Univerzita Karlova

1. lékařská fakulta

Autoreferát disertační práce

UNIVERZITA KARLOVA
1. lékařská fakulta

Účinnost a bezpečnost biologické léčby v terapii zánětlivých revmatických onemocnění

Effectiveness and safety of biological therapy in inflammatory rheumatic diseases

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

CONTENTS

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.

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.

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 treat-to-target strategy was established for patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA). 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). So far, SF-36 dimensions have not yet been frequently studied as possible predictors for remission achievements in RA (or PsA, axSpA) patients. 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 RA, PsA and axSpA 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 – rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. Clinical manifestation, diagnosis, therapeutical options and current treatment guidelines of the diseases are presented. The subsequent chapter briefly summarises 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 a chapter devoted to the ATTRA registry. This national, prospective, observational cohort study aims to evaluate the safety and effectiveness of biological/targeted therapy of patients with chronic inflammatory rheumatic diseases. The subsequent chapters are dedicated to the goals of the statistical analyses, followed by a description of used methods, results, discussion, conclusions and summary.

1 Hypotheses and aims of the 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.

1.1 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.

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

Second, we dealt with evaluating the predictive ability of two SF-36 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 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. We aimed to investigate whether these two questions could predict therapeutic response in patients with RA, PsA and axSpA starting their first TNFi therapy.

2 Methods – study population, design, statistical methods

In the following pages, only RA results are presented since they were statistically significant and published/submitted in journals.

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 b/ts DMARDs in patients with chronic inflammatory rheumatic diseases. Patients with RA (and axSpA, PsA, JIA and SLE) 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 b/ts DMARDs in the Czech Republic.

At the start of therapy, baseline data are collected including demographics, disease characteristics (disease duration, presence of rheumatoid factor and anti-citrullinated protein antibodies, 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) (Prevoo et al., 1995), simplified disease activity index (SDAI, 0–86) (Smolen et al. 2003), Health Assessment Questionnaire (HAQ) for patient function with values from 0 to 3 (the higher, the worse disability) (Bruce a Fries 2005), EuroQol EQ-5D questionnaire for quality of life with values from –0.59 to 1 (the higher, the better quality of life) (EuroQol Group 1990), 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 three and six months, and then every six months for three years, with disease activity and anti-rheumatic therapy data collected annually thereafter.

2.1 T2T strategy vs conservative approach

Study population

In this study, we included all bio-naive adult patients diagnosed with RA starting b/ts DMARDs within a period from 01/01/2012 to 31/12/2017. 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 from analyses.

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. 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). 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 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 the *C3* cohort). Regardless of T2T principles, they continued with the same treatment.

Outcome measures

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. We assessed disease activity through the composite index, particularly DAS28-ESR (Prevoo et al. 1995. 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 (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) 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, TJC and SJC, CRP, ESR, PtGA, MDGA) and quality of life (HAQ-DI, EQ-5D) after 6 and 12 months of the b/ts DMARDs treatment between cohorts *C3* and *C4*.

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, 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. The magnitude of parameter changes 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, HAQ and EQ-5D at baseline, 6 and 12 months) was relatively small; we excluded 1.8% of RA patients.

We used propensity score matching to match patients not switching to another therapy after not reaching treatment target at 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 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. Further, we 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 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).

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

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.

Study design

We divided patients meeting the inclusion criteria 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 analysed only patients who answered definitely/mostly yes/no, because we wanted to focus 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*'). We used two separate datasets (primary and validation) to validate our results. As part of a sensitivity analysis, we performed the whole analysis on the PS matched datasets as well.

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 TNFi. The therapeutic response was evaluated through REM achievements throughout the 1st year 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. 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 secondary) 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 did not impute missing data in this analysis and performed an available-case analysis.

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 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 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 (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 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).

3 Results

3.1 T2T strategy vs conservative approach

Baseline characteristics

In total, we included 1275 patients with RA. 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 the C4 subgroup. 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 the DAS28-ESR score with a median 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.

Disease activity after 12 months

We could see the best treatment results after 12 months in the 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 REM/LDA rates 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). Median DAS28-ESR values in groups C3 and C4 were within the range of MDA.

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

At the 6-month visit, RA patients from groups C3 and C4 differed in all tested parameters related to disease activity and quality of life. We observed lower disease activity and better quality of life in C4. 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 and EQ-5D. 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. Patients from C4 did not significantly improve in CRP and HAQ-DI. Comparing the size of changes, patients from C3 showed more significant improvements.

Odds for treatment target in C3 and C4 after 12 months

We employed propensity score matching to reduce selection bias by adjusting for potential confounding factors at the 6-month visit. 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 in concomitant therapy and glucocorticoids in concomitant therapy. Patients did not differ anymore in parameters related to disease activity and quality of life at the 6-month visit. 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). In group C3, 41% of patients achieved at least REM/LDA at the 12-month visit, while in group C4, it was 20%.

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

Rheumatoid arthritis – baseline characteristics

Within the **primary dataset**, 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*.

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.

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. 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.

Comparison of treatment responses within the first year of TNFi treatment

Within the **primary dataset**, patients who expected their health to worsen and those who seemed to get sick a little easier than other people at the treatment initiation achieved remission after 3, 6 and 12 months statistically significantly more often than patients who did not think that. 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*. Even after accounting for baseline disease activity and functional status, the odds for remission at the 6- and 12-month visits remained significantly higher.

Within the **validation dataset**, 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. 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.

Concurrently, we evaluated remission achievements in PS-matched datasets. Within **PS-matched primary dataset**, patients who answered *yes* to Q11A achieved remission significantly more often after six and twelve months than patients who answered *no*. Similarly, remission was achieved more often after six and twelve months in patients who responded positively to 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*. Within the **PS-matched validation dataset**, patients who responded *yes* to Q11A achieved remission more often after six and twelve months than patients who answered *no*. The difference was statistically significant only at the 12-month visit. Similarly, remission was achieved more often after six and twelve months in patients who responded positively to 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)

Drug retention

In the **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 than patients who did not think that (Q11A). 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. A similar result was obtained within the **PS-matched primary dataset**. In the **validation dataset** (as well as in PS-matched validation dataset), there was no statistically significant difference in the probability of staying on the first TNFi between either of the studied groups.

4 Discussion

4.1 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 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 b/ts DMARD therapy. 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. 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- to 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 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 of reaching REM one year after the baseline. This result is very similar to the OR obtained in our study, but 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).

Our study has shown that the implementation of the T2T strategy is insufficient in real clinical practice. 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).

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.

4.2 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 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. We used two 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 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. There was no statistically significant difference in the probability of treatment discontinuation between patients answering positively/negatively to the studied SF-36 questions in the validation dataset.

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 randomised 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. In the randomised controlled CareRA-trial, they studied how psychosocial aspects affect the probability of achieving sustained remission in early RA (Doumen et al. 2021). 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.

5 Conclusions and evaluation of hypotheses

First, we aimed to evaluate adhesion to treat-to-target strategy (T2T) within RA patients (1.1). 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 REM/LDA within the first six months of the treatment leads to a higher probability of achieving REM/LDA at the 12-month visit in RA patients.
- 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 results, we can state that the hypothesis about the superiority of the T2T strategy over the conservative approach was confirmed in patients with RA.

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*'. 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 (1.2).

- We showed that RA patients answering positively to Q11A/Q11C have significantly higher odds of reaching remission at 12-month visits than patients responding to these questions negatively.

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.

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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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- *2020 journal impact factor*: 13.146