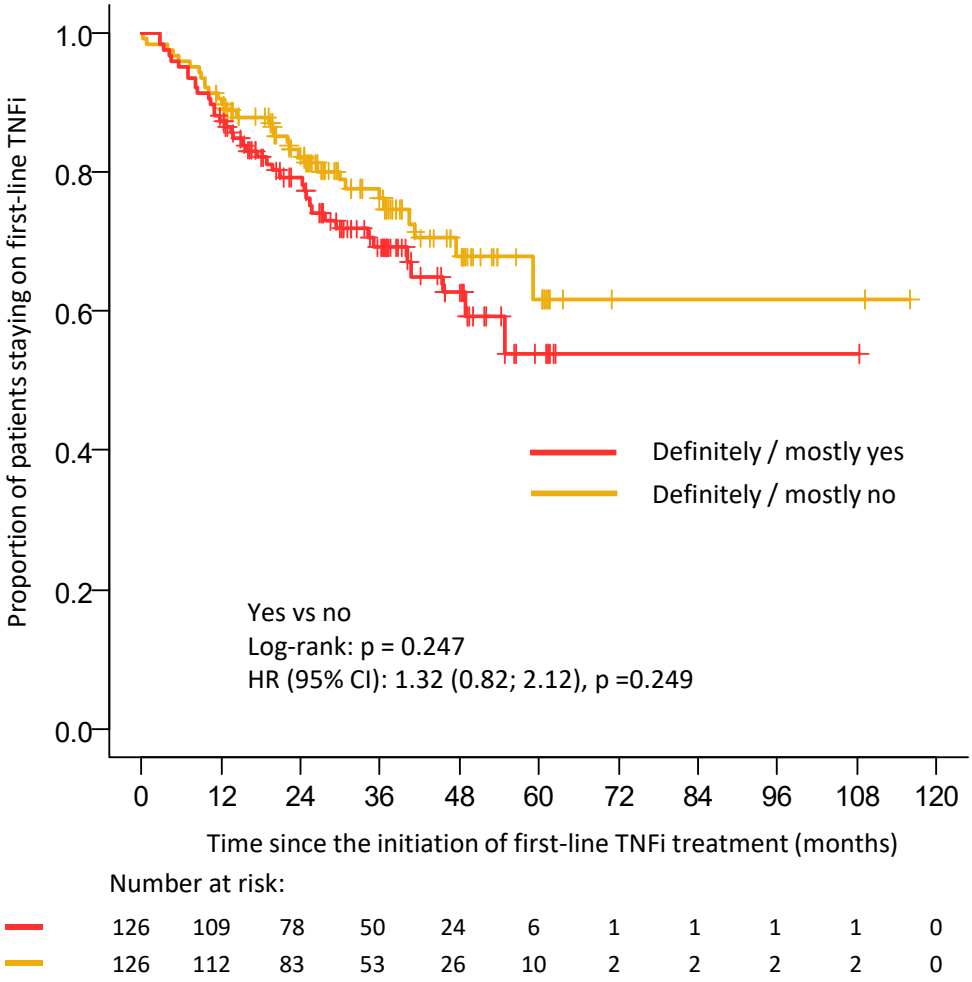


Figure 56 *Kaplan-Meier survival plot showing drug retention in axSpA patients (primary dataset – propensity score-matched data) answering yes (red) and no (yellow) to Q11A*

There was no statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. However, patients answering *yes* had higher tendency for treatment discontinuation (see **Figure 56**). The estimated 1-year retention rate was 80.5% (95% CI 72.4–89.5) in the '*yes'* group and 81.7% (95% CI 73.8–90.5) in the '*no'* group. The estimated 2-year retention rate was 69.3% (95% CI 60.0–80.1) and 73.8% (95% CI 64.3–84.8) in patients answering *yes* and *no*. The median survival was not reached. The frequency of

treatment discontinuation was 31% and 25% in the studied groups. The most frequent reason for treatment discontinuation was a loss of effect (*yes*: 38.5%; *no*: 48.4%) and side effects / adverse events (*yes*: 17.9%; *no*: 25.8%).

Within the **axSpA validation dataset**, for patients‘ groups based on answers to **Q11C**, the set of covariates selected for the PS model included gender, age at treatment initiation, baseline ASDAS, HLA-B27, MDGA, GCs in the previous history, csDMARDs and NSAIDs in concomitant therapy, year of administration and drug type. Out of 143 patients answering *yes* to the Q11C question had available values of these covariates together 135 patients. Out of 118 patients answering *no* to the question, 113 had all values of covariates available. Both groups included 100 patients after the matching. Patients did not statistically significantly differ anymore in any parameters. For patients answering *yes*/*no* to **Q11A**, the covariates selected for the PS model were gender, disease duration, age at treatment initiation, baseline ASDAS, MDGA, GC, csDMARDs and NSAIDs in concomitant therapy, joint involvement, year of administration and drug type. Out of 110 patients answering *yes*, 103 patients had all values of covariates available; out of 193 patients answering *no*, 175 had all values of covariates available. Both groups included 82 patients after the PS matching. Patients did not statistically significantly differ anymore in any parameters.

Patients who expected their health to get worse at the treatment initiation achieved remission less often after three months (28.4% vs 41.0%; p=0.065), six months (32% vs 38%; p=0.374) and twelve months (35% vs 39%; p=0.558) than patients who did not expect their health to get worse. However, the results were not statistically significant. Further, remission was achieved less often after three months (24.3% vs 30,5%; p=0.390), a little bit more often at six months (34.1% vs 32.9%; p=0.869) and less often at twelve months (30.5% vs 35.4%; p=0.506) in patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that.

There was no statistically significant difference in the probability of staying on the first TNFi between the patients who expected their health to get worse at the treatment initiation and patients who did not expect their health to get worse. The estimated 1-year retention rate was 84.0% (95% CI 77.1–91.5) and 85.0% (95% CI 78.3–92.3) in patients answering *yes* and *no*. The estimated 2-year retention rate was 74.7% (95% CI 66.2–84.3) and 78.3% (95% CI 70.3–87.1) in patients answering *yes* and *no*. The median survival was not reached. Patients answering *yes* and *no* discontinued the treatment in 29% and 26% of cases. The most frequent reason for the discontinuation was a loss of effect (*yes*: 31.0%; *no*: 42.3%) and inefficacy (*yes*: 27.6%; *no*: 11.5%).

There was no statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. The estimated 1-year retention rate was 80.5% (95% CI 72.4–89.5) in the '*yes'* group and 81.7% (95% CI 73.8–90.5) in the '*no'* group. The estimated 2-year retention rate was 69.3% (95% CI 60.0–80.1) and 73.8% (95% CI 64.3–84.8) in patients answering *yes* and *no*. The median survival was not reached. Patients answering *yes* and *no* discontinued the treatment in 34% and 27% of cases. The most frequent reason for treatment discontinuation was a loss of effect (*yes*: 35.7%; *no*: 13.6%) and pharmacoeconomic reasons (*yes*: 14.3%; *no*: 31.8%).

8 Discussion

8.1 T2T strategy vs conservative approach

In this prospective observational cohort study from real clinical practice in the Czech Republic, we have shown within the RA cohort that following the T2T strategy and switching the targeted drug to another therapy after not reaching REM/LDA at a 6-month visit increases the chance (2.8 times) of achieving REM/LDA at the 12-month visit as opposed to patients not following the treatment target. This finding within the RA cohort supports results from previous studies showing that T2T is efficient in daily clinical practice. Our study also provided a summary of four different courses of treatment management during the first year of bDMARD/tsDMARD therapy. We created four patients' cohorts based on switching the treatment and based on reaching a treatment target at six months. We described all four patients' groups at baseline and compared their treatment results after one year of treatment. Furthermore, we evaluated disease activity and quality of life at six months in groups C3 and C4 and compared the sizes of changes from the 6-month to the 12-month visit. In the RA cohort, we observed that patients not following the T2T at the 6-month visit (C4) had lower disease activity and better quality of life at six months than patients following T2T and switching to another therapy after not reaching the treatment target (C3). However, patients following the T2T strategy showed a more significant improvement both in disease activity and quality of life within the period from the 6-month to 12-month visit. RA patients from cohort C3 also had a higher rate of REM/LDA at 12 months in comparison with C4 (though not statistically significant; p=0.095).

In PsA patients, two cohorts included a very small number of patients (N=11 in C1 and N=29 in C3) which significantly influenced the power of statistical analyses. Therefore, the results of the PsA dataset should be interpreted with great caution. The results showed that PsA patients following the T2T strategy and switching the targeted drug to another therapy after not reaching REM/LDA at a 6-month visit (C3) have almost the same odds for achieving REM/LDA at the 12-month visit as patients not following the treatment target (C4). However, the number of patients in both cohorts after the PS matching was very small (21 and 35 patients in C3 and C4). Furthermore, patients from the two cohorts stayed statistically significantly different in BMI (lower in C3) and MDGA (higher in C3) at the 6-month visit even after PS matching. Before the matching, patients from the C4 cohort had statistically significantly lower disease activity compared to patients from the C3 cohort. At the 12-month visit, the differences

were not statistically significant anymore. Patients following the T2T strategy showed more significant improvements in disease activity (DAS28-ESR, DAPSA, TJC, SJC and MDGA) within the period from the 6-month to 12-month visit.

Within the axSpA cohort, following the T2T strategy and switching the targeted drug to another therapy after not reaching REM/LDA at a 6-month visit increases the chance of achieving REM/LDA (1.6 times) at the 12-month visit as opposed to patients not following the treatment target. However, the result was not statistically significant. Before the matching, patients from the C3 cohort had statistically significantly higher disease activity and worse quality of life compared to patients from the C4 cohort. At the 12-month visit, the differences were not statistically significant anymore (except MDA). Patients following the T2T strategy showed statistically more significant improvements both in disease activity and quality of life within the period from the 6-month to 12-month visit.

Overall, the T2T strategy has proven to be more effective than the conservative approach in patients with RA (statistically significantly) and with axSpA (numerically). In the PsA cohort, our study did not show the superiority of the T2T strategy, but it is probably related to a small number of studied patients and thus low power of statistical comparisons. Nevertheless, across all three diagnoses, patients following the T2T strategy (C3) showed significantly bigger improvements in disease activity and quality of life within the period from the 6- to 12-month visit than patients not following the strategy (C4).

A similar study investigated whether a tight control treatment strategy (i.e. optimising treatment by measurement of disease activity in order to make treatment adjustments to reach a predefined target LDA/REM) in early RA is more effective than treatment according to usual care in reaching REM (DAS28 < 2.6) after one year (Schipper et al. 2012). They compared two distinct early RA cohorts from two different regions in the Netherlands: the usual care cohort and the 'tight control' cohort. The OR adjusted for baseline DAS28 was 3.1 (95% CI 1.8–5.2). Therefore, patients treated according to tight control had approximately three times higher odds to reach REM at one year after the baseline. This result is very similar to the OR obtained in our study, though we evaluated LDA/REM instead. In another similar study, Norwegian authors compared patients following a T2T strategy (2010–2015) with patients from the pre-T2T cohort (2006–2009) following routine care (Brinkmann et al. 2019). They assessed the two-year effect on disease activity and health-related quality of life and showed significantly higher odds (multivariable OR 1.89, 95% CI 1.33–2.68) for SDAI remission (≤ 3.3) in patients following a T2T strategy. Within secondary outcomes, they also evaluated REM, according to DAS28 (OR 2.15, 95% CI 1.51–3.06). Sugihara et al. (2021) evaluated 3-year outcomes of patients with

elderly-onset RA following a T2T strategy. The primary outcome (remission: SDAI ≤ 3.2) was achieved after three years in 57.8% of patients adhering to T2T compared to 34.8% of patients not adhering to T2T.

A Dutch study investigated the 3-year results of a protocolised T2T strategy in daily clinical practice (Vermeer et al. 2013). Authors found out that T2T leads to high remission rates, improved physical function and quality of life, and limited radiographic damage after three years in daily clinical practice. In another study from the Netherlands, authors described a five-year continuous application of a T2T strategy in patients with early RA in daily clinical practice and confirmed the favourable disease- and patient-related outcomes (Versteeg et al. 2018). A longitudinal study of RA patients from 10 countries (RA BIODAM) investigated whether following a T2T strategy in daily clinical practice leads to more patients meeting REM (Ramiro et al. 2020). Application of T2T every three months did not yield a higher likelihood of REM according to DAS44 and DAS28 three months later, but sustained T2T (i.e. T2T followed in at least two consecutive visits) resulted in an increased likelihood of achieving DAS44 REM (OR 1.19, 95% CI 1.03–1.39).

In PsA, the TICOPA trial was the first to show improved clinical and patient-reported outcomes with a T2T approach (Coates et al. 2015). Currently, a multicentre observational PsA cohort study addressing real-life outcomes of a T2T approach in routine clinical practice is in progress (Coates et al. 2022). Unfortunately, studies from daily clinical practice concerning the advantage of following T2T over usual care in PsA are lacking, and more evidence is needed.

In axSpA, the TICOSPA trial aimed to evaluate the benefit of T2T strategies compared to usual care (Molto et al. 2021). T2T (tight control) was not significantly superior to usual care for the primary outcomes, but many secondary efficacy outcomes favoured the T2T. A randomised AScalate study is currently being conducted, and the first results are expected to be published in 2022 (Poddubnyy et al. 2020). This study aims to evaluate the efficacy of a T2T strategy in patients with axSpA treated with secukinumab in a first-line bDMARD, compared with standard treatment. More evidence is required to support the T2T approach in axSpA, similarly to PsA.

Our study has shown that the implementation of the T2T strategy is insufficient in real clinical practice in the Czech Republic. A substantial number of patients did not follow the T2T strategy and continued with the same treatment after not reaching the treatment target within six months. Other authors have also shown that the T2T strategy is underused within real clinical practice. In the data analysis from the Corrona RA registry, a considerable proportion

of patients continued without changing/accelerating treatment despite not reaching an adequate response to the initial TNF inhibitor therapy at 6 and 12 months (Pappas et al. 2018). Dures et al. (2020) examined factors/barriers affecting the usage of T2T in PsA within clinical practice.

Although the present study has a limitation of the absence of randomisation, we have partially overcome this problem by employing the propensity score matching at the 6-month visit. Thus, we have minimised confounding by other factors, and we obtained the effect of following/not-following the T2T principle in the evaluation of REM/LDA at the 12-month visit. A possible limitation of this study could be an absence of monitoring treatment intensification through increased dosages. Further, our study only concerned the first-line bDMARD/tsDMARD therapy. Thus, evaluating the T2T strategy implementation within subsequent lines of therapy could be a possible subject for future studies.

8.2 Predictive ability of self-perceived general health at TNFi therapy start

In this prospective observational cohort study from real clinical practice in the Czech Republic, we evaluated the predictive ability of two SF-36 questionnaire questions, specifically Q 11A '*I seem to get sick a little easier than other people*', and Q 11C '*I expect my health to get worse*'. We hypothesized that positive responses to these questions might correspond to more fragile, self-perceived general health status, thus serving as possible predictors of future patient disease outcomes. For each diagnosis, we used separate datasets to validate our hypothesis. Apart from univariable models to quantify odds and hazard ratios, we employed multivariable models adjusted for baseline disease activity and quality of life. Furthermore, we repeated the whole analysis within propensity score-matched patients to make both study groups (answering *yes*/*no* to Q11A and Q11C) comparable in baseline characteristics, thus reducing selection bias. By employing the propensity score matching at baseline, we have partially overcome missing randomisation in this study. Overall, we employed three ways to verify our results: 1) adjustment for baseline disease activity and functional status; 2) two separate datasets (primary and validation); 3) propensity-score matched datasets.

Within the primary dataset with RA patients, we have shown that patients answering positively to Q11A and patients answering positively to Q11C have significantly higher odds of reaching remission at 6- and 12-month visits than patients answering to these questions negatively. This difference in remission rates and odds ratios remained statistically significant even when computed on propensity score-matched patients who were balanced in baseline characteristics. We obtained analogical results in the validation dataset of RA patients as well.

Patients answering positively to Q11A (or Q11C) had significantly higher odds of remission achievement at the 12-month visit than patients responding to these questions negatively. Within the propensity score-matched dataset, patients responding '*yes'* to Q11A had significantly higher odds of remission at the 12-month visit than patients answering '*no'*. For Q11C, the difference was not statistically significant at the 12-month visit, but it was very close to the statistical significance (p=0.066). Overall, we provided robust evidence that self-perceived general health at the start of TNFi therapy predicts reaching remission at 12 months in patients with RA. In terms of treatment discontinuation, patients answering *yes* to Q11A had a significantly higher probability of treatment discontinuation than patients answering *no* within the primary dataset. In the validation dataset, there was no statistically significant difference in the probability of treatment discontinuation between patients answering positively/negatively to the studied SF-36 questions. The results of the primary dataset were presented at the 62nd Annual Congress of Czech and Slovak Rheumatologists in 2018, Prague.

Within the primary dataset with PsA patients, there was no statistically significant difference in remission achievements within the first year of TNFi therapy between the studied groups. The only significant difference was found in the probability of treatment discontinuation between patients responding *yes*/*no* to Q11C in the propensity score-matched dataset. Patients responding '*yes'* had a 2.9 times higher risk of treatment discontinuation than patients with the answer '*no'*. However, this result was not confirmed in the validation dataset. In the validation dataset of PsA patients, patients with the positive response to Q11A and Q11C had higher remission rates, even though the results were not statistically significant. This might be caused by relatively small numbers of patients. Due to the small number of patients in the validation dataset, propensity score-matched analysis was not very successful, and the results obtained within this dataset should be interpreted with caution.

Within the primary dataset with axSpA patients, there was no statistically significant difference in remission achievements within the first year of TNFi therapy between the studied groups (similarly to PsA). These insignificant differences were obtained in the propensity score-matched as well. The only significant difference was found in the probability of treatment discontinuation between patients responding *yes* and *no* to *Q11A,* with patients responding '*yes'* having a 1.6 times higher risk of treatment discontinuation than patients with the answer '*no'*. However, after matching patients based on the propensity score, the difference in drug retention became statistically insignificant (but the tendency remained). Insignificant differences in

remission rates and probability of treatment discontinuation between the studied groups were repeated in the validation dataset as well.

The predictive ability of SF-36 dimensions was not very studied so far. Kuusalo et al. (2017) studied PROs as predictors of remission in early RA within a randomized clinical trial. At baseline, they measured eight SF-36 questionnaire dimensions, PGA, HAQ, and pain (VAS). Remission at two years was associated with SF-36 dimensions: higher vitality (OR 2.0; 95% CI 1.2–3.4) and better emotional role functioning (OR 1.6; 95% CI 1.0–2.7). The *general health* dimension (to which our two studied questions belonged) was not associated with remission in this study. A three-year prospective observational study of a Brazilian early RA cohort evaluated whether baseline scores (HAQ and SF-36) can predict the achievement of remission (DAS28 <2.6) (da Mota et al. 2012). Neither initial HAQ nor SF-36 scores were associated with clinical remission. The baseline general health score was not significantly different between patients achieving and not achieving remission.

Our results within the RA cohort are quite surprising because we assumed that patients who expected their health to get worse at treatment initiation and patients who seemed to get sick a little easier than other people at treatment initiation would have lower odds of treatment response (achieving remission within one year) than patients who did not think that. However, the results showed the exact opposite. Thus, it would be interesting to include a psychologist in future studies to get a deeper insight. Including more questions from different SF-36 dimensions is another point for further studies.

9 Conclusions and evaluation of hypotheses

First, we aimed to evaluate adhesion to treat-to-target strategy (T2T) within the three diagnoses – RA, PsA and axSpA (5.1). We were interested in whether patients following the T2T strategy showed better results than patients not following the T2T strategy.

- We showed that the application of the T2T strategy is underused in daily clinical practice in the Czech Republic.
- Switching biological (targeted) treatment after not reaching remission/low disease activity within the first six months of the treatment leads to a higher probability of achieving remission/low disease activity at the 12-month visit in RA patients.
- Across all three diagnoses, patients following the T2T strategy showed more significant improvements in disease activity and quality of life within the period from the 6- to 12-month visit than patients not following the strategy.

Based on the obtained results, we can state that the hypothesis about the superiority of the T2T strategy over the conservative approach was confirmed in patients with rheumatoid arthritis. Further studies are needed to confirm the advantage of the T2T strategy over usual care in psoriatic arthritis and axial spondyloarthritis.

Second, we dealt with evaluating the predictive ability of two SF-36 questionnaire questions (Qs), specifically Q11A '*I seem to get sick a little easier than other people*', and Q11C '*I expect my health to get worse*' (5.2). We hypothesized that positive responses to these questions might correspond to more fragile, self-perceived general health status, thus serving as possible predictors of future patient disease outcomes.

- We showed that RA patients who answer positively to Q11A and those who answer positively to Q11C have significantly higher odds of reaching remission at 12-month visits than those who answer these questions negatively.
- We showed that PsA patients who answer positively to Q11C have a higher risk of treatment discontinuation than those who answer negatively (not confirmed in the validation dataset).

Based on the obtained results, we can state that the hypothesis about the predictive ability of two SF-36 questionnaire questions in terms of the treatment response at the 12-month visit in patients with RA was confirmed.

10 Summary

This thesis was concerned with evaluating the effectiveness of biological (targeted) therapy in chronic inflammatory rheumatic diseases (rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis) based on the data from the ATTRA registry.

In the theoretical part of the thesis, we characterised the diseases, gave insight into creating and maintaining the clinical registry and mentioned specifics related to the analysis of clinical registry data. In the practical part of the work, we performed two analyses to verify our hypotheses. First, we evaluated whether following a treat to target strategy after not reaching a treatment target within the first six months leads to a higher chance of meeting the treatment target at the twelve-month visit. Second, we studied the association between therapeutic response (achieving remission and drug retention) and patients‘ self-perceived general health status at the treatment initiation based on answers to two selected questions in the SF-36 questionnaire. Both goals were assessed within patients‘ cohorts with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis diagnoses.

Results of our first analysis showed that application of T2T principles and switching to another bDMARD/tsDMARD after not reaching the treatment target (at least low disease activity) within the first six months of bDMARD/tsDMARD treatment leads to a higher probability of achieving the treatment target in RA (statistically significantly) and axSpA (numerically) patients at the 12-month visit. Therefore, the T2T strategy showed superiority over traditional routine care in daily clinical practice. At the same time, the analysis revealed that the application of the T2T strategy is not very frequent in the Czech Republic so far.

Through our second analysis, we provided robust evidence that self-perceived general health at the start of TNFi therapy predicts reaching remission at 12 months in patients with RA. Patients who seemed to get sick a little easier than other people at treatment initiation and patients who expected their health to get worse at treatment initiation had significantly higher odds of reaching REM within the first year than patients who did not think that.

Souhrn

Tato práce se zabývala hodnocením účinnosti biologické (cílené) léčby u chronických zánětlivých revmatických onemocnění (revmatoidní artritida, psoriatická artritida and axiální spondyloartritida) na základě dat z národního registru ATTRA.

V teoretické části jsme se věnovali charakterizaci studovaných onemocnění, nastínili tvorbu a řízení klinického registru a zmínili specifika spojená s analýzou dat z registru. V praktické části práce jsme provedli dvě analýzy, abychom ověřili naše hypotézy. Nejprve jsme hodnotili, zda vede následování strategie léčby k cíli (T2T) po nedosažení léčebného cíle během prvních šesti měsíců k větší šanci na dosažení léčebného cíle při dvanáctiměsíční kontrole. Dále jsme studovali asociaci mezi léčebnou odpovědí (dosažení remise a setrvání na léčbě) a pacientovým vnímáním svého zdraví při zahájení léčby na základě odpovědí na vybrané dvě otázky z SF-36 dotazníku. Oba cíle byly hodnoceny na kohortách pacientů s diagnózou revmatoidní artritidy, psoriatické artritidy a axiální spondyloartritidy.

Výsledky naší první analýzy ukázaly, že aplikace principu léčby k cíli a změna biologické/cílené léčby po nedosažení léčebného cíle (alespoň nízké aktivity) během prvních šesti měsíců léčby vede k vyšší pravděpodobnosti dosažení léčebného cíle při dvanáctiměsíční kontrole u pacientů s revmatoidní artritidou (statisticky významně) a axiální spondyloartritidou (numericky). Strategie léčby k cíli tedy prokázala superioritu nad tradiční rutinní péčí v každodenní klinické praxi. Analýza zároveň ale ukázala, že je strategie léčby k cíli v klinické praxi stále málo aplikovaná.

Skrze naši druhou analýzu jsme poskytli poměrný silný důkaz, že lze využít pacientovo vnímání svého zdraví při zahájení léčby TNF inhibitory pro predikci remise při dvanáctiměsíční kontrole, a to v rámci kohorty pacientů s revmatoidní artritidou. Ukázalo se, že pacienti, kterým se při zahájení léčby zdá, že onemocní poněkud snadněji než ostatní lidé, mají významně větší šanci na dosažení remise během prvního roku léčby než pacienti, kteří takový pocit nemají. Obdobně, pacienti, kteří očekávají při zahájení léčby, že se jejich zdraví zhorší, mají významně vyšší šanci na dosažení remise v prvním roce léčby než pacienti, kteří zhoršení zdraví neočekávají.

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List of abbreviations

ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
AS	Ankylosing spondlitis
ASAS	Assessment in SpondyloArthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
AxSpA	Axial Spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Index
BASFI	Bath Ankylosing Spondylitis Functional Index
Bs	Biosimilar
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
DAPSA	Disease activity in psoriatic arthritis
DAS28	Disease activity score using 28 joints
DMARDs	Disease-modifying antirheumatic drugs
EBM	Evidence-based medicine
EDC	Electronic data capture
ESR	Erythrocyte sedimentation rate
EQ-5D	EuroQol-5D (instrument for measuring quality of life)
EULAR	European League Against Rheumatism
GDPR	General data protection regulation
GCs	Glucocorticoids
HAQ-DI	Health Assessment Questionnaire Disability Index
HDA	High disease activity
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
JAKi	Janus kinase inhibitors
JIA	Juvenille idiopatic arthritis
LDA	Low disease activity
MDA	Minimal disease activity or Medium disease activity

MTX	Methorexate
Nr-axSpA	Non-radiographic axial spondyloarthritis
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PASS	Post-authorisation safety studies
PRO	Patient reported outcome
PS	Propensity score
PsA	Psoriatic arthritis
PtGA	Patient's global assessment of disease activity
RA	Rheumatoid arthritis
REM	Remission
RF	Rheumatoid factor
RR	Relative risk or risk ratio
SDAI	Simplified disease activity index
SJC	Swollen joint count
SLE	Systemic lupus erythematosus
SpA	Spondyloarthritis
TJC	Tender joint count
TNFi	Tumor necrosis factor inhibitors
T2T	Treat-to-target
TT	Treatment target

List of publications

1) Publications *in extenso* which are the basis of PhD thesis

a. with impact factor

NEKVINDOVÁ, Lucie, Jiří VENCOVSKÝ, Karel PAVELKA, Pavel HORÁK, Zlatuše KŘÍSTKOVÁ a Jakub ZÁVADA, 2021. Switching first-line targeted therapy after not reaching low disease activity within 6 months is superior to conservative approach: a propensity score-matched analysis from the ATTRA registry. Arthritis Research & Therapy [online]. 23(1), 11. ISSN 1478-6362. Dostupné z: doi:10.1186/s13075-020-02393-8

- *2020 journal impact factor*: 5.156

2) Publications *in extenso* which are not the basis but are related to the topic of PhD thesis

a. with impact factor

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Appendix

Apendix includes two publications that are the basis of PhD thesis. The first article was published in the journal *Arthritis Research & Therapy* in 2021. The second article (draft) was not published so far (beginning of April 2022) but was sent to other co-authors. After that, it will be submitted to a journal.

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Switching first-line targeted therapy after not reaching low disease activity within 6 months is superior to conservative approach: a propensity score-matched analysis from the ATTRA registry

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Abstract

Background: Treat-to-target (T2T) is a widely accepted strategy for patients with rheumatoid arthritis (RA). It recommends attaining a goal of at least low disease activity (LDA) within 6 months; otherwise, the current therapy should be modified. We aimed to investigate whether switching a first-line targeted therapy (TT) in patients not reaching LDA within 6 months leads to a higher probability of meeting LDA at the 12-month visit in daily clinical practice using data from Czech registry ATTRA.

Methods: We included patients with RA starting the first-line TT from 1 January 2012 to 31 January 2017 with at least 1-year follow-up. We created four mutually exclusive cohorts based on (1) switching to another TT within the first year and (2) reaching a treatment target (DAS28-ESR ≤ 3.2) at the 6-month visit. The primary outcome was the comparison of odds for reaching remission (REM) or LDA at the 12-month visit between patients switching and not switching TT after not reaching treatment target at 6 months. Before using logistic regression to estimate the odds ratio, we employed the propensity score to match patients at the 6-month visit.

Results: A total of 1275 patients were eligible for the analysis. Sixty-two patients switched within the first 5 months of the treatment before evaluating treatment response at the 6-month visit (C1); 598 patients reached the treatment target within 6 months of therapy (C2); 124 patients did not reach treatment response at 6-month visit and switched to another therapy (C3), and 491 patients continued with the same treatment despite not reaching LDA at the 6-month visit (C4). We matched 75 patients from cohort C3 and 75 patients from C4 using the propensity score. Patients following the T2T principle (C3) showed 2.8 (95% CI 1.4–5.8; $p = 0.005$) times increased likelihood of achieving REM/LDA at the 12-month visit compared to patients not following the T2T strategy (C4).

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Conclusions: In daily clinical practice, the application of the T2T strategy is underused. Switching TT after not reaching REM/LDA within the first 6 months leads to a higher probability of achieving REM/LDA in RA patients at the 12-month visit.

Keywords: Registry, Treat-to-target, Rheumatoid arthritis, Propensity score

Background

Currently, patients with rheumatoid arthritis (RA) have multiple drug options with different mechanisms of actions to address the heterogeneous nature of the disease. Patients may require multiple successive therapies throughout their lives. In 2010, the European League Against Rheumatism (EULAR) developed its first recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs (DMARDs) [1]. There were several updates throughout the years with the last update so far at the end of 2019 [2]. Treating toward a target of remission (REM) or at least a low disease activity (LDA) has become the standard of care for patients. Achievement of the treatment target often requires switching between drugs. According to EULAR recommendations, therapy with conventional synthetic (cs) DMARDs should be started as soon as the diagnosis of RA is made, and methotrexate (MTX) should be the first choice. If the treatment target is not reached with the first csDMARDs, and poor prognostic factors are present (i.e. presence of rheumatoid factor/anti-citrullinated protein antibodies, high disease activity early, joint damage, failure of two or more csDMARDs), a biological (b) DMAR D or targeted synthetic (ts) DMARD should be added. If there is no improvement within 3 months after the start of treatment or if patients have not reached the treatment target with bDMARD/tsDMARD by 6 months, therapy should be adjusted, and treatment with another bDMARD or tsDMARD should be considered [2].

The approach currently recommended for RA treatment involves titrating medication dosages until prespecified disease activity targets (either REM or LDA) have been met and maintaining these targets over time. Such so-called treat-to-target strategies (T2T) have proven to be more effective and to generate better outcomes than usual care [3, 4]. The efficacy of the T2T approach has been evaluated in many randomised controlled clinical trials [5–11]. Even though the T2T strategy has been widely applied in daily clinical practice nowadays, studies from daily clinical practice concerning the advantage of following T2T over usual care are still required. Several studies evaluating the efficacy of T2T in real clinical practice have been already done [4, 12–17], but more evidence through real-life data is needed to support the implementation of T2T.

The primary aim of this study was to assess whether following a T2T strategy after not reaching treatment target (REM/LDA) within the first 6 months leads to a higher probability of meeting the treatment target at the 12-month visit in daily clinical practice. We also described four groups of patients based on different courses of their treatment with the first bDMARD/tsDMARD.

Methods

Study setting and data source

The ATTRA registry, established in 2002, is a prospective, national, observational cohort study. Its main purpose is to evaluate the safety and effectiveness of bDMARDs (and lately also tsDMARDs) in patients with chronic inflammatory rheumatic diseases. Patients with RA (and ankylosing spondylitis, psoriatic arthritis and juvenile idiopathic arthritis) starting bDMARDs or tsDMARDs are recruited from fifty practice sites (private or academic), which captures more than 95% of patients with RA treated with bDMARDs/tsDMARDs in the Czech Republic (CZ). Targeted therapy (TT) has been reimbursed for patients with RA if DAS28 > 5.1 despite therapy with csDMARDs until 2019. Since 2019, the cut-off for DAS28 was lowered to 3.2 in CZ. Initial TT should include either TNF inhibitors (TNFis) or tsDMARDs. At the time of this analysis, the ATTRA database included information on 5050 patients with RA.

At the start of therapy, baseline data are collected including demographics (gender, age at diagnosis, age at the start of first-line treatment, height, weight, smoking status, presence of comorbidities), disease characteristics (disease duration, presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), presence of joint erosions on X-ray), disease activity (swollen and tender joint count (0–28), patient global assessment (PTGA) of disease activity and physician global assessment of disease activity (MDGA) on a 100-mm visual analogue scale (VAS; 0—best, 100—worst), erythrocyte sedimentation rate (ESR, mg/h) and C-reactive protein (CRP, mg/L)) and 28-joint disease activity score index (DAS28; 0–10) [18], Simplified Disease Activity Index (SDAI, 0–86) [19], Health Assessment Questionnaire (HAQ) for patient function with values from 0 to 3 (the higher, the worse disability) [20], EuroQol EQ-5D questionnaire for quality of life with values from − 0.59 to 1 (the higher, the better quality of life) [21], and current or

previous anti-rheumatic therapies (csDMARDs, bDMARDs, tsDMARDs) and therapy with glucocorticoids (GCs). Follow-up data on disease activity, disease function and anti-rheumatic therapies are collected after 3 and 6 months, and then every 6 months for 3 years, with disease activity and anti-rheumatic therapy data collected annually thereafter.

Ethics approval for ATTRA was granted by the Czech Multicentre Research Ethics Committee, no. 201611 S300, and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic, no. 10113/2016. No additional ethical approval was required for the current analysis. All subjects provided their written consent for the collection and storage of data before participation. All procedures were performed following the Declaration of Helsinki.

Study population

In this study, we included all bio-naive adult patients diagnosed with RA starting bDMARDs/tsDMARDs within a period from 1 January 2012 to 31 January 2017 with at least 1-year follow-up. Patients without available DAS28-ESR at baseline, 6-month and 12-month visit or without HAQ and EQ-5D at baseline and 12-month visit were excluded (see Supplementary Figure 1).

Study design

We divided patients into four cohorts based on a treatment result at the 6-month visit and based on switches to another therapy during the first year of the treatment (Fig. 1). First, we evaluated whether patients switched to another therapy within the first 5 months of the treatment. Next, we assessed if patients reached remission or low disease activity at the 6-month visit (defined as DAS28-ESR ≤ 3.2). Finally, we checked whether patients changed the therapy within months 6–11 provided they did not achieve the treatment target. Cohort C1 includes patients that changed bDMARD/tsDMARD therapy during the first months (usually at 3-month visit) before evaluating treatment response at the 6-month visit. These patients were either not responding to the treatment at all, or were not tolerating the treatment (e.g. side effects) within the first months of the first-line therapy. Cohort C2 consists of patients ideally responding to the treatment because they achieved the treatment target after 6 months of therapy without a need to switch. Cohort C3 comprises the group of patients not responding to the treatment, because they did not achieve the treatment target after the first 6 months of therapy. Following T2T principles, they switched to a different treatment. The last cohort C4 is represented by patients not responding to the treatment since they did not achieve the treatment target (similarly to the C3 cohort). Regardless of T2T principles, they continued with the same treatment.

Objectives and outcome measures

The primary objective of this study was to compare odds for the achievement of REM or at least LDA after 1 year of the treatment between patients following and not following the T2T strategy (C3 vs C4). We assessed disease activity DAS28-ESR index; specifically, LDA was defined as DAS28-ESR ≤ 3.2 and REM was defined as DAS28-ESR < 2.6. In terms of the secondary outcomes, we compared treatment results based on DAS28-ESR after 12 months between all studied cohorts. The proportion of patients with remission (REM; DAS28-ESR < 2.6), low disease activity (LDA; 2.6 ≤ DAS28-ESR ≤ 3.2), moderate disease activity (MDA; 3.2 < DAS28-ESR ≤ 5.1) and high disease activity (HDA; DAS28-ESR > 5.1) at baseline and 12-month visit were compared across the studied cohorts C1–C4. Next, we compared changes in parameters

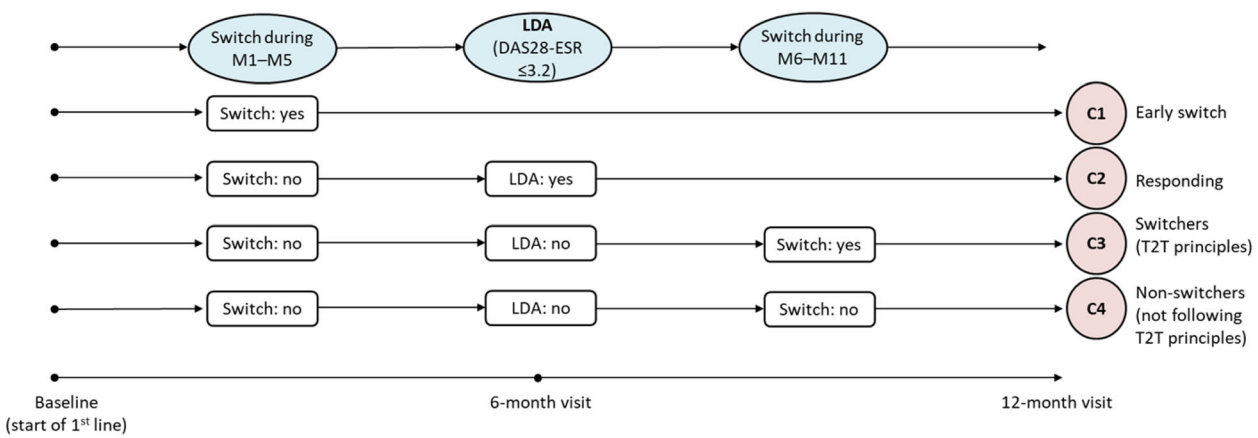


Fig. 1 Definition of studied cohorts (C1–C4). Patients were classified based on the achievement of treatment response at the 6-month visit and based on switching to another therapy within the first year of the therapy

related to disease activity (DAS28-ESR, SDAI, tender and swollen joint count, CRP, ESR, PTGA, MDGA) and quality of life (HAQ-DI, EQ-5D) after 6 and 12 months of the bDMARD/tsDMARD treatment between cohorts C3 and C4.

Statistical methods

Descriptive summary of patients' demographic and treatment characteristics and disease activity measurements was performed for all four studied cohorts C1–C4. For continuous variables, we calculated the median with interquartile range (IQR, 25th–75th percentiles). For a description of categorical variables, we used absolute and relative frequencies (i.e. percentages). To test differences between two patients' groups, we performed the non-parametric Mann-Whitney *U* test for continuous variables and Pearson's chi-squared test for categorical variables. The magnitude of changes in parameters over two visits was tested through the paired Wilcoxon test. For all tests, p values < 0.05 were considered to be statistically significant. We did not impute missing data in this analysis and performed a complete-case analysis instead. The percentage of missing data in outcome variables (i.e. DAS28-ESR, HAQ and EQ-5D at baseline, 6 and 12 months) was relatively small; we excluded 1.8% of patients in total.

We used propensity score matching to match patients not switching to another therapy after not reaching treatment target at the 6-month visit (C4) to patients switching to a different treatment after not reaching treatment target (C3). For matching, we performed logistic regression with outcome variable C3 (= 1) vs C4 (= 0) and covariates: gender, age at the start of first-line therapy, disease duration, number of previous csDMARDs, glucocorticoids in previous therapy, swollen joint count, tender joint count, PTGA, ESR, CRP, HAQ, RF positivity, presence of comorbidities, smoking, csDMARDs in concomitant therapy and glucocorticoids in previous therapy. We chose the matching ratio 1:1 and set the calliper to a value 0.2. We used matching to make both groups comparable in characteristics at the 6-month visit and to minimise confounding by other factors in the evaluation of achieving REM/LDA at the 12-month visit. After we carried out propensity score matching, we employed binary logistic regression to determine the odds for reaching REM/LDA at the 12-month visit in cohorts C3 and C4. We did all descriptive statistics and testing using IBM SPSS Statistics 25.0. The propensity score model was performed in R (version 3.5.3).

Results

Patients' characteristics at baseline

In total, we included 1275 patients fulfilling the inclusion criteria into the analysis (see Supplementary Figure 1). Cohort C1 was represented by 62 (4.9%) patients, C2 consisted of 598 (46.9%) patients, C3 included 124 (9.7%) patients and 491 (38.5%) patients belonged to C4 subgroup (see Supplementary Figure 1). The most frequently administered drug was bio-original adalimumab (ranging from 27.4 to 40.3% in studied cohorts), bio-original etanercept (from 10.5 to 32.3%) and golimumab (from 6.5 to 15.5%). Tofacitinib as the only Janus kinase inhibitor administered in analysed patients was present only in one patient from C2 and one patient from C4. Out of 61 patients from C1 treated with TNFi in the first line, 42 (68.9%) switched before the 6-month visit to another TNFi, 11 (18.0%) switched to an interleukin-6 inhibitor (tocilizumab or sarilumab), 7 (11.5%) switched to abatacept and 1 (1.6%) switched to rituximab. One patient from C1 who was treated with tocilizumab in the first line switched to anakinra. Out of 120 patients from the C3 cohort that were treated with TNFi, 72 (60.0%) patients switched after the 6 months to another TNFi, 28 (23.3%) switched to an interleukin-6 drug (tocilizumab or sarilumab), 13 (10.8%) switched to abatacept and 7 (5.8%) switched to rituximab. Out of two C3 patients with tocilizumab, one switched to rituximab and the other to abatacept. Out of two C3 patients with rituximab, one switched to etanercept and the other to abatacept.

We present baseline characteristics of all four studied cohorts in Table 1. The median age at the start of the first bDMARD/tsDMARD was between 51 years (C1) and 55 years (C4 cohort). Females represented from 72.1% (C2 cohort) to 83.9% (C1 cohort) patients. Patients from all studied cohorts had high baseline disease activity according to DAS28-ESR score with median 6.4 (5.7–7.0) in C1, 5.9 (5.3–6.5) in C2, 6.2 (5.6–6.8) in C3 and 6.3 (5.8–6.8) in C4. Patients from cohorts C3 and C4 significantly differed only in age at the start of the first therapy ($p = 0.016$) and the number of previous csDMARDs ($p = 0.025$). The median age was 52.0 (44.5–61.0) years in C3 and 55.0 (48.0–63.0) years in C4. Cohorts C1 and C2 significantly differed in gender (84% vs 72% females; $p = 0.046$) and in almost all parameters related to baseline disease activity and quality of life. Patients from cohort C1 had higher disease activity than the C2 cohort according to DAS28-ESR (median 6.4 vs 5.9; $p < 0.001$), TJC (median 14 vs 12; $p = 0.005$), CRP (median 22 vs 12; $p = 0.002$), PTGA (median 78 vs 70; $p = 0.008$), MDGA (median 74 vs 65; $p = 0.015$) and worse physical function and quality of life according to HAQ-DI (median 1.8 vs 1.4; $p = 0.001$) and EQ-5D (median 0.1 vs 0.2; $p = 0.048$), respectively. Additional baseline characteristics including the presence of comorbidities, BMI, drug usage, number of concomitant csDMARDs and MTX and prednisone doses are presented in Supplementary Table 1.

Table 1 Baseline characteristics of patients in cohorts C1–C4 ($N = 1275$)

	C1 ($n = 62$)	C2 ($n = 598$)	C3 ($n = 124$)	C4 ($n = 491$)
Female, *n* (%)	52 (83.9%)	431 (72.1%)	102 (82.3%)	390 (79.4%)
Age at diagnosis, years, median (IQR)	44.0 (34.0–52.0)	43.5 (33.0–52.0)	45.0 (34.0–51.5)	47.0 (38.0–54.0)
Age at start of 1st line, years, median (IQR)	51.0 (42.0–58.0)	53.0 (41.0–60.0)	52.0 (44.5–61.0)	55.0 (48.0–63.0)
Disease duration, years, median (IQR)	5.6 (3.0–7.8)	6.0 (2.5–11.8)	5.0 (2.2–12.1)	6.2 (3.0–12.9)
RF positive, *n* (%)	47 (75.8%)	428 (71.6%)	92 (74.2%)	389 (79.6%)
ACPA positive, *n*/total (%)	44/61 (72.1%)	399/587 (68.0%)	91/120 (75.8%)	348/480 (72.5%)
Presence of erosions, *n*/total (%)	25/38 (65.8%)	210/295 (71.2%)	46/67 (68.7%)	22/290 (76.6%)
Currently smoking, *n*/total (%)	10/53 (18.9%)	102/504 (20.2%)	26/103 (25.2%)	93/413 (22.5%)
Number of previous csDMARDs, *n* (%)				
0	0 (0.0%)	8/592 (1.4%)	2 (1.6%)	6/484 (1.2%)
1	13 (21.0%)	226/592 (38.2%)	27 (21.8%)	131/484 (27.1%)
2	18 (29.0%)	147/592 (24.8%)	30 (24.2%)	165/484 (34.1%)
3	17 (27.4%)	112/592 (18.9%)	35 (28.2%)	113/484 (23.3%)
4+	14 (22.6%)	99/592 (16.7%)	30 (24.2%)	69/484 (14.3%)
Glucocorticoids in previous history, *n* (%)	56 (90.3%)	519/597 (86.9%)	112 (90.3%)	442 (90.0%)
Concomitant csDMARDs, *n* (%)	54 (87.1%)	549 (91.8%)	107 (86.3%)	440 (89.6%)
Concomitant MTX, *n* (%)	44 (71.0%)	454 (75.9%)	77 (62.1%)	349 (71.1%)
Concomitant GCs, *n* (%)	49 (79.0%)	446 (74.6%)	96 (77.4%)	402 (81.9%)
DAS28-ESR (0–10), median (IQR)	6.4 (5.7–7.0)	5.9 (5.3–6.5)	6.2 (5.6–6.8)	6.3 (5.8–6.8)
TJC (28 joints), median (IQR)	14.0 (11.0–19.0)	12.0 (9.0–16.0)	14.5 (9.0–19.0)	13.0 (10.0–18.0)
SJC (28 joints), median (IQR)	10.0 (7.0–13.0)	9.0 (6.0–12.0)	9.5 (6.0–12.5)	10.0 (7.0–13.0)
ESR (mm/h), median (IQR)[a]	33.5 (16.0–53.0)	28.0 (16.0–40.0)	32.0 (18.0–50.0)	34.0 (23.0–50.0)
CRP (mg/l), median (IQR)[b]	22.0 (9.4–34.0)	12.0 (5.3–23.5)	15.0 (7.9–31.0)	16.8 (8.0–33.1)
SDAI (0–86), median (IQR)[c]	40.5 (32.7–47.8)	35.6 (29.5–42.4)	39.3 (33.0–48.2)	39.0 (32.6–45.9)
PTGA (0–100), median (IQR)	78.0 (69.0–84.0)	70.0 (59.0–80.0)	75.0 (62.5–81.5)	75.0 (60.0–85.0)
MDGA (0–100), median (IQR)[d]	74.0 (60.0–80.0)	65.0 (52.0–75.0)	70.0 (58.5–80.0)	70.0 (60.0–80.0)
HAQ-DI (0–3), median (IQR)	1.8 (1.3–2.0)	1.4 (1.0–1.8)	1.8 (1.4–2.0)	1.8 (1.4–2.0)
EQ-5D (− 0.59–1), median (IQR)	0.1 (0.0–0.6)	0.2 (0.1–0.7)	0.1 (0.0–0.5)	0.1 (0.0–0.5)

IQR interquartile range, *RF* rheumatoid factor, *ACPA* anti-citrullinated protein, *TNFi* tumour necrosis factor inhibitor, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs, *MTX* methotrexate, *DAS28-ESR* 28-joint disease activity score with ESR, *TJC* tender joint count, *SJC* swollen joint count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SDAI* Simplified Disease Activity Index, *PTGA* patient general assessment of disease activity, *MDGA* physician general assessment of disease activity, *HAQ-DI* Health Assessment Questionnaire, *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

[a] $n = 62$ (C1), $n = 573$ (C2), $n = 118$ (C3), $n = 486$ (C4)

[b] $n = 60$ (C1), $n = 576$ (C2), $n = 123$ (C3), $n = 480$ (C4)

[c] $n = 55$ (C1), $n = 560$ (C2), $n = 119$ (C3), $n = 465$ (C4)

[d] $n = 57$ (C1), $n = 582$ (C2), $n = 120$ (C3), $n = 476$ (C4)

Disease activity after 3 months in C1–C4

Disease activity according to DAS28-ESR score after 3 months of the first-line treatment in cohorts C1–C4 is shown in Supplementary Figure 2. We observed the highest proportion of patients with REM/LDA after 3 months in cohort C2 in almost 70% of patients. This result was statistically significantly higher compared to other cohorts ($p < 0.001$). There was also a statistically significant difference in the proportion of patients with REM/LDA between patients in the groups C3 and C4. While in group C3 it was 10.6% of patients, in group C4 it was 20.4% ($p = 0.016$). The median value of DAS28-ESR in group C1 corresponded to the high disease activity range; group C2 had median DAS28-ESR belonging to low disease activity; the median DAS28-ESR value in cohorts C3 and C4 fell into the category of moderate disease activity.

Disease activity after 12 months in C1–C4

Comparison of disease activity according to the DAS28-ESR score after 1 year of treatment in cohorts C1–C4 is illustrated in Fig. 2. We could see the best treatment results after 12 months in group C2 with almost 79% patients with REM/LDA compared to 48% patients in

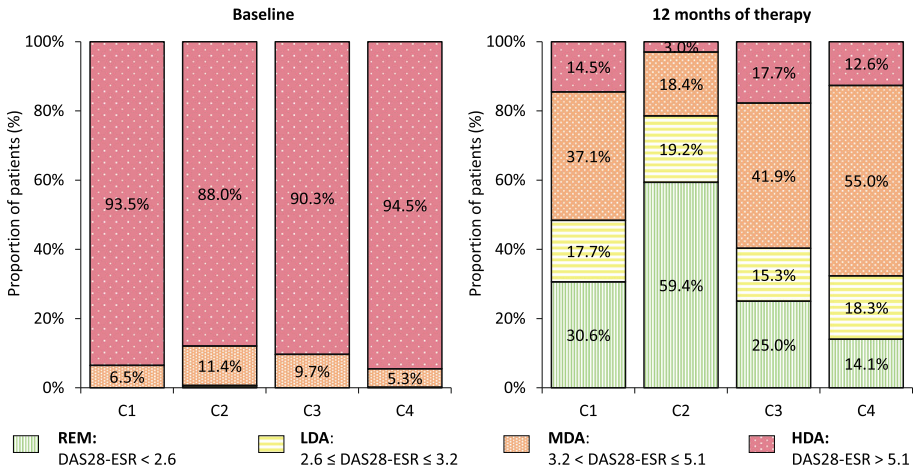
group C1 ($p < 0.001$), 40% patients in group C3 ($p < 0.001$) and 32% in group C4 ($p < 0.001$). Although there was no statistically significant difference in the proportion of patients with REM/LDA between groups C3 (following T2T strategy) and C4 (not following T2T strategy) after 12 months ($p = 0.095$), we could observe slightly better results in group C3 (40% vs 32% with REM/LDA). We observed the lowest median value of DAS28-ESR in group C2, and it falls within the level of remission. The median value of DAS28-ESR in group C1 corresponded to the upper bound of low disease activity, and median DAS28-ESR values in groups C3 and C4 were within the range of moderate disease activity.

Comparison of cohorts C3 and C4 at 6-month and 12-month visit

At the 6-month visit, patients from groups C3 and C4 differed in all tested parameters related to disease activity and quality of life (Table 2). We observed lower disease activity and better quality of life in C4. Patients from C3 and C4 did not significantly differ in concomitant therapy, but numerically more changes in dosage of glucocorticoids and methotrexate have been observed in the C3 cohort compared to the C4 cohort between M6 and M12 (see Supplementary Table 2). At the 12-month visit, patients from both groups did not significantly differ in most of the parameters related to disease activity; they only differed in PTGA ($p = 0.044$) and EQ-5D ($p = 0.017$). In terms of the magnitude of changes across the two visits, patients from C3 significantly improved in all parameters related to disease activity and quality of life (see Supplementary Table 3). Patients from C4 did not significantly improve in CRP and HAQ-DI. In the comparison of the size of changes between the two groups, patients from C3 showed better results (i.e. more significant improvements) in all tested parameters (see Supplementary Table 3).

Odds for treatment target in C3 vs C4 at the 12-month visit

We employed propensity score matching to reduce selection bias by adjusting for potential confounding factors at the 6-month visit. We show a description of patients' characteristics at the 6-month visit after using propensity score matching in Table 3. Both groups included 75 patients after the matching. Density plots of propensity score before and after matching are displayed in Supplementary Figure 3. Patients did not differ anymore in parameters related to disease activity and quality of life (see Table 3). The most frequently administered drugs at the 12-month visit were tocilizumab (27%), certolizumab (17%), abatacept (15%) and etanercept (12%) in C3. Patients from C4 were most frequently treated with adalimumab (35%), etanercept (21%), golimumab (16%) and certolizumab (13%). To compare odds for reaching treatment target at the 12-month visit in patients following the T2T principle at 6-month visit (C3) vs patients staying on the first treatment (C4), we employed a logistic regression model with outcome DAS28-ESR ≤ 3.2. Patients following the T2T principle



Month	DAS28-ESR	C1 (*n*=62)	C2 (*n*=598)	C3 (*n*=124)	C4 (*n*=491)
0	Median (IQR)	6.4 (5.7–7.0)	5.9 (5.3–6.5)	6.2 (5.6–6.8)	6.3 (5.8–6.8)
12	REM+LDA	30 (48.4%)	470 (78.6%)	50 (40.3%)	159 (32.4%)
	Median (IQR)	3.2 (2.4–4.3)	2.4 (1.7–3.1)	3.7 (2.6–4.7)	3.7 (3.0–4.4)

Fig. 2 Disease activity according to DAS28-ESR at baseline and after 1 year of treatment. DAS28-ESR, 28-joint disease activity score with erythrocyte sedimentation; REM, remission; LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity; IQR, interquartile range

Table 2 Comparison of parameters related to disease activity, quality of life and concomitant therapy between C3 and C4 cohorts at the 6-month and 12-month visit

	6 months			12 months		
	C3 (*n* = 124)	C4 (*n* = 491)	*p* value	C3 (*n* = 124)	C4 (*n* = 491)	*p* value
DAS28-ESR (0–10)	5.4 (4.6–6.3)	4.0 (3.5–4.5)	< **0.001**	3.7 (2.6–4.7)	3.7 (3.0–4.4)	0.710
TJC (28 joints)	9.0 (4.0–14.0)	3.0 (2.0–5.0)	< **0.001**	3.0 (1.0–7.0)	2.0 (1.0–5.0)	0.490
SJC (28 joints)	6.0 (2.0–9.5)	2.0 (1.0–4.0)	< **0.001**	2.0 (0.0–4.0)	2.0 (0.0–3.0)	0.498
ESR (mm/h)	28.0 (16.5–46.5)	22.0 (13.0–33.0)	< **0.001**	16.5 (6.5–32.0)	19.0 (11.0–30.5)	0.052
CRP (mg/l)	15.0 (7.9–28.9)	5.7 (2.5–13.7)	< **0.001**	4.7 (1.6–17.0)	5.0 (2.3–11.3)	0.766
SDAI (0–86)	30.2 (19.7–39.5)	13.9 (10.7–18.3)	< **0.001**	13.8 (8.0–20.9)	11.3 (7.7–17.4)	0.093
PTGA (0–100)	61.0 (50.0–75.0)	40.0 (26.0–50.0)	< **0.001**	36.0 (25.0–60.0)	33.0 (20.0–50.0)	**0.044**
MDGA (0–100)	58.0 (40.0–70.0)	30.0 (20.0–40.0)	< **0.001**	25.0 (15.0–45.0)	25.0 (15.0–40.0)	0.812
HAQ-DI (0–3)	1.5 (1.1–1.9)	1.3 (0.9–1.6)	< **0.001**	1.3 (0.9–1.9)	1.3 (0.9–1.6)	0.140
EQ-5D (− 0.59–1)	0.2 (0.1–0.7)	0.7 (0.5–0.7)	< **0.001**	0.6 (0.1–0.7)	0.7 (0.5–0.8)	**0.017**
Concomitant csDMARDs	98 (79.0%)	414 (84.3%)	0.159	94 (75.8%)	407 (82.9%)	0.070
Concomitant MTX	79 (63.7%)	341 (69.5%)	0.220	77 (62.1%)	332 (67.6%)	0.245
Concomitant GCs	95 (76.6%)	374 (76.2%)	0.918	92 (74.2%)	370 (75.4%)	0.789

Continuous variables are described through the median (interquartile range); categorical variables are characterised by *n* (%)
DAS28-ESR 28-joint disease activity score with ESR, *TJC* tender joint count, *SJC* swollen joint count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SDAI* Simplified Disease Activity Index, *PTGA* patient general assessment of disease activity, *MDGA* physician general assessment of disease activity, *HAQ-DI* Health Assessment Questionnaire, *EQ-5D* EuroQol 5 Dimension for measuring the quality of life, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs, *MTX* methotrexate, *GCs* glucocorticoids

(C3) showed 2.8 (CI 1.4–5.8) times higher odds for reaching at least LDA at the 12-month visit ($p = 0.005$) compared to patients not following the T2T principle (C4). In group C3, 41% of patients achieved at least REM/LDA at the 12-month visit, while in group C4, it was 20% (see Supplementary Table 4).

Discussion

In this prospective observational cohort study from real clinical practice in the Czech Republic, we have shown that following the T2T strategy and switching the targeted drug to another therapy after not reaching REM/LDA at the 6-month visit increases the chance of achieving REM/LDA at the 12-month visit as opposed to patients not following the treatment target. This finding support results from previous studies showing that T2T is efficient in daily clinical practice. Our study also provided a summary of four different courses of treatment management during the first year of bDMARD/tsDMARD therapy. We created four patients' cohorts based on switching the treatment and based on reaching a treatment target at 6 months. We described all four patients' groups at baseline and compared their treatment results after 1 year of treatment. Furthermore, we evaluated disease activity and quality of life at 6 months in groups C3 and C4 and compared the sizes of changes from the 6-month to the 12-month visit. We observed that patients not following the T2T at the 6-month visit (C4) had lower disease activity and better quality of life at 6 months than patients following T2T and switching to another therapy after not reaching the treatment target (C3). However, patients following the T2T strategy showed a more significant improvement both in disease activity and quality of life within the period from the 6-month visit to the 12-month visit. Patients from cohort C3 also had a higher rate of REM/LDA at 12 months in comparison with C4 (though not statistically significant; $p = 0.095$).

A similar study investigated whether a tight control treatment strategy (i.e. optimising treatment by measurement of disease activity in order to make treatment adjustments to reach a predefined target LDA/REM) in early RA is more effective than treatment according to usual care in reaching REM (DAS28 < 2.6) after 1 year [4]. They compared two distinct early RA cohorts from two different regions in the Netherlands: the usual care cohort and the 'tight control' cohort. The OR adjusted for baseline DAS28 was 3.1 (95% CI 1.8–5.2). Therefore, patients treated according to tight control had approximately three times higher odds to reach REM at 1 year after the baseline. This result is very similar to the OR obtained in our study, though we evaluated achievement of LDA/REM instead. In another similar study, Norwegian authors compared patients following a T2T strategy (2010–2015) with patients from the pre-T2T cohort (2006–2009) following routine care [13]. They assessed the 2-year effect on disease activity and health-related quality of life and showed significantly higher odds (multivariable OR 1.89, 95% CI 1.33–2.68) for SDAI remission (≤ 3.3) in patients following a T2T strategy. Within

Table 3 Description of patients from C3 and C4 cohorts at the 6-month visit after applying propensity score matching

	C3 (*n* = 75)	C4 (*n* = 75)	*p* value
Female, *n* (%)*	60 (80.0%)	61 (81.3%)	0.836
Age at diagnosis, years, median (IQR)	45.0 (36.0–53.0)	45.0 (37.0–53.0)	0.678
Age at start of 1st line, years, median (IQR)*	52.0 (45.0–61.0)	55.0 (44.0–61.0)	0.811
Disease duration, years, median (IQR)*	5.0 (2.4–12.7)	5.8 (3.0–13.1)	0.937
RF positive, *n* (%)*	60 (80.0%)	54 (72.0%)	0.251
Presence of comorbidities, *n* (%)*	54 (72.0%)	55 (73.3%)	0.855
Currently smoking, *n* (%)*	21 (28.0%)	21 (28.0%)	1.000
Number of previous csDMARDs, *n* (%)*			
0	2 (2.7%)	0 (0.0%)	0.230
1	16 (21.3%)	15 (20.0%)	
2	20 (26.7%)	28 (37.3%)	
3	17 (22.7%)	20 (26.7%)	
4+	20 (26.7%)	12 (16.0%)	
Glucocorticoids in previous history, *n* (%)*	67 (89.3%)	66 (88.0%)	0.797
Concomitant csDMARDs, *n* (%)*	61 (81.3%)	63 (84.0%)	0.666
Concomitant GCs, *n* (%)*	56 (74.7%)	55 (73.3%)	0.852
DAS28-ESR (0–10), median (IQR)	5.0 (4.2–5.9)	5.0 (4.1–5.7)	0.717
TJC (28 joints), median (IQR)*	8.0 (4.0–12.0)	6.0 (3.0–11.0)	0.677
SJC (28 joints), median (IQR)*	4.0 (2.0–8.0)	4.0 (2.0–7.0)	0.973
ESR (mm/h), median (IQR)*	27.0 (15.0–37.0)	25.0 (12.0–41.0)	0.844
CRP (mg/l), median (IQR)*	15.0 (8.0–22.2)	8.4 (3.5–25.7)	0.090
SDAI (0–86), median (IQR)	25.5 (15.6–34.9)	22.7 (16.1–30.9)	0.531
PTGA (0–100), median (IQR)*	60.0 (40.0–71.0)	50.0 (40.0–71.0)	0.519
MDGA (0–100), median (IQR)	55.0 (35.0–70.0)	45.0 (30.0–60.0)	0.059
HAQ-DI (0–3), median (IQR)*	1.5 (1.1–1.9)	1.5 (1.1–1.9)	0.877
EQ-5D (− 0.59–1), median (IQR)[a]	0.2 (0.1–0.7)	0.6 (0.1–0.7)	0.290

These parameters were included in the propensity score model
IQR interquartile range, *RF* rheumatoid factor, *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs, *GCs* glucocorticoids, *DAS28-ESR* 28-joint disease activity score with ESR, *TJC* tender joint count, *SJC* swollen joint count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *SDAI* Simplified Disease Activity Index, *PTGA* patient general assessment of disease activity, *MDGA* physician general assessment of disease activity, *HAQ-DI* Health Assessment Questionnaire, *EQ-5D* EuroQol 5 Dimension for measuring the quality of life
[a] *n* = 74 (C3), *n* = 75 (C4)

secondary outcomes, they also evaluated REM, according to DAS28 (OR 2.15, 95% CI 1.51–3.06).

A Dutch study investigated the 3-year results of a protocolised T2T strategy in daily clinical practice [16]. The authors found out that T2T leads to high remission rates, improved physical function and quality of life, and limited radiographic damage after 3 years in daily clinical practice. In another study from the Netherlands, the authors described a 5-year continuous application of a T2T strategy in patients with early RA in daily clinical practice and confirmed the favourable disease- and patient-related outcomes [12]. A longitudinal study of RA patients from 10 countries (RA BIODAM) investigated whether following a T2T strategy in daily clinical practice leads to more patients meeting REM [14]. Application of T2T every 3 months did not yield a higher likelihood of REM according to DAS44 and DAS28 3 months later, but sustained T2T (i.e. T2T followed in at least two consecutive visits) resulted in an increased likelihood of achieving DAS44 REM (OR 1.19, 95% CI 1.03–1.39).

Our study has shown that a substantial number of patients did not follow the T2T strategy and continued with the same treatment after not reaching the treatment target within 6 months. This finding is probably not unique for the Czech Republic. Others have also shown that the T2T strategy is underused in real clinical practice; e.g. in the analysis from the Corrona RA registry, a considerable proportion of patients continued without changing/accelerating treatment despite not reaching an adequate response to the initial TNF inhibitor therapy at 6 and 12 months [22].

Although the present study has a limitation of the absence of randomisation, we have partially overcome this problem by employing the propensity score matching at the 6-month visit. Thus, we have minimised confounding by other factors, and we obtained the effect of following/not following the T2T principle in the evaluation of REM/LDA at the 12-month visit. A possible limitation of this study could be an absence of monitoring treatment intensification through increased dosages. Further, our study only concerned the first-line bDMARD/tsDMARD therapy. Thus, evaluating of implementation of the T2T strategy within subsequent lines of therapy could be a possible subject for future studies.

Conclusion

In conclusion, the application of T2T principles and switching to another bDMARD/tsDMARD after not reaching REM/LDA within the first 6 months of bDMARD/tsDMARD treatment leads to a higher probability of achieving REM/LDA in RA patients at the 12-month visit. In this study, the T2T strategy showed superiority over traditional routine care in daily clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-020-02393-8.

Additional file 1: Supplementary Table 1. Additional baseline characteristics of patients in cohorts C1–C4 (*N*=1275).

Additional file 2: Supplementary Table 2. Changes in comedication with glucocorticoids and methotrexate during the first year in cohorts C1–C4.

Additional file 3: Supplementary Table 3. Comparison of differences in parameters from month 6 to 12 between cohort C3 and C4.

Additional file 4: Supplementary Table 4. Results of logistic regression with outcome DAS28-ESR ≤ 3.2 for C3 vs C4.

Additional file 5: Supplementary Figure 1. Flow chart showing individual steps to final dataset (a) and division into four cohorts (b).

Additional file 6: Supplementary Figure 2. Disease activity according to DAS28-ESR after three months of treatment.

Additional file 7: Supplementary Figure 3. Propensity score densities of cohorts C3 and C4 before and after matching.

Abbreviations

ACPA: Anti-citrullinated protein antibodies; bDMARDs: Biological disease-modifying anti-rheumatic drugs; CI: Confidence interval; CRP: C-reactive protein; csDMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; CZ: Czech Republic; DAS28-ESR: 28-joint disease activity score using the erythrocyte sedimentation rate; DMARD: Disease-modifying anti-rheumatic drug; EQ-5D: EuroQol-5 Dimensions; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; GCs: Glucocorticoids; HAQ-DI: Health Assessment Questionnaire Disability Index; HDA: High disease activity; IQR: Interquartile range; LDA: Low disease activity; MDA: Moderate disease activity; MDGA: Physician global assessment of disease activity; MTX: Methotrexate; OR: Odds ratio; PTGA: Patient global assessment of disease activity; RA: Rheumatoid arthritis; REM: Remission; RF: Rheumatoid factor; SDAI: Simplified disease activity index; T2T: Treat-to-target; TNFi: Tumour necrosis factor inhibitor; tsDMARDs: Targeted disease-modifying anti-rheumatic drugs; TT: Targeted therapy; VAS: Visual analogue scale

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Authors' contributions

All authors were involved in drafting the manuscript or revising it critically for content. LN planned and performed the analysis, interpreted patients' data and wrote the manuscript. JV, KP and PH revised the manuscript. ZK managed the project. JZ designed the project, supervised its conduct and helped to write the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request. Requests will be considered by the Czech Rheumatological Society.

Ethics approval and consent to participate

All procedures in this study were in accordance with the ethical standards of the institutional and national research committee (Czech Multicentre Research Ethics Committee, no. 201611 S300, and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic, no. 10113/2016) and with the 1964 Helsinki declaration and its later amendments. All subjects provided their written consent for the collection and storage of data before participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

Title Page

Title

Self-perceived general health at start of TNFi therapy predicts therapeutic response in patients with rheumatoid arthritis: analysis from the ATTRA registry

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Abstract

Background: Patient-reported outcomes (PROs) have been shown to predict various disease outcomes. One of the most widely used PRO instruments is the Short Form (SF) 36 questionnaire which evaluates the patient's health status. Our goal was to evaluate the association between therapeutic response and patients' self-perceived general health status at TNFi initiation based on answers to two selected questions (Qs) in the SF-36 questionnaire.

Methods: We included two separate datasets with RA patients (pts) initiating the first-line TNFi within period 01/01/2001–31/12/2017 (primary dataset) and 01/01/2018–01/01/2020 (validation dataset) with at least one-year follow-up and filled SF-36 questionnaire at baseline. Patients were grouped according to their response ('definitely/mostly yes' vs 'definitely/mostly no') to Q11A and Q11C at baseline. The primary outcome was remission (REM) according to DAS28-ESR (<2.6) at the 12-month visit. REM rates were compared across patients' groups with Pearson's chi-squared test. Using logistic regression, crude and adjusted (to baseline DAS28-ESR and HAQ) odds ratios (ORs) were computed. Drug retentions were obtained through the Kaplan-Meier method. We repeated the analysis on propensity score-matched patients at baseline as a sensitivity analysis.

Results: Within the primary dataset (648/792 pts answering positively/negatively to Q11A; 730/580 pts answering positively/negatively to Q11C), patients answering '*yes*' to Q11A/Q11C had 1.5/1.4 times higher odds for REM at 12-month visit than patients answering '*no*'. The odds remained significantly different even after accounting for baseline DAS28-ESR and HAQ and within propensity score-matched datasets. Further, patients answering '*yes*' to Q11A had a 1.3 times higher risk of TNFi discontinuation than patients answering '*no*'. The validation dataset analysis (216/254 pts answering '*yes*'/'*no*' to Q11A; 231/201 answering '*yes*'/'*no*' to Q11C) gave similar results. Patients answering '*yes*' to Q11A/Q11C had 1.7 times higher odds of reaching REM at the 12-month visit than patients responding '*no*'. Even after accounting for baseline disease activity and functional status and within PS-matched datasets, the odds remained significantly higher. However, there was no statistically significant difference in drug retentions.

Conclusions: We provide strong evidence that self-perceived general health at TNFi initiation predicts reaching remission at 12 months in pts with RA.

Keywords

Registry; TNFi; SF-36; Rheumatoid arthritis; Propensity score; Remission; drug retention

Background

One of the main therapy targets in patients with rheumatoid arthritis (RA) is an optimisation of the quality of life. Several instruments were developed to evaluate patients' quality of life and functioning. Patient-reported outcomes (PROs) provide reports directly from patients about their own health, quality of life, or functional status associated with the health care or receiving treatment (1). One of the most widely used PRO instruments is the Short Form (SF) 36 questionnaire which evaluates the patient's health status using eight dimensions and includes 36 questions in total (2). PROs have been shown to predict various disease outcomes in a number of diseases (3–7).

For RA, multiple factors have been identified as predictors of remission, e.g., male sex, young age, short disease duration, or baseline lower disease activity (8,9). Several studies have evaluated the predictive ability of PROs at baseline in patients with early RA (5,10). So far, SF-36 dimensions have not yet been frequently studied as possible predictors for remission achievements in RA patients.

Our primary goal in this study was to evaluate the association between therapeutic response (achieving remission within the first year) and patients' self-perceived general health status at TNFi initiation based on answers to two selected questions from the *general health* dimension in the SF-36 questionnaire. We aimed to compare drug retentions between the studied groups as the secondary goal. We hypothesised that positive responses to questions (Q) 11A '*I seem to get sick a little easier than other people*' and 11C '*I expect my health to get worse*' from the general health (GH) domain of the SF-36 questionnaire may correspond to a more fragile self-perceived GH status, and thus serve as possible predictors of future disease outcomes in patients with RA.

Methods

Study setting and data source

The ATTRA registry, established in 2001, is a non-interventional, prospective, national, observational cohort study. Its primary purpose is to evaluate the safety and effectiveness of bDMARDs/tsDMARDs in patients with chronic inflammatory rheumatic diseases. Patients with RA (and ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis and systemic lupus erythematosus) starting bDMARDs or tsDMARDs are recruited from fifty-six practices sites (private or academic), and the registry captures more than 95% of patients with RA treated with bDMARDs/tsDMARDs in the Czech Republic (CZ).

At the start of therapy, baseline data are collected including demographics (gender, age at diagnosis, age at the start of 1st line treatment, height, weight, presence of comorbidities), disease characteristics (disease duration, presence of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), presence of joint erosions on X-ray), disease activity (swollen and tender joint count (0–28), patient global assessment (PtGA) of disease activity and physician global assessment of disease activity (MDGA) on a 100-mm visual analogue scale (VAS; 0 – best, 100 – worst), erythrocyte sedimentation rate (ESR, mg/h) and C-reactive protein (CRP, mg/L)) and 28-joint disease activity score index (DAS28; 0–10) (11), Health Assessment Questionnaire (HAQ) for patient function with values from 0 to 3 (the higher, the worse disability) (12), EuroQol EQ-5D questionnaire for quality of life with values from –0.59 to 1 (the higher, the better quality of life) (13), and current or previous anti-rheumatic therapies and therapy with glucocorticoids (GCs). Follow-up data on disease activity, disease function and anti-rheumatic therapies are collected after three and six months, and then every six months for three years, with disease activity and anti-rheumatic therapy data collected annually after that.

Ethics approval for ATTRA was granted by the Czech Multicentre Research Ethics Committee (no. 201611 S300) and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic (no. 10113/2016). No additional ethical approval was required for the current analysis. All subjects provided their written consent for collecting and storing data before participation. All procedures were performed following the Declaration of Helsinki.

Study population

In this study, we used two separate datasets for analyses to validate our results – primary dataset (older cohort) and validation dataset (newer cohort). The primary dataset included all bio-naive adult patients diagnosed with RA starting TNFi therapy within a period from the registry data collection start (2001) until 31/12/2017. The validation dataset consisted of all bio-naive adult patients with RA diagnosis starting TNFi therapy between 01/01/2018 and 01/01/2020. Patients without filled SF-36 questionnaire at baseline and without at least one-year follow-up with available 6-month and 12-month visits were excluded from the analysis (see flow charts **Figure 1**).

Study design

We divided patients meeting the inclusion criteria according to their response (definitely/mostly yes, definitely/mostly no, do not know) to Q11A '*I seem to get sick a little easier than other people*', and Q11C '*I expect my health to get worse*' at baseline. We further analysed only patients who answered definitely/mostly yes/no, because we focused only on decisive patients. Therefore, patients who responded '*definitely yes*' and '*mostly yes*' were analysed together (as well as patients responding '*definitely no*' and '*mostly no*'). Patients' subgroups based on their responses are shown in pie charts **Supplementary Figure 1**. We used two separate cohorts (primary and validation datasets) to validate our results. As part of a sensitivity analysis, we performed the whole analysis on the propensity-score matched datasets as well.

Objectives and Outcome measures

Our goal was to investigate whether the two selected SF-36 questions Q11A '*I seem to get sick a little easier than other people*' and Q11C '*I expect my health to get worse*', could predict therapeutic response in patients starting their first TNFi therapy. The therapeutic response was evaluated through remission achievements throughout the first year of TNFi therapy and drug retention.

Our primary outcome was remission (REM) achievement at 6 and 12 months since TNFi treatment initiation. Remission was defined through the disease activity index as DAS28-ESR < 2.6. Besides remission rates, odds ratios (ORs) of remission with '*no*' group as a reference were calculated. Our secondary outcome was drug retention, computed as the time from the first-line TNFi initiation until the date of drug discontinuation (for any reason) or the last update of patients in the registry. Primary and secondary outcomes were evaluated across studied subgroups ('*definitely*/*mostly yes*' vs '*definitely*/*mostly no*') in both datasets (primary and validation) and propensity-score matched datasets afterwards.

Statistical methods

A descriptive summary of patients' demographic and treatment characteristics and disease activity measurements was performed for patients answering '*definitely/mostly yes'* and '*definitely/mostly no*' to Q11A and Q11C. For continuous variables, we calculated the median with interquartile range (IQR,

25th–75th percentiles). For a description of categorical variables, we used absolute and relative frequencies (i.e., percentages). We performed the non-parametric Mann-Whitney *U* test for continuous variables (after normality checks) and Pearson's chi-squared test for categorical variables to test differences between two patients' groups. In case the assumption of Pearson's chi-squared test was violated, Fisher's exact test was used instead. For all tests, P values < 0.05 were considered to be statistically significant.

We computed univariable logistic regression models to obtain odds ratios of remission achievement after 6/12 months of treatment for patients answering '*yes*' vs '*no*' to studied questions. Next, we performed multivariable logistic regression models with baseline HAQ and DAS28-ESR to obtain odds ratios adjusted for potential confounders.

Drug retention was computed through the Kaplan-Meier survival method. Drug survival probabilities were displayed through Kaplan-Meier curves and supplemented by numbers of patients at risk beneath the graphs. We also present numbers of discontinuations, one-year and two-year survival rates and median survival time with corresponding confidence intervals. The probabilities of drug discontinuations were compared across the studied groups through the Log-rank test. If the curves were crossing, we also computed the Breslow and Tarone-Ware tests. Finally, we employed Cox regression models to estimate hazard ratios (HRs) for treatment discontinuation for patients answering '*yes*' vs '*no*' to studied questions. Besides crude hazard ratios, we obtained adjusted versions with baseline HAQ and DAS28-ESR as confounders.

For the sensitivity analysis, we created balanced datasets for both subgroups (answering '*yes*' and '*no*'). We used propensity score matching to match patients answering '*yes*' to patients responding '*no*' within each studied question. We performed logistic regression with the outcome variable '*yes*' (=1) vs '*no*' (=0) and selected baseline covariates for matching. The covariates were chosen based on statistically significant differences in baseline characteristics with respect to clinical relevance and multicollinearity. We chose the matching ratio 1:1 and set the caliper to 0.2. The adequacy of the final propensity score model was checked through the balance diagnostics (standardised mean differences should be less than 0.1 to ensure balance in selected covariates). We used matching to make both groups comparable in baseline characteristics and to minimise confounding by other factors in evaluating REM achievements at the 6-/12-month visit and in the evaluation of drug retentions.

We did not impute missing data in this analysis and performed an available-case analysis instead. We used IBM SPSS Statistics 25.0 to compute all descriptive statistics and comparisons. The propensity score model was performed in R (version 3.5.3).

Results

Patients' characteristics at baseline

Within the primary dataset (older cohort), 648 (45.0%) / 792 (55.0%) patients responded positively/negatively to Q11A and 730 (55.7%) / 580 (44.3%) patients answered '*yes*'/'*no*' to Q11C.

There was a statistically significantly higher percentage of women, higher frequency of comorbidities, a higher number of previous csDMARDs, more frequent GCs in previous therapy, and a higher percentage of csDMARDs and GCs in concomitant therapy in patients answering '*yes*' to Q11A compared to patients answering '*no*'. Further, patients answering '*yes*' had statistically significantly higher disease activity (DAS28-ESR), worse quality of life (lower EQ-5D, higher HAQ), but lower MDGA. Patients answering '*yes*' to Q11C had significantly longer disease duration, a bigger number of previous csDMARDs, worse quality of life (lower EQ 5D, higher HAQ), and lower MDGA compared to patients answering '*no*'. The summary of baseline characteristics can be found in **Table 1**.

Together 216 (46.0%) / 254 (54.0%) patients responded positively/negatively to Q11A in the validation dataset (newer cohort). Within Q11C, 231 (53.3%) / 201 (46.5%) patients responded '*yes*'/'*no*'. There was a statistically significantly higher number of previous csDMARDs, higher disease activity (e.g. DAS28-ESR), worse quality of life (lower EQ-5D, higher HAQ) and higher frequency of biosimilars in patients answering '*yes*' to Q11A compared to patients responding '*no*'. Patients answering '*yes*' to Q11C had statistically significantly higher disease activity (e.g. DAS28-ESR), worse quality of life (lower EQ-5D, higher HAQ) and higher frequency of biosimilars than patients responding negatively. The overview of all baseline characteristics for each patients' group is presented in **Supplementary Table 1a**.

For a sensitivity analysis, we prepared propensity score-matched datasets. Within the primary dataset, 574 patients responding '*yes*' and 574 responding '*no*' to Q11A were matched based on the computed PS. Further, 550 from the group answering '*yes*' and 550 from the group answering '*no*' to Q11C were matched based on the computed PS. After the matching, patients only differed in the quality of life parameters (EQ-5D, HAQ). We did not include these parameters in the PS model as they correlated with the SF-36 questionnaire (and thus with our studied groups). Summary of baseline characteristics in each propensity score-matched group is presented in **Supplementary Table 1b**. In the validation dataset, both patients answering '*yes*'/'*no*' to Q11A included 185 patients after the matching. For patients answering '*yes*'/'*no*' to Q11C, both groups included 169 patients. Patients only differed in EQ-5D after the matching. Summary of baseline characteristics in each propensity score-matched group is presented in **Supplementary Table 1c**.

Comparison of remission achievement within the first year

Comparison of remission rates according to DAS28-ESR score after 3, 6 and 12 months of TNFi treatment between patients answering '*yes*' and '*no*' to Q11A and Q11C within the primary dataset (older cohort) is displayed in **Figure 2**. We could observe a statistically significantly higher frequency of remission at all visits within the first year (e.g. 38.8% vs 30.1% at 12 months) in patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. Similarly, remission was achieved statistically significantly more frequently after 3, 6 and 12 (37.3% vs 29.5%) months in patients who expected their health to get worse at the treatment initiation than patients who did not expect it. Remission rates remained significantly different even when computed within patients staying on the treatment through the Lundex index (not shown here) (14).

Patients answering '*yes*' to Q11A had almost 1.5 × higher odds for remission both at the 6- and 12-month visit than patients answering '*no*'. Patients answering '*yes*' to Q11C had 1.7 (1.4) × higher odds for remission at the 6-month (12-month) visit than patients answering '*no*'. Both crude and adjusted odds ratios for reaching remission are shown in **Table 2**. Even after accounting for baseline disease activity and functional status, the odds for remission remained significantly different.

Within the validation dataset (newer cohort), remission was achieved statistically significantly more often after 6 and 12 months in patients answering '*yes*' to Q11A than patients answering '*no*'. At the 3-month visit, the difference was not statistically significant. Similarly, patients answering '*yes*' to Q11C achieved remission after 12 months statistically significantly more often than patients answering '*no*'. Even though the remission rates did not statistically significantly differ at 3- and 6-month visits, there were also tendencies for the more frequent occurrence of remission in patients answering '*yes*' to Q11C (see **Supplementary Figure 2**). Both patients answering '*yes*' to Q11C and Q11A had significantly higher odds (1.7 times) of reaching remission at the 12-month visit than patients answering '*no*' to these questions. The odds remained significantly higher after accounting for baseline disease activity and functional status (see **Supplementary Table 2a**).

Concurrently, we evaluated remission achievements in PS-matched datasets. Within PS-matched primary dataset, patients who seemed to get sick a little easier than other people at the treatment initiation (Q11A) achieved remission more often after six months (31.4% vs 24.2%; p=0.007) and twelve months (36.3% vs 28.5%; p=0.005) than patients who did not think that. Similarly, remission was achieved more often after six months (32.5% vs 23.0%; p<0.001) and twelve months (36.6% vs 29.7%; p=0.015) in patients who expected their health to get worse at the treatment initiation than patients who did not expect their health to get worse (Q11C). Patients answering '*yes*' to Q11A had 1.4 × higher odds for remission at both 6- and 12-month visits than patients answering '*no*'. Patients answering '*yes*' to Q11C had 1.6 (1.4) × higher odds for remission at the 6-month (12-month) visit than patients answering '*no*' (see **Supplementary Table 2b**). Within PS-matched validation dataset, patients who seemed to get sick a little easier than other people at the treatment initiation (Q11A) achieved remission more often after six months (36.1% vs 30.8%) and twelve months (47.8% vs 35.0%) than patients who did not think that. The difference was statistically significant only at the 12-month visit. Similarly, remission was achieved more often after six months (40.5% vs 35.7%) and twelve months (46.7% vs 36.7%) in patients who expected their health to get worse at the treatment initiation than patients who did not expect their health to get worse (Q11C). Patients answering '*yes*' to Q11A had 1.7 × higher odds for remission both at the 12-month visit than patients answering '*no*' (p=0.013). Patients answering '*yes*' to Q11C had 1.5 × higher odds for remission at the 12-month visit than patients answering '*no*', but the result was only close to statistical significance (p=0.066). See **Supplementary 2b** for an overview of logistic regression results.

Comparison of drug retentions

Comparison of probabilities of staying on the first-line TNFi in patients answering '*yes*'/'*no*' to Q11A and Q11C within the primary dataset (older cohort) is presented in **Figure 3**. There was found a

statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation than patients who did not think that. Patients answering '*yes*' had a 1.3 times higher risk of treatment discontinuation than patients answering '*no*'. Even after adjustment for baseline DAS28-ESR and HAQ, the risk remained 1.3 times higher in the '*yes*' group. The estimated 1-year retention rate was 83.2% (95% CI 80.4–86.1) in the '*yes*' group and 86.4% (95% CI 84.0–88.8) in the '*no*' group. The estimated 2-year retention rate was 67.8% (95% CI 64.2–71.5) and 73.3% (95% CI 70.2–76.5) in patients answering '*yes*' and '*no*'. The numbers of discontinuations and median survival times are presented in **Table 3**. The median length of follow-up in patients answering '*yes*' was 61 months, and in patients answering '*no*', it was 68 months. The most frequent reason for discontinuation was a loss of effect and inefficacy. There was no statistically significant difference (p-values of Log-rank, Breslow and Tarone-Ware test > 0.05) in the probability of staying on the first TNFi between the patients who expected their health to get worse at treatment initiation and patients who did not expect their health to get worse (see **Figure 3**).

Within the validation dataset (newer cohort), there was no statistically significant difference in drug retentions between patients answering *yes* and *no* to Q11A/Q11C (see **Supplementary Figure 3a**).

Drug retentions computed on the PS-matched datasets are presented in **Supplementary Figure 3b**. Within the PS-matched primary dataset, there was a statistically significant difference in probabilities of staying on the first TNFi between patients who seemed to get sick a little easier than other people at the treatment initiation (Q11A) than patients who did not think that. The median survival was 42.8 (CI 36.0–49.6) months in the '*yes*' groups and 66.4 (CI 52.7–80.2) months in the '*no*' group. Within the PS-matched validation dataset, there was no statistically significant difference in TNFi retention probabilities between the studied groups.

Discussion

In this prospective observational cohort study from real clinical practice in the Czech Republic, we evaluated the predictive ability of two SF-36 questionnaire questions, specifically Q 11A '*I seem to get sick a little easier than other people*', and Q 11C '*I expect my health to get worse*'. We hypothesised that positive responses to these questions might correspond to more fragile, self-perceived general health status, thus serving as possible predictors of future patient disease outcomes. For each diagnosis, we used separate datasets to validate our hypothesis. Apart from univariable models to quantify odds and hazard ratios, we employed multivariable models adjusted for baseline disease activity and quality of life. Furthermore, we repeated the whole analysis within propensity score-matched patients to make both study groups (answering '*yes*'/'*no*' to Q11A and Q11C) comparable in baseline characteristics, thus reducing selection bias. By employing the propensity score matching at baseline, we have partially overcome missing randomisation in this study. Overall, we employed three ways to verify our results: 1) adjustment for baseline disease activity and functional status; 2) two separate datasets (primary and validation); 3) propensity-score matched datasets.

The results of the primary dataset were presented within the 62nd Annual Congress of Czech and Slovak Rheumatologists in 2018, Prague. We have shown that patients answering positively to Q11A and patients answering positively to Q11C have significantly higher odds of reaching remission at 6- and 12-month visits than patients answering to these questions negatively. This difference in remission rates and odds ratios remained statistically significant even when computed on propensity score-matched patients who were balanced in baseline characteristics. We obtained analogical results in the validation dataset of RA patients as well. Patients answering positively to Q11A (or Q11C) had significantly higher odds of remission achievement at the 12-month visit than patients responding to these questions negatively. Within the propensity score-matched dataset, patients responding 'yes' to Q11A had significantly higher odds of remission at the 12-month visit than patients answering 'no'. For Q11C, the difference was not statistically significant at the 12-month visit, but it was very close to the statistical significance (p=0.066). Overall, we provided robust evidence that self-perceived general health at the start of TNFi therapy predicts reaching remission at 12 months in patients with RA. In terms of treatment discontinuation, patients answering '*yes*' to Q11A had a significantly higher probability of treatment discontinuation than patients answering '*no*' within the primary dataset (older cohort). In the validation dataset (newer cohort), there was no statistically significant difference in the probability of treatment discontinuation between patients answering positively/negatively to the studied SF-36 questions.

The predictive ability of SF-36 dimensions was not very investigated so far. A randomised clinical trial studied PROs as predictors of remission in early RA (5). At baseline, they measured eight SF-36 questionnaire dimensions, PGA, HAQ, and pain (VAS). Remission at two years was associated with SF-36 dimensions: higher vitality (OR 2.0; 95% CI 1.2–3.4) and better emotional role functioning (OR 1.6; 95% CI 1.0–2.7). The general health dimension (to which our two studied questions belonged) was not associated with remission in this study. A three-year prospective observational study of a Brazilian early RA cohort evaluated whether baseline scores (HAQ and SF-36) can predict the achievement of remission (DAS28 <2.6) (10). Neither initial HAQ nor SF-36 scores were associated with clinical remission. The baseline general health score was not significantly different between patients achieving and not achieving remission. In the randomised controlled CareRA-trial, they studied how psychosocial aspects affect the probability of achieving sustained remission in early RA (15). Suboptimal psychosocial wellbeing and negative illness perceptions were associated with lower odds of sustained remission. The general health dimension of the SF-36 questionnaire was not investigated in this study. They only focused on mental dimensions.

Our results within the RA cohort are quite surprising because we assumed that patients who expected their health to get worse at treatment initiation and patients who seemed to get sick a little easier than other people at treatment initiation would have lower odds of treatment response (achieving remission within one year) than patients who did not think that. However, the results showed the exact opposite. Thus, it would be interesting to include a psychologist in future studies to get a deeper insight. Including more questions from different SF-36 dimensions is another point for further studies.

Conclusion

In conclusion, we provided robust evidence that self-perceived general health at the start of TNFi therapy predicts reaching remission at 12 months in patients with RA. Patients who seemed to get sick a little easier than other people at treatment initiation and patients who expected their health to get worse at treatment initiation had significantly higher odds of reaching REM within the first year than patients who did not think that.

List of abbreviations

ACPA: anti-citrullinated protein antibodies

bDMARDs: biological disease-modifying anti-rheumatic drugs

CI: confidence interval

CRP: C-reactive protein

csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs

CZ: Czech Republic

DAS28-ESR: 28-joint disease activity score using the erythrocyte sedimentation rate

DMARD: disease-modifying anti-rheumatic drugs

EQ-5D: EuroQol-5 Dimensions

ESR: erythrocyte sedimentation rate

GCs: glucocorticoids

HAQ-DI: health assessment questionnaire disability index

HR: hazard ratio

IQR: interquartile range

MDGA: physician global assessment of disease activity

MTX: methotrexate

OR: odds ratio

PROs: patient-reported outcomes

PtGA: patient global assessment of disease activity

Qs: questions

RA: rheumatoid arthritis

REM: remission

RF: rheumatoid factor

SF-36: 36-item short form survey

SDAI: simplified disease activity index

TNFi: tumour necrosis factor inhibitor

tsDMARDs: targeted disease-modifying anti-rheumatic drugs

VAS: visual analogue scale

Declarations

Ethics approval and consent to participate

All procedures in this study were in accordance with the ethical standards of the institutional and national research committee (Czech Multicentre Research Ethics Committee, no. 201611 S300 and Institutional Ethics Committee of Institute of Rheumatology, Prague, Czech Republic, no. 10113/2016) and with the 1964 Helsinki declaration and its later amendments. All subjects provided their written consent for the collection and storage of data before participation.

Consent for publication

Not applicable

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request. Requests will be considered by the Czeach Rheamatological Society.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

All authors were involved in drafting the manuscript or revising it critically for content. LN planned and performed the analysis, interpreted patients' data and wrote the manuscript. JV, KP and PH revised

the manuscript. RR managed the project. JZ designed the project, supervised its conduct, and helped to write the manuscript. All authors read and approved the final manuscript.

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Figures, tables and additional files

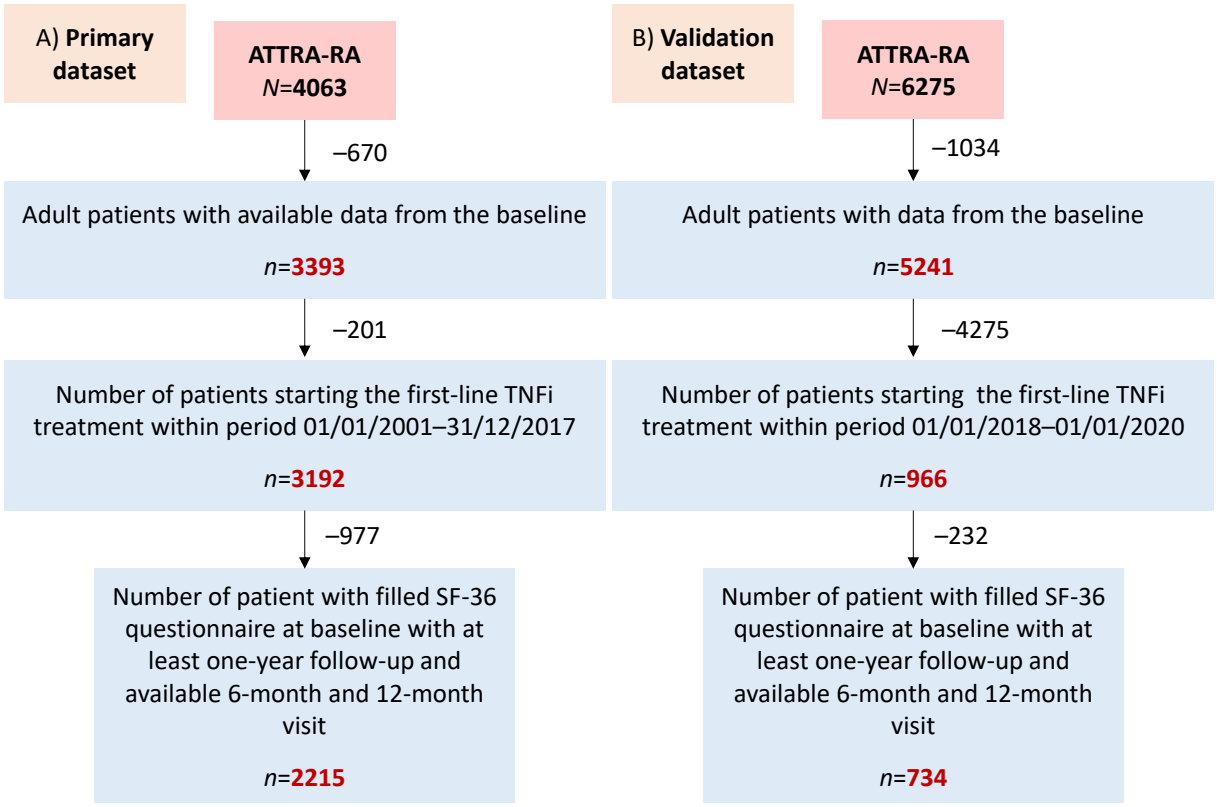
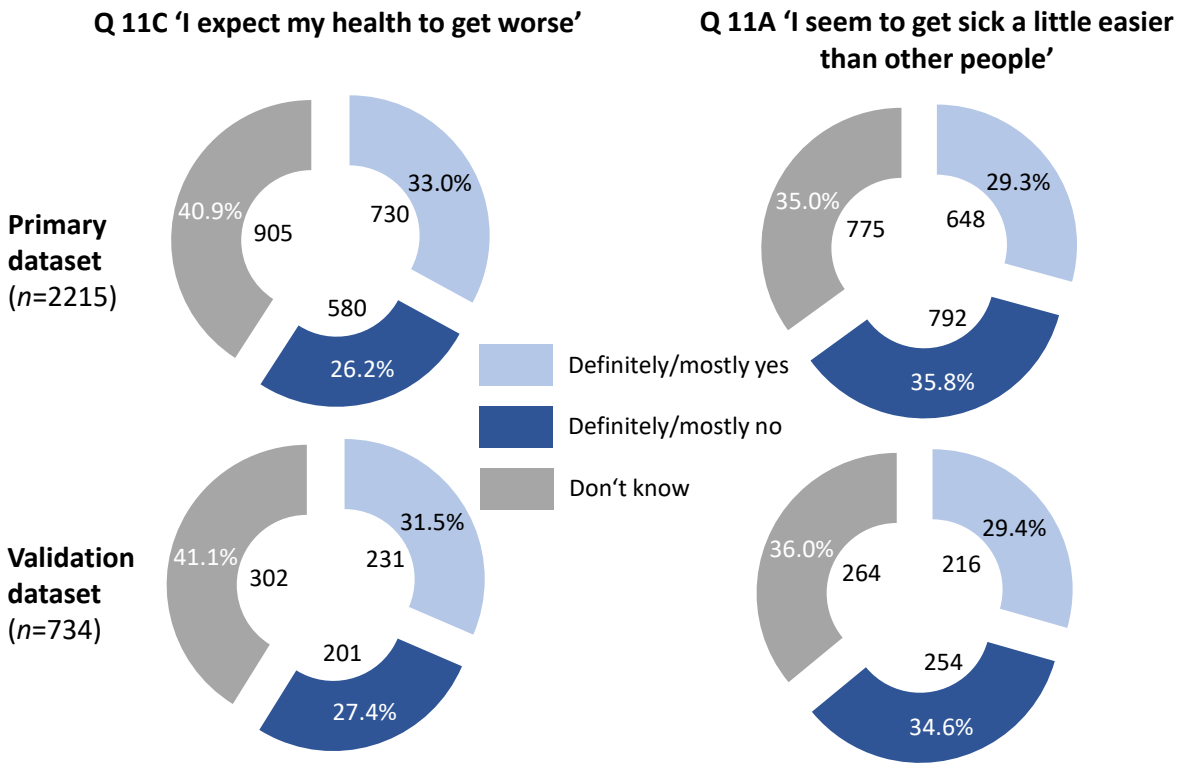


Figure 1. Flow chart showing individual steps to the final datasets.

(A) primary dataset (older cohort); (B) validation dataset (newer cohort)



Supplementary Figure 1 Division of RA patients based on their answers to two selected SF-36 questions

Table 1 Baseline characteristics of patients answering '*yes*'/'*no*' to studied questions within primary dataset

	Q11A (*N*=1440)		**Q11C** (*N*=1310)	
Characteristic	***Yes*** (*n*=648)	***No*** (*n*=792)	***Yes*** (*n*=730)	***No*** (*n*=580)
Female	**539** (**83.2%**)	**612** (**77.3%**)	577 (79.0%)	468 (80.7%)
Age at diagnosis, years	43.0 (33.0–51.0)	42.0 (33.0–51.0)	42.0 (33.0–50.0)	43.0 (32.0–52.0)
Age at start of 1st line, years	52.0 (43.0–60.0)	52.0 (43.0–59.0)	52.0 (44.0–60.0)	52.5 (42.0–60.0)
Disease duration, years	7.3 (3.4–12.8)	6.8 (3.2–13.1)	**7.8** (3.8–13.4)	**6.1** (2.9–12.5)
RF positive	453/595 (76.1%)	499/689 (72.4%)	487/649 (75.0%)	374/511 (73.2%)
ACPA positive	377/548 (68.8%)	438/621 (70.5%)	405/588 (68.9%)	341/469 (72.7%)
Presence of comorbidities	**356 (54.9%)**	**377 (47.6%)**	374 (51.2%)	298 (51.4%)
BMI[a]	25.6 (22.9–29.4)	25.6 (22.6–28.8)	25.7 (22.8–29.4)	25.5 (22.9–28.7)
Previous csDMARDs				
0–1	**93/641 (14.5%)**	**173/784 (22.1%)**	**110/724 (15.2%)**	**140/576 (24.3%)**
2	**123/641 (19.2%)**	**193/784 (24.6%)**	**142/724 (19.6%)**	**157/576 (27.3%)**
3	**126/641 (19.7%)**	**174/784 (22.2%)**	**146/724 (20.2%)**	**118/576 (20.5%)**
4+	**299/641 (46.6%)**	**244/784 (31.1%)**	**326/724 (45.0%)**	**161/576 (28.0%)**
GCs in previous history	**601/646 (93.0%)**	**701/787 (89.1%)**	669/726 (92.1%)	526/578 (91.0%)
Concomitant csDMARDs	**551** (**85.0%**)	**633** (**79.9%**)	604 (82.7%)	463 (79.8%)
Concomitant MTX	415 (64.0%)	522 (65.9%)	465 (63.7%)	384 (66.2%)
Concomitant GCs	**417** (**64.4%**)	**451** (**56.9%**)	459 (62.9%)	342 (59.0%)
DAS28-ESR (0–10)	**6.3** (5.8–6.8)	**6.2** (5.6–6.8)	6.3 (5.7–6.8)	6.3 (5.6–6.9)
TJC (28 joints)	13.0 (10.0–18.0)	13.0 (9.0–17.0)	13.0 (10.0–17.0)	13.0 (9.0–18.0)
SJC (28 joints)	10.0 (8.0–14.0)	10.0 (7.0–14.0)	10.0 (8.0–14.0)	10.0 (7.0–14.0)
ESR (mm/h)	**35.0** (22.0–50.0)	**32.0** (21.0–47.0)	35.0 (22.0–48.0)	32.0 (22.0–50.0)
CRP (mg/l)	**18.9** (9.3–34.0)	**15.5** (6.7–32.6)	17.4 (8.9–33.0)	16.9 (7.1–32.5)
PtGA (0–100)	70.0 (60.0–80.0)	70.0 (59.0–80.0)	70.0 (60.0–80.0)	70.0 (60.0–80.0)
MDGA (0–100) [b]	**60.0** (50.0–75.0)	**68.0** (52.0–80.0)	**60.0** (50.0–75.0)	**66.0** (52.0–78.0)
HAQ-DI (0–3)	**1.6** (1.3–2.0)	**1.5** (1.0–1.9)	**1.6** (1.3–2.0)	**1.5** (1.0–1.9)
EQ-5D (-0.59–1)	**0.1** (0.0–0.5)	**0.2** (0.1–0.7)	**0.1** (0.0–0.5)	**0.2** (0.1–0.7)
Year od administration				
2001–2011	**383 (59.1%)**	**452 (57.1%)**	455 (62.3%)	317 (54.7%)
2012–2013	**105 (16.2%)**	**99 (12.5%)**	97 (13.3%)	84 (14.5%)
2014–2015	**93 (14.4%)**	**159 (20.1%)**	115 (15.7%)	111 (19.1%)
2016–2017	**67 (10.3%)**	**82 (10.4%)**	63 (8.6%)	68 (11.7%)
TNFi: adalimumab	**278 (42.9%)**	**348 (43.9%)**	311 (42.6%)	247 (42.6%)
TNFi: etanercept	**186 (28.7%)**	**162 (20.5%)**	186 (25.5%)	120 (20.7%)
TNFi: infliximab	**103 (15.9%)**	**175 (22.1%)**	147 (20.1%)	130 (22.4%)
TNFi: certolizumab	**33 (5.1%)**	**52 (6.6%)**	35 (4.8%)	40 (6.9%)
TNFi: golimumab	**48 (7.4%)**	**55 (6.9%)**	51 (7.0%)	43 (7.4%)
Bs ADA/ETA/INF	22/567 (3.9%)	30/685 (4.7%)	30/644 (4.7%)	28/497 (5.6%)

IQR interquartile range; *RF* rheumatoid factor; *ACPA* anti-citrullinated protein; TNFi tumour necrosis factor inhibitor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented. Statistical significant differences (p<0.05) across patients' groups are marked in bold.

[a] BMI: *n*=352 (Q11A '*yes*'), *n*=392 (Q11A '*no*'), *n*=510 (Q11C 'yes'), *n*=398 (Q11C 'no')

[b] MDGA: *n*=352 (Q11A '*yes*'), *n*=392 (Q11A '*no*'), *n*=365 (Q11C 'yes'), *n*=305 (Q11C 'no')

Supplementary Table 1a Baseline characteristics of patients answering '*yes*'/'*no*' to studied questions within validation dataset

	Q11A (*N*=470)		**Q11C** (*N*=432)	
Characteristic	***Yes*** (*n*=216)	***No*** (*n*=254)	***Yes*** (*n*=231)	***No*** (*n*=201)
Female	178 (82.4%)	196 (77.2%)	181 (78.4%)	163 (81.1%)
Age at diagnosis, years	46.0 (34.0–54.5)	46.0 (35.0–55.0)	47.0 (35.0–55.0)	44.0 (35.0–55.0)
Age at start of 1st line, years	54.5 (43.0–64.0)	55.0 (44.0–63.0)	55.0 (46.0–64.0)	53.0 (43.0–63.0)
Disease duration, years	6.0 (2.8–11.7)	6.0 (2.1–10.4)	5.7 (2.8–11.8)	5.7 (2.0–10.4)
RF positive	147/214 (68.7%)	179/247 (72.5%)	158/228 (69.3%)	133/199 (66.8%)
ACPA positive	151/209 (72.2%)	168/246 (68.3%)	155/223 (69.5%)	137/199 (68.8%)
Presence of comorbidites	150 (69.4%)	170 (66.9%)	158 (68.4%)	132 (65.7%)
BMI	27.3 (23.7–31.5)	25.7 (23.0–30.1)	27.1 (23.5–30.3)	26.7 (24.0–30.8)
Previous csDMARDs				
0–1	**61 (28.2%)**	**82 (32.3%)**	61 (26.4%)	63 (31.3%)
2	**63 (29.2%)**	**99 (39.0%)**	84 (36.4%)	81 (40.3%)
3	**57 (26.4%)**	**45 (17.7%)**	51 (22.1%)	42 (20.9%)
4+	**35 (16.2%)**	**28 (11.0%)**	35 (15.2%)	15 (7.5%)
GCs in previous history	198 (91.7%)	231 (90.9%)	205 (88.7%)	186 (92.5%)
Concomitant csDMARDs	188 (87.0%)	229 (90.2%)	199 (86.1%)	183 (91.0%)
Concomitant MTX	162 (75.0%)	191 (75.2%)	172 (74.5%)	154 (76.6%)
Concomitant GCs	151 (69.9%)	156 (61.4%)	151 (65.4%)	133 (66.2%)
DAS28-ESR (0–10)	**6.3** (5.7–7.1)	**6.0** (5.3–6.7)	**6.3** (5.6–6.9)	**6.0** (5.3–6.5)
TJC (28 joints)	**14.0** (10.0–19.0)	**13.0** (9.0–17.0)	**14.0** (10.0–18.0)	**13.0** (9.0–17.0)
SJC (28 joints)	10.0 (6.0–13.5)	9.0 (6.0–12.0)	**10.0** (7.0–13.0)	**8.0** (5.0–11.0)
ESR (mm/h)	**34.0** (22.0–49.0)	**30.0** (16.5–43.5)	30.0 (19.0–45.0)	27.0 (15.0–40.0)
CRP (mg/l)	15.0 (7.0–25.0)	13.0 (5.3–25.0)	14.7 (6.0–25.0)	13.2 (6.0–22.7)
PtGA (0–100)	**80.0** (70.0–85.0)	**70.0** (60.0–85.0)	**75.0 (65.0–85.0)**	**70.0 (60.0–80.0)**
MDGA (0–100)	70.0 (50.0–80.0)	70.0 (60.0–80.0)	68.0 (50.0–80.0)	70.0 (60.0–80.0)
HAQ-DI (0–3)	**1.6** (1.3–2.1)	**1.5** (1.1–2.0)	**1.5** (1.1–2.0)	**1.4** (1.0–2.0)
EQ-5D (-0.59–1)	**0.1** (0.0–0.2)	**0.2** (0.1–0.7)	**0.1** (0.0–0.3)	**0.2** (0.1–0.7)
Year od administration				
2018	69 (31.9%)	93 (36.6%)	69 (29.9%)	72 (35.8%)
2019	147 (68.1%)	161 (63.4%)	162 (70.1%)	129 (64.2%)
TNFi				
Adalimumab	102 (47.2%)	103 (40.6%)	110 (47.6%)	79 (39.3%)
Etanercept	66 (30.6%)	89 (35.0%)	75 (32.5%)	61 (30.3%)
Infliximab	10 (4.6%)	9 (3.5%)	6 (2.6%)	14 (7.0%)
Certolizumab	24 (11.1%)	27 (10.6%)	20 (8.7%)	21 (10.4%)
Golimumab	14 (6.5%)	26 (10.2%)	20 (8.7%)	26 (12.9%)
Bs ADA/ETA/INF	**96/178 (53.9%)**	**64/201 (31.8%)**	**100/191 (52.4%)**	**56/154 (36.4%)**

IQR interquartile range; *RF* rheumatoid factor; *ACPA* anti-citrullinated protein; TNFi tumour necrosis factor inhibitor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life
For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented. Statistical significant differences (p<0.05) across patients' groups are marked in bold.

Supplementary Table 1b Baseline characteristics of patients answering 'yes'/'no' to studied questions within propensity score-matched primary dataset

	Q11A (*N*=1148)		**Q11C** (*N*=1100)	
Characteristic	***Yes*** (*n*=574)	***No*** (*n*=574)	***Yes*** (*n*=550)	***No*** (*n*=550)
Female*	469 (81.7%)	455 (79.3%)	438 (79.6%)	443 (80.5%)
Age at diagnosis, years	43.0 (32.0–50.0)	42.0 (34.0–50.0)	42.0 (33.0–51.0)	43.0 (32.0–52.0)
Age at start of 1st line, years	52.0 (43.0–59.0)	52.0 (44.0–59.0)	52.0 (43.0–60.0)	53.0 (42.0–60.0)
Disease duration*, years	7.2 (3.3–13.0)	7.2 (3.5–13.3)	7.4 (3.3–13.0)	6.1 (3.0–13.0)
RF positive	397 (76.1%)	374 (73.0%)	362 (74.2%)	355 (73.0%)
ACPA positive	334 (69.9%)	328 (71.9%)	310 (69.2%)	325 (73.0%)
Presence of comorbidities	312 (54.4%)	285 (49.7%)	294 (53.5%)	281 (51.1%)
BMI[a]	25.5 (22.8–29.7)	25.3 (22.4–28.8)	25.5 (22.7–29.4)	25.4 (22.8–28.4)
Previous csDMARDs*				
0–1	93 (16.2%)	96 (16.7%)	109 (19.8%)	125 (22.8%)
2	123 (21.4%)	129 (22.5%)	134 (24.4%)	147 (26.7%)
3	124 (21.6%)	130 (22.6%)	121 (22.0%)	118 (21.5%)
4+	234 (40.8%)	219 (38.2%)	186 (33.8%)	160 (29.1%)
GCs in previous history	532 (92.7%)	519 (90.6%)	499 (90.7%)	499 (90.9%)
Concomitant csDMARDs*	481 (83.8%)	477 (83.1%)	455 (82.7%)	438 (79.6%)
Concomitant MTX	371 (64.6%)	381 (66.4%)	354 (64.4%)	361 (65.6%)
Concomitant GCs*	363 (63.2%)	347 (60.5%)	339 (61.6%)	330 (60.0%)
DAS28-ESR* (0–10)	6.3 (5.8–6.9)	6.3 (5.6–6.9)	6.3 (5.7–6.8)	6.3 (5.6–6.9)
TJC (28 joints)	14.0 (10.0–18.0)	13.0 (9.0–18.0)	13.0 (10.0–18.0)	13.0 (9.0–18.0)
SJC (28 joints)	10.0 (8.0–14.0)	10.0 (7.0–14.0)	10.0 (8.0–14.0)	10.0 (7.0–14.0)
ESR (mm/h)	34.0 (21.0–50.0)	16.2 (7.0–32.3)	33.0 (21.0–46.0)	32.0 (22.0–49.0)
CRP (mg/l)	17.9 (8.4–32.4)	32.0 (21.0–47.0)	16.0 (8.3–31.9)	16.8 (7.1–32.0)
PtGA (0–100)	70.0 (60.0–80.0)	70.0 (60.0–80.0)	70.0 (60.0–80.0)	70.0 (60.0–80.0)
MDGA (0–100) [b]	**60.0 (50.0–75.0)**	**68.0 (53.0–80.0)**	**60.0 (50.0–75.0)**	**69.0 (52.0–80.0)**
HAQ-DI (0–3)	**1.6 (1.3–2.0)**	**1.5 (1.0–1.9)**	**1.6 (1.3–2.0)**	**1.5 (1.0–1.9)**
EQ-5D (-0.59–1)	**0.1 (0.0–0.5)**	**0.2 (0.1–0.7)**	**0.1 (0.0–0.5)**	**0.2 (0.1–0.7)**
Year od administration*				
2001–2011	339 (59.1%)	346 (60.3%)	316 (57.5%)	307 (55.8%)
2012–2013	54 (14.6%)	78 (13.6%)	80 (14.5%)	82 (14.9%)
2014–2015	89 (15.5%)	89 (15.5%)	97 (17.7%)	104 (18.9%)
2016–2017	62 (10.8%)	61 (10.6%)	57 (10.4%)	57 (10.4%)
Adalimumab*	259 (45.1%)	244 (42.5%)	232 (42.2%)	234 (42.5%)
Etanercept*	142 (24.7%)	145 (25.3%)	133 (24.2%)	117 (21.3%)
Infliximab*	100 (17.4%)	108 (18.8%)	111 (20.2%)	121 (22.0%)
Certolizumab*	30 (5.2%)	32 (5.6%)	33 (6.0%)	37 (6.7%)
Golimumab*	43 (7.5%)	45 (7.8%)	41 (7.5%)	41 (7.5%)
Bs ADA/ETA/INF	20 (4.0%)	22 (4.4%)	25 (5.3%)	25 (5.3%)

IQR interquartile range; *RF* rheumatoid factor; *ACPA* anti-citrullinated protein; TNFi tumour necrosis factor inhibitor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented. Statistical significant differences (p<0.05) across patients' groups are marked in bold.

[a] BMI: *n*=426 (Q11A '*yes*'), *n*=383 (Q11A '*no*'), *n*=393 (Q11C 'yes'), *n*=373 (Q11C 'no')

[b] MDGA: *n*=313 (Q11A '*yes*'), *n*=273 (Q11A '*no*'), *n*=299 (Q11C 'yes'), *n*=283 (Q11C 'no')

* Variables included in the propensity score model.

Supplementary Table 1c Baseline characteristics of patients answering 'yes'/'no' to studied questions within propensity score-matched validation dataset

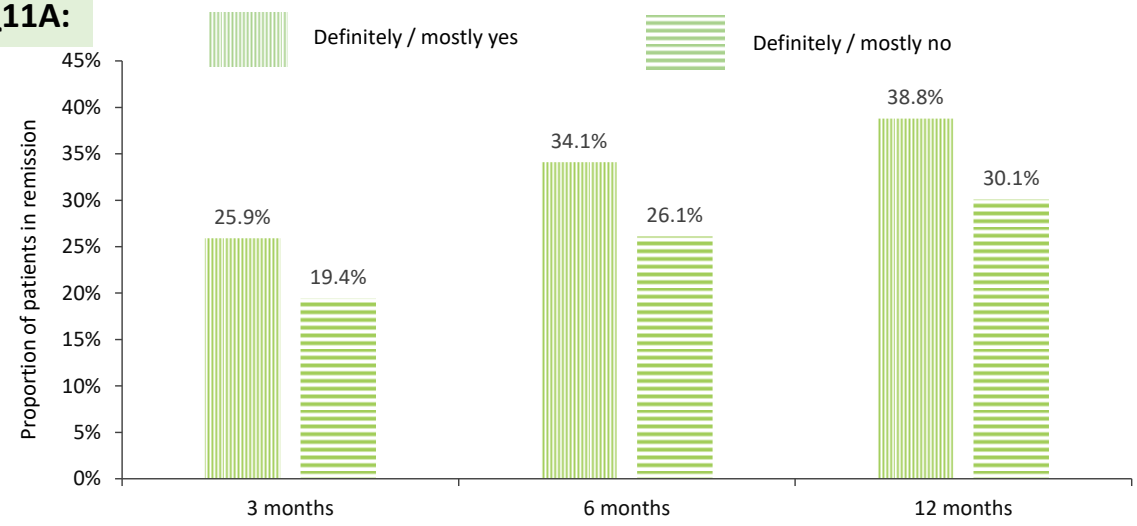
	Q11A (*N*=370)		**Q11C** (*N*=338)	
Characteristic	***Yes*** (*n*=185)	***No*** (*n*=185)	***Yes*** (*n*=169)	***No*** (*n*=169)
Female*	150 (81.1%)	150 (81.1%)	131 (77.5%)	133 (78.7%)
Age at diagnosis, years	45.0 (32.0–55.0)	44.0 (34.0–55.0)	47.0 (35.0–54.0)	45.0 (35.0–55.0)
Age at start of 1st line*, yrs	55.0 (43.0–64.0)	53.0 (43.0–63.0)	55.0 (47.0–63.0)	53.0 (43.0–64.0)
Disease duration, years	6.5 (3.2–11.9)	6.0 (2.2–10.7)	6.2 (3.1–11.5)	5.7 (1.9–10.3)
RF positive*	126 (68.9%)	123 (68.3%)	115 (68.5%)	113 (67.7%)
ACPA positive	128 (71.9%)	116 (64.4%)	115 (69.7%)	112 (67.1%)
Presence of comorbidities	133 (71.9%)	126 (68.1%)	120 (71.0%)	111 (65.7%)
BMI	27.2 (23.4–31.7)	25.5 (22.9–29.7)	27.1 (23.1–30.1)	26.6 (24.0–30.4)
Previous csDMARDs				
0–1	56 (30.3%)	55 (29.7%)	45 (26.7%)	52 (30.8%)
2	52 (28.1%)	72 (38.9%)	63 (37.3%)	67 (39.6%)
3	46 (24.9%)	34 (18.4%)	31 (18.3%)	36 (21.3%)
4+	31 (16.8%)	24 (13.0%)	30 (17.8%)	14 (8.3%)
GCs in previous history*	168 (90.8%)	166 (89.7%)	155 (91.7%)	154 (91.1%)
Concomitant csDMARDs	161 (87.0%)	165 (89.2%)	147 (87.0%)	153 (90.5%)
Concomitant MTX*	138 (74.6%)	131 (70.8%)	129 (76.3%)	129 (76.3%)
Concomitant GCs	124 (67.0%)	115 (62.2%)	112 (66.3%)	111 (65.7%)
DAS28-ESR* (0–10)	6.2 (5.6–6.9)	6.1 (5.4–6.8)	6.1 (5.4–6.7)	6.0 (5.4–6.6)
TJC (28 joints)	14.0 (10.0–19.0)	14.0 (10.0–18.0)	14.0 (9.0–18.0)	13.0 (10.0–17.0)
SJC (28 joints)	10.0 (6.0–13.0)	9.0 (6.0–14.0)	9.0 (6.0–13.0)	8.0 (5.0–12.0)
ESR (mm/h)	32.0 (20.0–48.0)	32.0 (18.0–47.0)	29.0 (16.0–41.0)	27.0 (16.0–40.0)
CRP (mg/l)	13.9 (6.0–24.6)	14.9 (5.8–27.7)	13.2 (5.8–23.1)	14.0 (6.2–23.0)
PtGA (0–100)	80.0 (70.0–85.0)	75.0 (60.0–88.0)	75.0 (60.0–80.0)	70.0 (60.0–80.0)
MDGA (0–100)	70.0 (55.0–80.0)	70.0 (60.0–80.0)	70.0 (52.0–80.0)	70.0 (60.0–80.0)
HAQ-DI (0–3)	1.6 (1.3–2.1)	1.5 (1.1–2.0)	1.5 (1.1–2.0)	1.4 (1.0–2.0)
EQ-5D (-0.59–1)	**0.1 (0.0–0.2)**	**0.2 (0.1–0.7)**	**0.1 (0.1–0.5)**	**0.2 (0.1–0.7)**
Year od administration*				
2018	64 (34.6%)	65 (35.1%)	56 (33.1%)	56 (33.1%)
2019	121 (65.4%)	120 (64.9%)	113 (66.9%)	113 (66.9%)
Adalimumab*	80 (43.2%)	79 (42.7%)	72 (42.6%)	69 (40.8%)
Etanercept*	61 (33.0%)	57 (30.8%)	55 (32.5%)	53 (31.4%)
Infliximab*	7 (3.8%)	7 (3.8%)	6 (3.6%)	8 (4.7%)
Certolizumab*	23 (12.4%)	24 (13.0%)	17 (10.1%)	17 (10.1%)
Golimumab*	14 (7.6%)	18 (9.7%)	19 (11.2%)	22 (13.0%)
Bs ADA/ETA/INF	68 (45.9%)	59 (41.3%)	57 (42.9%)	51 (39.2%)

IQR interquartile range; *RF* rheumatoid factor; *ACPA* anti-citrullinated protein; TNFi tumour necrosis factor inhibitor; *csDMARDs* conventional synthetic disease-modifying anti-rheumatic drugs; *MTX* methotrexate; *DAS28-ESR* 28-joint disease activity score with ESR; *TJC* tender joint count; *SJC* swollen joint count; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *PtGA* patient general assessment of disease activity; *MDGA* physician general assessment of disease activity; *HAQ-DI* Health Assessment Questionnaire; *EQ-5D* EuroQol 5 Dimension for measuring the quality of life

For continuous variables, the median (interquartile range) is presented. For categorical variables, absolute *(*relative) frequencies are presented. Statistical significant differences (p<0.05) across patients' groups are marked in bold.

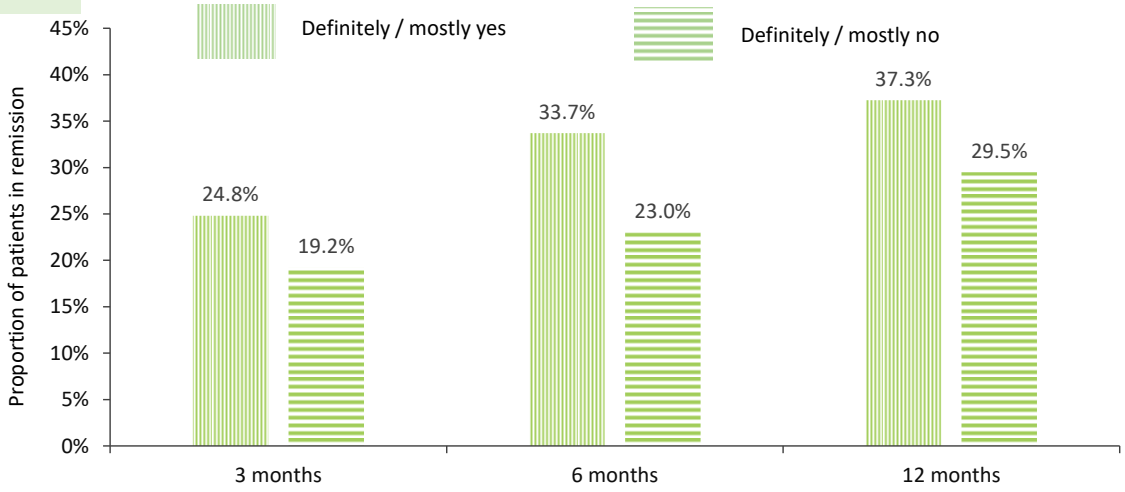
* Variables included in the propensity score model.

Q11A:



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=1372)	156 (25.9%)	602	149 (19.4%)	770	<**0.001**
6-month visit (*n*=1434)	220 (34.1%)	646	206 (26.1%)	788	<**0.001**
12-month visit (*n*=1420)	247 (38.8%)	637	236 (30.1%)	783	<**0.001**

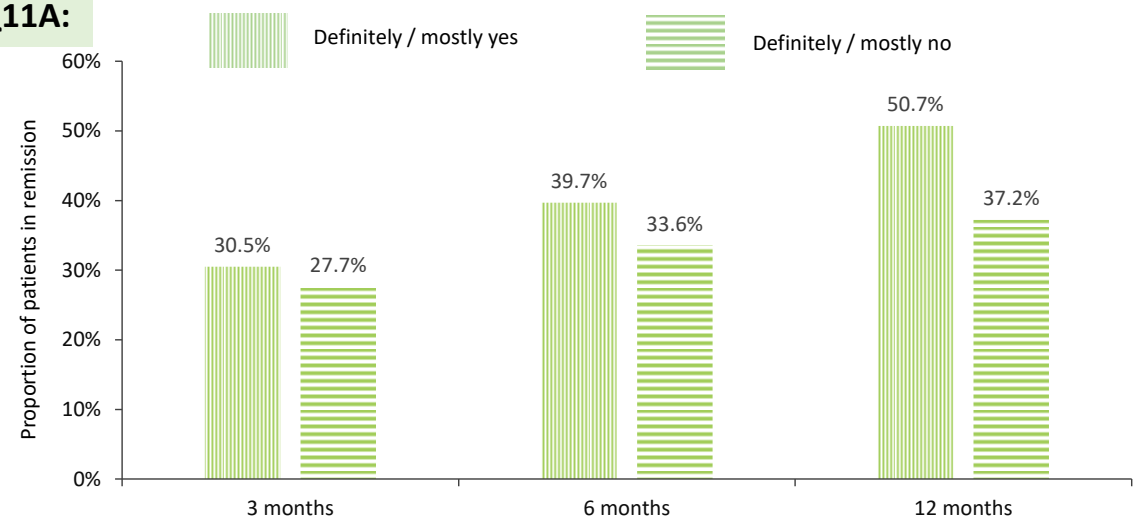
Q11C:



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=1239)	168 (24.8%)	677	108 (19.2%)	562	**0.018**
6-month visit (*n*=1305)	245 (33.7%)	727	133 (23.0%)	578	<**0.001**
12-month visit (*n*=1287)	266 (37.3%)	714	169 (29.5%)	573	<**0.001**

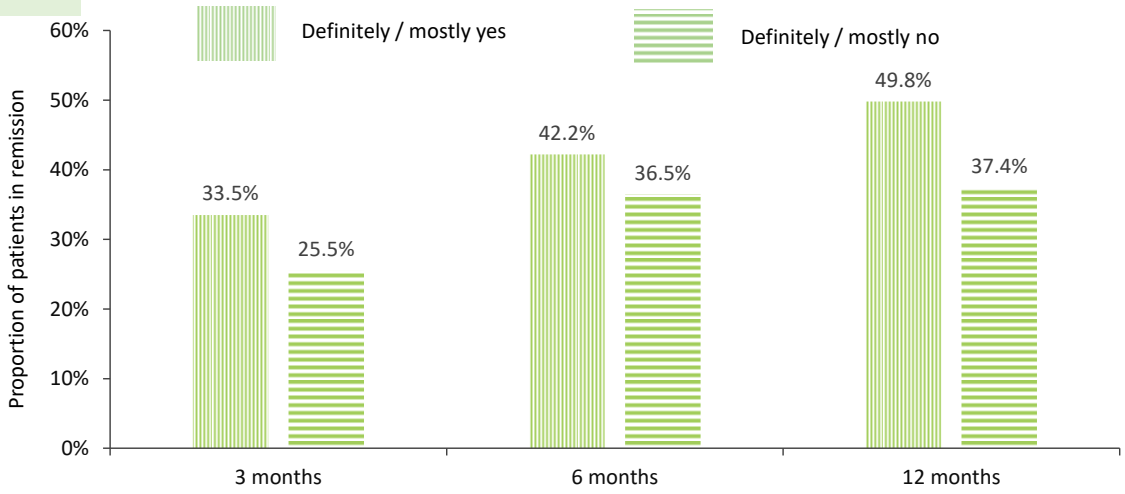
Figure 2 Remission rates (DAS28-ESR<2.6) within the first year of TNFi treatment – primary dataset. Patients answering '*yes*'/'*no*' to Q11A (upper graph) and Q11C (lower graph).

Q11A:



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=429)	57 (30.5%)	187	67 (27.7%)	242	0.303
6-month visit (*n*=467)	85 (39.7%)	214	85 (33.6%)	253	**0.041**
12-month visit (*n*=463)	108 (50.7%)	213	93 (37.2%)	250	**<0.001**

Q11C:



Remission rate	Definitely / mostly yes	*n*	Definitely / mostly no	*n*	P-value
3-month visit (*n*=393)	66 (33.5%)	197	50 (25.5%)	196	0.082
6-month visit (*n*=430)	97 (42.2%)	230	73 (36.5%)	200	0.280
12-month visit (*n*=427)	114 (49.8%)	229	74 (37.4%)	198	**0.010**

Supplementary Figure 2 Remission rates (DAS28-ESR<2.6) within the first year of TNFi treatment – validation dataset.

Patients answering '*yes*'/'*no*' to Q11A (upper graph) and Q11C (lower graph).

Table 2 Univariable and multivariable logistic regression models for reaching remission at 6 and 12 months – primary dataset. Patients are grouped based on answers to Q11A/Q11C at treatment initiation.

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Univariable models				
Q11A: Yes vs no	**1.46** (1.16; 1.83)	**0.001**	**1.47** (1.18; 1.83)	<**0.001**
Q11C: Yes vs no	**1.70** (1.33; 2.18)	<**0.001**	**1.42** (1.12; 1.80)	**0.003**
Multivariable model				
Q11A: Yes vs no	**1.82** (1.43; 2.33)	<**0.001**	**1.75** (1.39; 2.21)	<**0.001**
Baseline HAQ	**0.58** (0.48; 0.69)	<**0.001**	**0.63** (0.53; 0.74)	<**0.001**
Baseline DAS28-ESR	**0.57** (0.50; 0.64)	<**0.001**	**0.64** (0.56; 0.72)	<**0.001**
Multivariable model				
Q11C: Yes vs no	**1.91** (1.47; 2.47)	<**0.001**	**1.53** (1.20; 1.95)	<**0.001**
Baseline HAQ	**0.59** (0.49; 0.70)	<**0.001**	**0.65** (0.55; 0.77)	<**0.001**
Baseline DAS28-ESR	**0.57** (0.50; 0.65)	<**0.001**	**0.64** (0.57; 0.72)	<**0.001**

DAS28-ESR 28-joint disease activity score with ESR; *HAQ-DI* Health Assessment Questionnaire; OR – odds ratio; CI – confidence interval

The outcome in the logistic regression model is DAS28-ESR<2.6 (1 – yes; 0 – no).

Q11A: '*I seem to get sick a little easier than other people*'; Q11C: '*I expect my health to get worse*'

Supplementary Table 2a Univariable and multivariable logistic regression models for reaching remission at 6/12 months – validation dataset. Patients are grouped according to answers to Q11A/Q11C at treatment initiation.

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Univariable models				
Q11A: Yes vs no	1.30 (0.89; 1.90)	0.171	**1.74** (1.20; 2.52)	**0.004**
Q11C: Yes vs no	1.27 (0.86; 1.87)	0.230	**1.66** (1.13; 2.45)	**0.010**
Multivariable model				
Q11A: Yes vs no	**1.57** (1.05; 2.35)	**0.029**	**2.04** (1.37; 3.03)	<**0.001**
Baseline HAQ	**0.52** (0.38; 0.71)	<**0.001**	**0.45** (0.33; 0.62)	<**0.001**
Baseline DAS28-ESR	**0.77** (0.65; 0.91)	**0.002**	0.89 (0.76; 1.05)	0.165
Multivariable model				
Q11C: Yes vs no	**1.57** (1.04; 2.38)	**0.033**	**1.91** (1.26; 2.88)	**0.002**
Baseline HAQ	**0.52** (0.39; 0.71)	<**0.001**	**0.46** (0.34; 0.62)	<**0.001**
Baseline DAS28-ESR	**0.77** (0.65; 0.91)	**0.002**	0.91 (0.77; 1.06)	0.232

DAS28-ESR 28-joint disease activity score with ESR; *HAQ-DI* Health Assessment Questionnaire; OR – odds ratio; CI – confidence interval

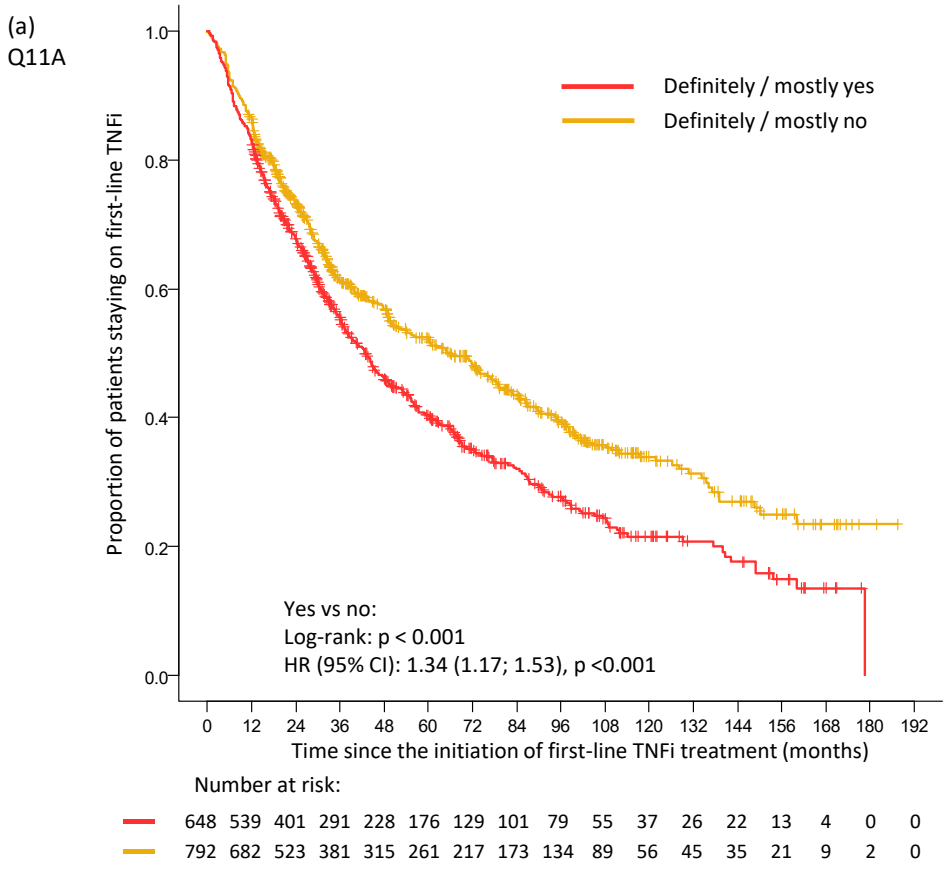
The outcome in the logistic regression model is DAS28-ESR<2.6 (1 – yes; 0 – no).

Q11A: '*I seem to get sick a little easier than other people*'; Q11C: '*I expect my health to get worse*'

Supplementary Table 2b Univariable logistic regression models for reaching remission at 6 and 12 months within propensity score-matched primary and validation datasets. Patients are grouped based on answers to Q11A/Q11C

	Remission after 6 months		Remission after 12 months	
Parameter	OR (95% CI)	p	OR (95% CI)	*p*
Propensity score-matched primary dataset				
Q11A: Yes vs no	1.43 (1.11; 1.86)	**0.007**	1.43 (1.11; 1.83)	**0.005**
Q11C: Yes vs no	1.62 (1.24; 2.11)	<**0.001**	1.37 (1.06; 1.77)	**0.015**
Propensity score-matched validation dataset				
Q11A: Yes vs no	1.27 (0.82; 1.96)	0.286	1.70 (1.12; 2.59)	**0.013**
Q11C: Yes vs no	1.22 (0.79; 1.90)	0.369	1.51 (0.97; 2.34)	0.066

OR – odds ratio; CI – confidence interval



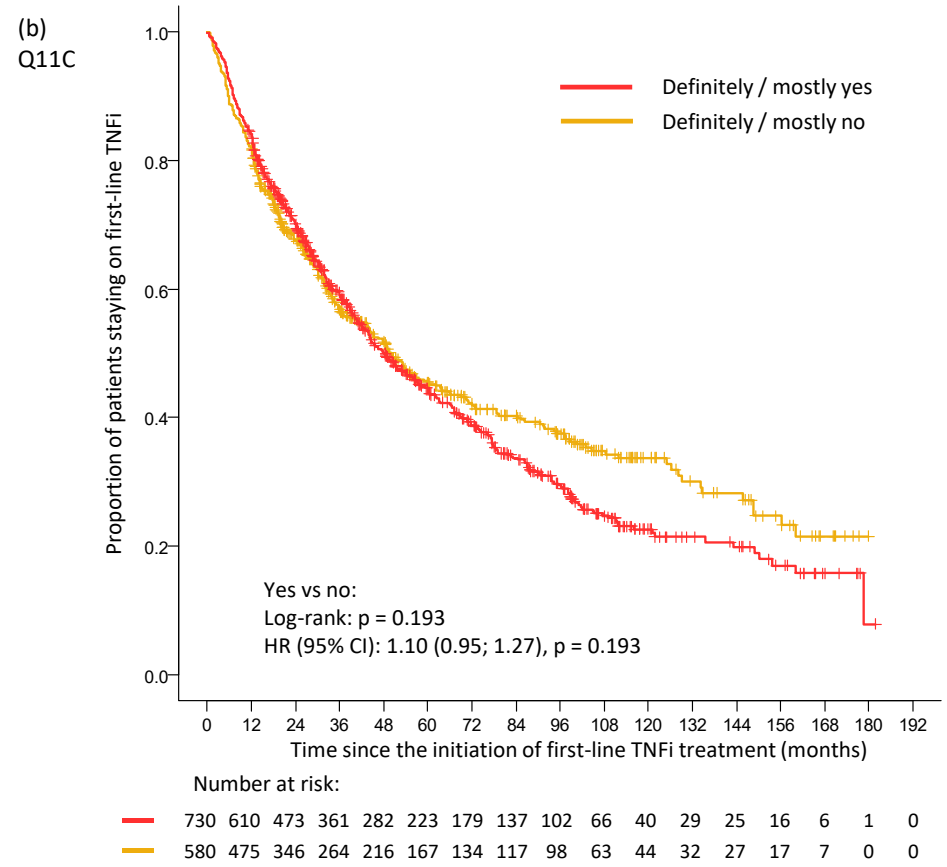
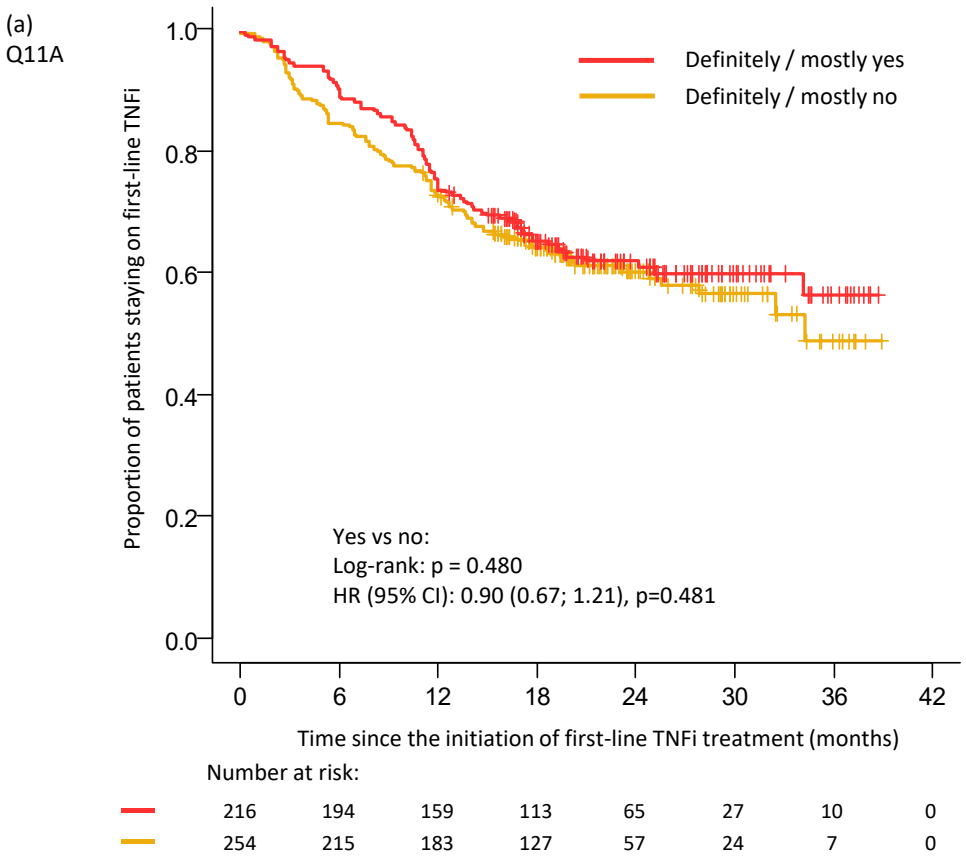
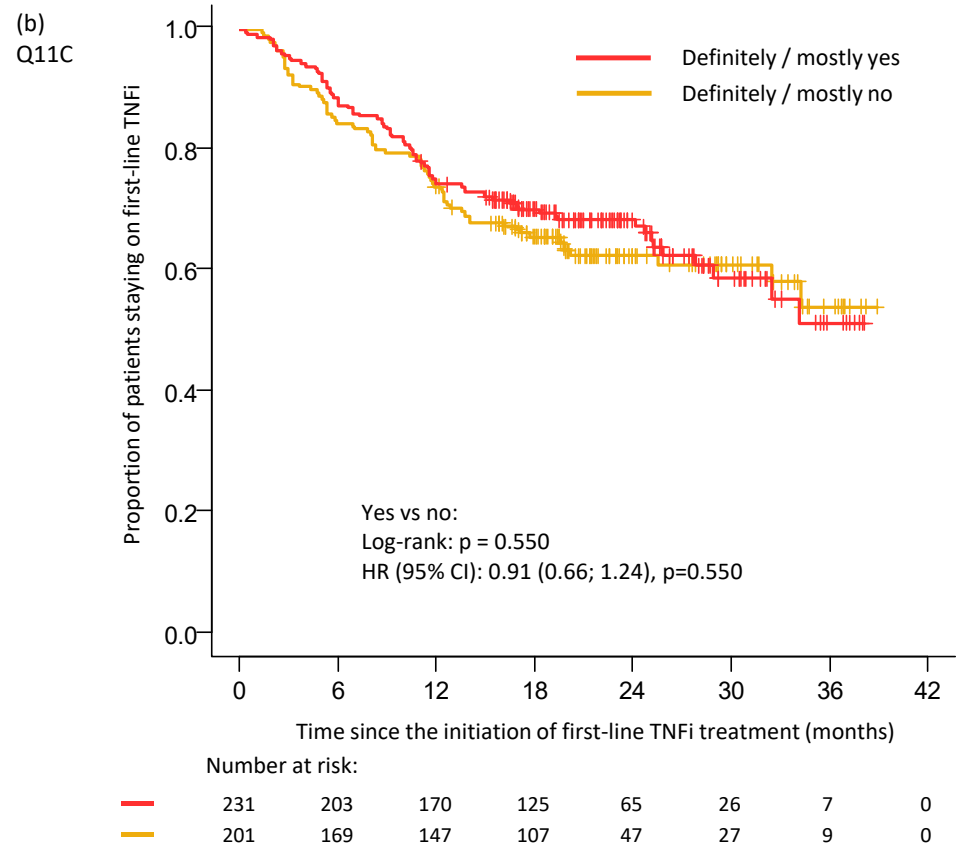
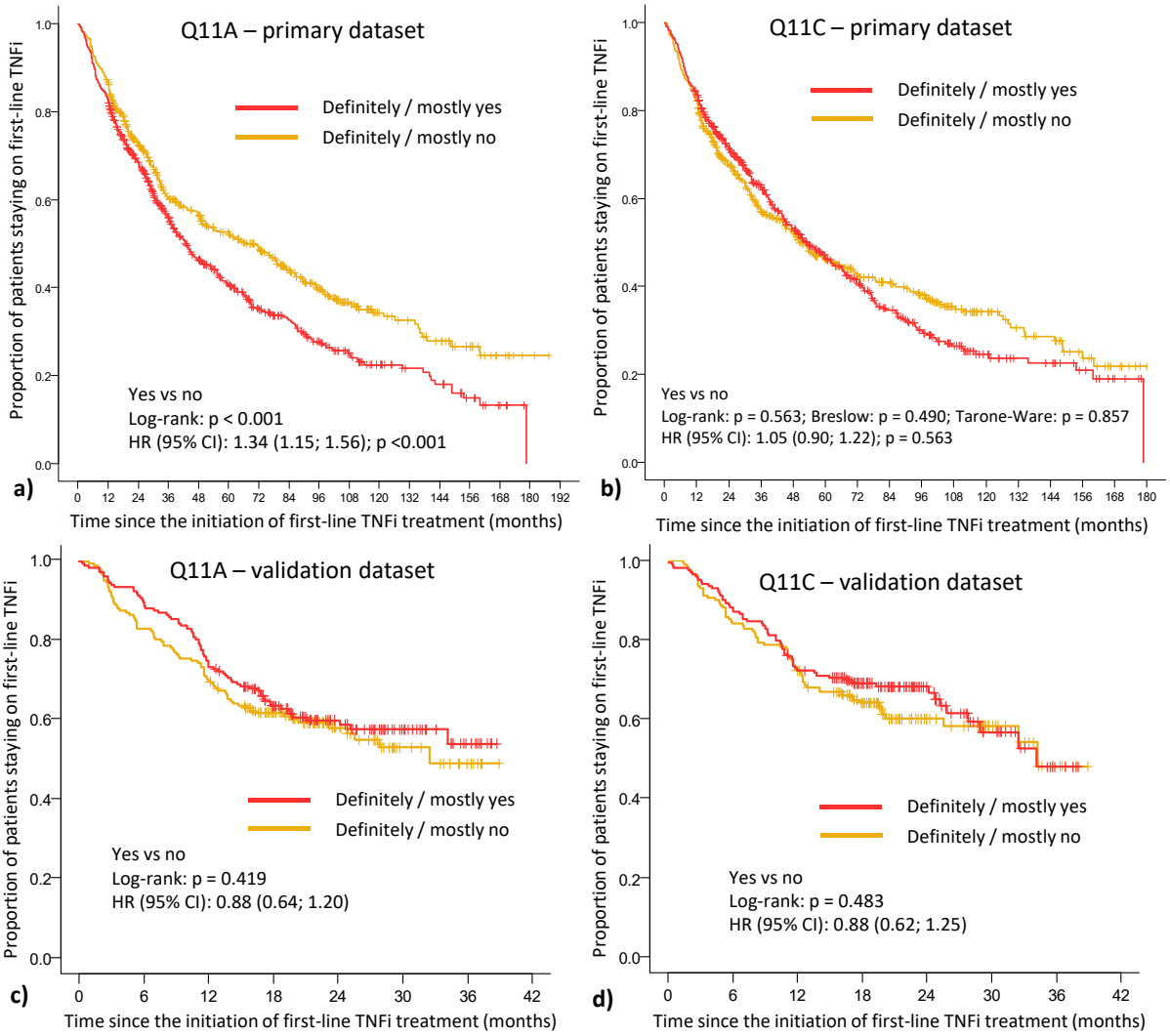


Figure 3 Kaplan-Meier survival plots showing drug retention in patients answering '*yes*'/'*no*' to Q11A (a) and Q11C (b). HR – hazard ratio; CI – confidence interval; primary dataset





Supplementary Figure 3a Kaplan-Meier survival plots showing drug retention in patients within validation dataset. (a) patients answering 'yes'/'no' to Q11A; (b) patients answering 'yes'/'no' to Q11C; HR – hazard ratio; CI – confidence interval



Supplementary Figure 3b Kaplan-Meier survival plots showing drug retention in primary and validation datasets after propensity score matching

a) patients answering 'yes' (red) and 'no' (yellow) to Q11A within primary dataset

b) patients answering 'yes' (red) and 'no' (yellow) to Q11C within primary dataset

a) patients answering 'yes' (red) and 'no' (yellow) to Q11A within validation dataset

b) patients answering 'yes' (red) and 'no' (yellow) to Q11C within validation dataset

HR – hazard ratio; CI – confidence interval

Table 3 Number of TNFi discontinuations and median survival time of patients responding negatively/positively to Q11A/11C

		Discontinuations, *n* (%)	**Median survival time** in months (95% CI)
Primary dataset (older cohort)	*Q11A*		
	Definitely / mostly yes (*n*=648)	417 (64.4%)	42.8 (37.4; 48.2)
	Definitely / mostly no (*n*=792)	420 (53.0%)	66.0 (54.6; 77.4)
	Q11C		
	Definitely / mostly yes (*n*=730)	462 (63.3%)	48.1 (41.6; 54.6)
	Definitely / mostly no (*n*=580)	327 (56.4%)	49.9 (40.6; 59.2)
Validation dataset (newer cohort)	*Q11A*		
	Definitely / mostly yes (*n*=216)	82 (38.0%)	Not reached
	Definitely / mostly no (*n*=254)	101 (39.8%)	34.3 (–)
	Q11C		
	Definitely / mostly yes (*n*=231)	81 (35.1%)	Not reached
	Definitely / mostly no (*n*=201)	76 (37.8%)	Not reached

CI – confidence interval

Q11A: 'I seem to get sick a little easier than other people'; Q11C: 'I expect my health to get worse'