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Adverse events of biologic therapy in psoriasis

Nežádoucí účinky biologické léčby psoriázy

Doctoral Thesis

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Emanuel Carvalheiro Marques

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Abstract

This doctoral thesis focuses on psoriasis vulgaris and its therapy, especially biologic agents and their safety profiles. The objectives of this research were to identify prognostic factors of severe psoriasis, compare the safety profiles of different therapy types (topical compounds, non-biologic systemic agents and biologic agents) and those of biologic agents themselves (adalimumab, etarnecept, infliximab, secukinumab, ustekinumab). A total of 289 psoriatic patients were followed up for 30 months; these were divided into 3 groups according to therapy type. Comorbidities, epidemiological parameters, and rates of adverse events were compared between the three groups and, also, between each of the 5 biologic agents, and the data were statistically analysed. It was concluded that psoriasis severity is directly related to an increased risk of cardiovascular disease, depression, hyperuricemia, and nonspecific noninfectious liver disease. Male gender, increased height, early age at disease onset, viral upper respiratory infections and periods of hormonal changes seem to be prognostic of higher levels of psoriasis severity. When comparing therapy types, biologic agents were the most effective therapies; however, they were associated with higher rates of adverse events and treatment discontinuation. A higher incidence of adverse events was observed among adalimumab- and infliximab-treated patients, with ustekinumab found to have the safest profile. Our results demonstrate that a personalized approach, including evaluation of a patient's risk profile, is necessary before commencing a biologic. Further research is warranted to confirm the findings of this study.

Keywords

adalimumab, biologic agents, etarnecept, infliximab, psoriasis prognostic factors, psoriasis vulgaris, safety profile of biologic agents, secukinumab, ustekinumab

Nežádoucí účinky biologické léčby psoriázy

Abstrakt

Disertační práce je zaměřena na psoriázu vulgaris, její terapii, zejména na biologická léčiva a jejich bezpečnostní profil. Cílem výzkumu bylo stanovit prognostické faktory těžké psoriázy, porovnat bezpečnostní profil různých typů terapie psoriázy (topická léčba, nebiologická systémová léčiva a biologické preparáty) a vzájemně porovnat jednotlivé biologické preparáty (adalimumab, etarnecept, infliximab, secukinumab, ustekinumab). Sledovali jsme 30 měsíců 289 pacientů s psoriázou; podle typu léčby byli rozděleni do 3 skupin. U jednotlivých skupin pacientů léčených biologickými léčivy jsme porovnávali komorbidity, epidemiologické parametry a četnost nežádoucích účinků. Data jsme statisticky analyzovali. Zjistili jsme, že závažnost psoriázy zvyšuje riziko kardiovaskulárních onemocnění, depresi, hyperurikemii a nespecifické neinfekční onemocnění jater. Výsledky naznačují, že mužské pohlaví, vyšší tělesná výška, manifestace onemocnění v mladším věku, virové infekce horních cest dýchacích a období hormonálních změn jsou prognostickými rizikovými faktory pro závažné formy psoriázy. Léčba psoriázy byla nejúčinnější biologickými prepráty, provázela ji vyšší míra nežádoucích účinků a nutnost přerušení léčby. Vyšší výskyt nežádoucích účinků byl pozorován u pacientů léčených adalimumabem a infliximabem, nejbezpečnějším byl ustekinumab. Výsledky naznačují, že před zahájením biologické léčby je nezbytný personalizovaný přístup, včetně vyhodnocení rizikového profilu pacienta. Výsledky studie vyžadují další výzkum.

Klíčová slova: adalimumab, biologická léčba, etarnecept, infliximab, prognostické faktory psoriázy, psoriáza vulgaris, bezpečnostní profil biologicých preparátů, secukinumab, ustekinumab.

LIST OF ABBREVIATIONS

*	Statistical significant p-value
ACE	Angiotensin converting enzyme
ADA	Adalimumab
AE	Adverse event
Altern.	Alternative
ALT	Alanine Transaminase
ATB	Antibiotic
BA	Biologic agent
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
Chi-SQ	Chi-square tests
Conv.	Conventional
CRP	C-reactive protein
CVD	Cardiovascular risk of death
CSD	Conventional systemic drugs
Discont.	Discontinuation
DM	Diabetis mellitus
EMA	European Medicines Agency
ETN	Etarnecept
Fab	Fragment antigen-binding
Fig.	Figure
GGT	Gamma-glutamyltransferase
HIV	Immunodefiency virus
HPV	Human papilloma virus
IFX	Infliximab
IL	Interleukin
IgG	Immunoglobulin G

IP-10	Interferon-inducible protein-10
LSD	Least significance difference
mAb	Monoclonal antibody
MCP-1	Monocyte chemotactic protein 1
N	Number of patients
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NSAID	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
P	p-value (probability significance)
PASI	Psoriasis area severity index
Perman.	Permanent
PSOLAR	Psoriasis Longitudinal Assessment and Registry
PUVA	Psoralen and ultraviolet A (phototherapy)
QNF-TB	quantiFERON-TB Gold
Rheum.	Rheumatic
SAE	Serious adverse events
SEC	Secukinumab
SPC	Summary of Product Information
SLE	Systemic Lupus Erythematosus
Stat.	Statistical
SUAC	Serum uric acid concentrations
Syst.	Systemic
TB	Tuberculosis
Temp.	Temporary
Th	T helper
TNF	Tumour necrosis factor
TT	Topical therapy
USA	United States of America
UST	Ustekinumab
Vit.	Vitamin

Vs	Versus

TABLE OF CONTENTS

INTRODUCTION

Background

Psoriasis vulgaris is a chronic inflammatory skin disease with a prevalence estimated to be 1.5–4.7%. It is considered a non-infectious inflammatory T-cell-mediated disease characterized by dysregulation of our immune system. Although known to have a multifactorial etiopathogenesis, genetics seems to play a big role. It presents with a variety of clinical manifestations: the skin can be affected to a small or large extent; in severe cases, lesions can cover one's entire body – a state called erythroderma. In addition to the skin, also genitals, nails and joints can be affected. Inflammation of the joints due to psoriasis is referred to as psoriatic arthritis. While usually not endangering patients' lives, it can significantly impair their quality of life (Hercogová 2011) (Votrubova et al. 2014).

Today, severe psoriasis is seen as a systemic inflammatory disease associated with an increased risk of complications such as metabolic syndrome, cardiovascular and gastrointestinal disease (Votrubova et al. 2014) (Juzlova et al. 2016) (Lotti, Hercogova, and Prignano 2010). These comorbidities are responsible for further health complications – these patients live roughly 3–4 years less than psoriasis-free individuals (de Oliveira, Rocha, and Duarte 2015).

Different types of treatment are available: these are planned depending on where and how patients are affected (extent of the disease). Topical compounds are usually the first recommendation for the less severe forms of the disease (corticosteroids, keratolytics, usually in the form of ointments, gels, body lotions, etc.). The main advantage of this type of treatment is good tolerability, minimal systemic absorption, thus reducing the risk of possible systemic adverse events (AEs). For more severe cases, so-called conventional systemic drugs or non-biologic systemic agents (in the form of tablets or injections) might be recommended – the most common drugs given in the Czech Republic are methotrexate, cyclosporine and acitretin. Biologic agents (BAs) are reserved for cases where these drugs have proved ineffective or, exceptionally, where patients did not tolerate them due to the occurrence of adverse events – currently, BAs are considered the most effective type of therapy available (Zweegers et al. 2016).

Detailed research of intercellular signalling molecules and their interactions within the disease process has led to the development of targeted drugs that act at the subcellular level. Biologic agents are produced by recombinant DNA technology and represent the latest in the treatment of psoriasis. Pro-inflammatory cytokines IL-12, IL-17, IL-23, and TNF-α are known to play a fundamental role in the pathogenesis of psoriasis, and BAs are directed against these signalling molecules (Nast et al. 2017a).

However, the high efficacy in the treatment of severe psoriasis and psoriatic arthritis may be offset by some adverse events. The cytokine TNF-alpha is involved in antimicrobial type 1 immunity, therefore patients treated with these agents can theoretically be at higher risk of infections, mainly upper respiratory tract infections. The risk of opportunistic infections, specifically fungal infections, and tuberculosis, is of special concern. In addition, higher rates of lymphomas, demyelinating disorders and solid tumours have been reported. Interleukin-17 also seems to mediate the immune responses against bacterial and fungal infections. Besides, it has been reported to be highly upregulated at sites of inflamed tissues in inflammatory and autoimmune conditions (Antonelli, Khan, and Magrey 2015). Interleukins 12 and 23 help in driving an adaptive immune response by inducing naïve CD4+ lymphocytes to differentiate into Th1 and Th17 cells – these play key roles in the inflammatory process of psoriasis vulgaris (McKenzie, Kastelein, and Cua 2006). Patients who are genetically deficient in IL-12/23 and IL-12Eβ1 may be more susceptible to mycobacterial, salmonella and Candida infections (Papp et al. 2013). Also, preclinical studies in murine models have raised awareness of possible tumour promotion when inhibiting IL-12/23 (Langowski et al. 2006).

Clinical trials report that BA-treated patients are more prone to develop serious infections. In addition, these are at increased risk of developing hematopoietic, oncological, neurological, cardiopulmonary, gastrointestinal, immune, and psychiatric disorders (“Summary of Product Information - Humira (adalimumab),” n.d.) (“Summary of Product Information - Enbrel (etanercept),” n.d.) (“Summary of Product Information - Remicade (infliximab),” n.d.) (“Summary of Product Information - Stelara (ustekinumab),” n.d.) (“Summary of Product Information - Consentyx (secukinumab),” n.d.). Hence, BA-treated patients should be closely monitored and carefully examined before, during and after

treatment discontinuation – physicians should keep in mind that elimination of these agents may take several months.

Gaps in research evidence

Severe psoriasis has a significant detrimental effect on patients' quality of life, affecting not only their self-esteem, but also their productivity at work (Hercogová 2011) (Sohn et al. 2006). Understanding how different comorbidities and epidemiological factors are related to psoriasis severity can help in estimating patients' clinical outcome; in other words, such factors may help us predict whether a certain patient will be at high risk. Several studies have reported how some conditions may be associated with severe psoriasis (Duarte and da Silva 2014), (Huang et al. 2010), (García-Diez et al. 2008). Patients' clinical characteristics (e.g., PASI, BSA) at diagnosis and their association with long-term psoriasis prognosis have also been investigated. To the best of our knowledge, there are no studies using different types of therapy to stratify psoriasis severity levels, and further identifying direct and independent prognostic factors of severe psoriasis.

Due to their exceptional efficacy rates, BAs have revolutionized psoriasis therapy. However, we do know that these agents have toxic effects in the human body, and that such toxicity is related to an increased incidence of numerous diseases (Sandborn 2010). These can have unintended effects on our immune function that can compromise host defenses and lead to serious infections, autoimmune diseases, or malignancies (Eisenberg R 2014), (Teo, Chew, and Phipps 2016), (Lonial et al. 2016). The literature is scarce in studies directly comparing the safety profiles of non-biologic systemic agents (NBSAs) with those of BAs (Table 1) – in fact, all studies published to date have suggested BAs are as safe as NBSA, or even safer. Apart from clinical trials, there are few real-world, consistent and well-designed long-term studies on the safety of these agents compared with the other forms of therapy. With the implementation of longer follow-ups, reports of serious adverse events are slowly emerging (Kothary et al. 2011). In an era where biologic use is expanding in all fields of medicine and physicians tend to prescribe them more and earlier in the disease process, it is imperative, therefore, to be familiar with the benefits as well as the possible serious adverse events associated with these agents.

Tab. 1 Main articles comparing the safety profiles of BAs and NSBAs

References	Investigated drugs	Number of patients included in the study	Conclusion
Reich K (K. Reich et al. 2015)	Cyclosporin, methotrexate and fumaric acid ester versus (vs) adalimumab, etanercept, infliximab, ustekinumab	2444	No significant safety differences between NBSAs and BAs
Carretero G (Carretero et al. 2015)	Acitretin, methotrexate, cyclosporine, vs adalimumab, etanercept, infliximab, efalizumab and ustekinumab	1956	Increased risk of alterations of investigations, and gastrointestinal, nervous system, vascular, metabolic, nutrition, endocrine, congenital, familial and genetic disorders in patients treated with NBSAs, overall lower risk of AE incidence in patients treated with BAs vs. NBSAs
Medina C (Medina et al. 2015)	Acitretin, methotrexate, cyclosporine vs adalimumab, etanercept, infliximab, efalizumab, ustekinumab	1793	Risk of AEs in patients treated with BAs was lower than in those treated with NBSAs
Reich K (Kristian Reich et al. 2010)	Methotrexate vs adalimumab vs placebo	270	BAs demonstrated 4 times as many AE-free response days than NBSAs

Garber C (Garber C, Plotnikova N, Au SC, Sorensen EP 2015)	Acitretin, methotrexate, cyclosporine vs adalimumab, etanercept, infliximab, efalizumab, ustekinumab, golimumab, certolizumab	194	No statistically significant difference found in the rates of AEs within the nonelderly cohort; in the elderly cohort there was a higher rate of AEs in patients treated with CSDs than with BAs
Piaserico S (Piaserico et al. 2014)	Acitretin, methotrexate, cyclosporine, PUVA vs adalimumab, etanercept, infliximab, efalizumab and ustekinumab	187	CSDs and BAs showed comparable rates of AE incidence among elderly psoriatic patients
Montes-Torres A (Montes-Torres et al. 2019)	Cyclosporine, methotrexate, vs adalimumab, etanercept, infliximab, efalizumab, ustekinumab	23	BAs seem to be safer for HIV psoriatic patients than CSDs

AE = adverse events; BA = biologic agent; CSD = conventional systemic drugs; HIV = Human Immunodeficiency Virus; NBSA = non-biologic systemic agent; PUVA = Psoralen plus ultraviolet A

Despite all concerns regarding BA safety, patients with very severe psoriasis will eventually need them. Fortunately, the understanding of how the cytokines IL-12, IL-17, IL-23, TNF-α are involved in the pathogenesis of psoriasis has ushered in a new era in the treatment of the disease. Based on these findings, a number of drugs targeting each of these cytokines was developed: adalimumab, etarnecept and infliximab are all anti-TNF-alpha inhibitors, secukinumab is directed against the cytokine IL-17, while ustekinumab is an anti-IL-12/23 agent (Nast et al. 2017b). Due to their exceptional efficacy, prescription of these agents is on the rise. Although we do have some information about their safety profiles, most of it comes from clinical trials ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information -

Consentyx (Secukinumab)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)," n.d.). However, quite often, the patient populations enrolled in clinical trials do not always reflect those encountered in our daily clinical practice – they may be of a different age, suffer from different or multiple comorbidities, and eventually have a different demographic background (Topaloğlu Demir et al. 2020). Thus, it is not always easy to select a BA to treat a specific patient – a number of factors related to each drug and each individual patient should be taken in account when making this decision. In this fashion, comparing the safety profiles of different BAs in real life is essential to improve clinicians' decision making.

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OBJECTIVES, METHODS AND OUTLINE OF THE THESIS

Objectives of the thesis

Chapter 1

To review the latest available information about the disease called psoriasis vulgaris, its epidemiology, pathophysiology, clinical picture, classification, diagnostic methods, associated comorbidities, treatment options – specifically biologic agents – and their possible related adverse events.

Chapter 2

To study and compare a variety of comorbidities and epidemiological factors of severe psoriasis; therefore, this research aimed to identify possible trigger and prognostic factors of severe psoriasis.

Chapter 3

To compare the occurrence of adverse events in three groups of psoriatic patients on different therapeutic regimens (topical therapy, non-biologic systemic agents, biologic therapy). Based on this comparison, this study aimed to determine the type of therapy with the lowest safety profile.

Chapter 4

To investigate and compare possible differences in the occurrence of adverse events in individual groups of patients with psoriasis treated with different biologic agents (TNF-alpha inhibitors: adalimumab, etanercept, infliximab; anti-IL-17: secukinumab; and anti-IL-12/23: ustekinumab).

Research methods of the thesis

The first chapter is conceptualized as a narrative review of the literature focused on psoriasis vulgaris and its therapeutic options. Data were acquired using the search engines PubMed, Embase, and MEDLINE databases, keywords such as "psoriasis", "psoriasis vulgaris", "epidemiology of psoriasis", "etiology of psoriasis", "pathogenesis of psoriasis", "pathophysiology of psoriasis", "classification of psoriasis", "types of psoriasis", "clinical picture of psoriasis", "symptoms of psoriasis", "diagnosis of psoriasis", "diagnostic methods of psoriasis", "treatment of psoriasis", "psoriasis topical therapy", "psoriasis conventional systemic agents", "psoriasis systemic non-biologic systemic agents", "psoriasis biologic agents", "adverse events of biologic therapy in psoriasis", "adalimumab adverse events", "etanercept adverse events", "infliximab adverse events", "secukinumab adverse events", "ustekinumab adverse events". In order to improve the validity and reliability of collected data, only studies from journals registered in the Web of Science platform were included. Studies were excluded if they were in a language other than English. An independent reviewer (the first author, E.M.) screened titles and abstracts, followed by full-text articles. Collected data were organized into two parts: the first provides a comprehensive review of the disease while the second presents a general overview on biologic agents, their use and possible adverse events.

The remaining three chapters cover a cross-sectional observational study incorporated into a prospective study, where a population of 289 psoriatic patients was followed up for 29 months. Included were 156 men (54%) and 133 women (46%). Their mean age (in years) was 48 ± 80, BMI 28.3 ± 52.2. A total of 118 patients were on topical therapy (corticosteroids, keratolytics, vitamin D derivatives, tacrolimus/pimecrolimus and coal tar or derivatives). Another group of 98 patients used conventional systemic agents or non-biologic systemic agents: 34 used acitretin, 13 were on cyclosporine and 51 were treated with methotrexate. The last group included 124 patients: 11 on infliximab, 17 on secukinumab, 22 on etanercept, 33 on ustekinumab, and 41 on adalimumab. Patients suffered from different forms of the disease: 227 (78.5%) patients had plaque psoriasis, 130 (45.0%)

scalp, 112 (38.7%) nail, 23 (8.0%) palmoplantar, 9 (3.1%) inverse, and 1 (0.3%) the guttate form of the disease.

The only exclusion criteria were unwillingness to participate in the study or use of any agent for less than 8 weeks.

A variety of comorbidities and epidemiological factors in the 3 groups of psoriatic patients treated differently was studied: age, gender, phototype, height, weight, BMI, history of skin, thyroid, gastrointestinal, autoimmune, oncological or rheumatologic diseases, HIV, organ transplantation, osteoporosis, hyperuricemia, depression, chronic heart failure, dyslipidemia, hypertension, diabetes mellitus, education level, profession, smoking and alcohol drinking habits, use of beta-blockers, ACE inhibitors, diuretics, acetylsalicylic acid, statins, proton pump inhibitors, lithium, antimalarials, nonsteroidal anti-inflammatory drugs, interferon, benzodiazepines, antidepressants, family history of psoriasis, age at psoriasis onset, possible trigger factors such as drug use, hormonal changes, stress, trauma, infections, food, alcohol, weight changes. Patients' psoriasis treatment history was also explored: study participants were asked as to whether they been previously treated by their general practitioners or a dermatologist, whether they had received psychological support to better cope with psoriasis, used alternative topical compounds, balneotherapy, heliotherapy, topical corticosteroids, tar compounds, cignolin (ditranol, antralin), localized or systemic phototherapy, non-biologic systemic agents, biologic agents or whether they had been hospitalized in the past for psoriasis. Each patient's history was obtained by means of a questionnaire. We defined alternative topical therapies as those not mentioned in the respective European recommendations (Nast et al. 2015) (Nast et al. 2017). Puberty and perimenopausal/periandropausal periods were considered times of hormonal variations. Nonspecific noninfectious liver disease was defined as a history of elevated liver tests/enzymes or ultrasound-documented liver disease (fatty liver disease, steatosis, steatohepatitis or cirrhosis) of noninfectious etiology within the past 30 months.

Once our study started, all patients were requested to attend regular follow-up visits every three months. During these visits, detailed records of each patient's status, disease progression, and possible adverse events were obtained. Complete physical examinations

were performed, and body surface area (BSA) plus Psoriasis Area Severity Index (PASI) scores recorded at each visit. Furthermore, five ml of urine (U) and 12 ml of serum (S) and plasma (P) each were collected for basic laboratory tests. Patients treated with a biologic agent were also tested for autoantibodies and Quanti-FERON-TB Gold, followed by annual lung function tests.

All patients were treated according to the recommendations of the Summary of Product Characteristics of each drug. During our study, some patients were forced to rotate different agents within their stratum/type of therapy, while others had to be shifted to a different therapy type. The most common reasons were drug intolerance or loss of treatment efficacy. Specifically, 24 (8.3%) of our patients used both systemic non-biologic systemic agents and biologics during our research period – of these, 9 (3.1%) individuals used acitretin and methotrexate concomitantly with biologic agents, the remaining 15 (5.2%) were treated with only one systemic agent at a time. For this reason, our patients were included in as many groups as many therapy(ies) they had – that is, if a patient was on systemic non-biologic systemic agents, but was later forced to initiate biologic therapy, then he/she was included in both groups, that is, "systemic non-biologic systemic agents" and "biologic agents". All adverse events and lab results corresponding to each six-month interval were carefully paired with the type of therapy or the biologic agent used during the very same time interval.

We used Edwards' definition of adverse events (Edwards and Aronson 2000) (Edwards and Aronson 2000) and European Medicines Agency's (EMA) ("Serious Adverse Reaction | European Medicines Agency" n.d.) definition of serious adverse events. Serious infections were defined as all serious adverse events classified as "infections and infestations" according to the System Organ Class of the Medical Dictionary for Regulatory Activities (version 16.0) (SAS 2013). Based on this system (SAS 2013), we grouped the adverse events according to the affected system with two minor adaptations. The first one consisted of all infections and infestations corresponding to each affected system, with the exception of dermatological, respiratory and urinary infections. The second one was the creation of a separate category for all oral cavity-related disorders. For systemic antibiotics that patients failed to identify, a separate category designated as "unknown antibiotics" was created.

Results were then statistically analyzed using standard ANOVA with one fixed factor (type of therapy) and one repeated factor (six-month interval). Fisher's least significant difference (LSD) post-hoc tests were then applied to all statistically significant results. Lastly, chi-squared tests were performed for all parameters to check whether there was a statistically significant difference between the expected versus observed frequencies.

This study was approved by our faculty's Ethics Committee, and patients were recruited into the study after informed consent had been obtained.

Outline of the thesis

Chapter 1

This chapter presents a non-systematic review of the literature that provides information on the fundamentals of epidemiology, diagnosis and treatment of psoriasis. Special emphasis was placed on the most modern form of therapy: biologics agents. Available data about their production, role and possible adverse events are discussed in detail.

Chapter 2

This chapter presents the results of an epidemiological study performed in patients with psoriasis. By statistically analysing epidemiological data of three groups with different severity grades, it investigates possible trigger and prognostic factors of patients with severe psoriasis – high-need patients.

Chapter 3

This chapter outlines the results of a research focused on the occurrence of adverse events according to the type of therapy used to treat psoriasis vulgaris. It is a prospective, observational cohort study where three groups of patients on three different therapeutic regimens are followed – by comparing the occurrence of adverse events between them, it identified the safest therapeutic regimen.

Chapter 4

This chapter describes the results of a sub-study exploring the safety profiles of five different biologic agents. It is a part of the above observational cohort prospective study. In this case, the occurrence of adverse events between the five groups of patients treated with different biologic agents is investigated in an attempt to identify the drug with the safest profile.

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CHAPTER 1

The use of biologic agents in the therapy of psoriasis vulgaris

Full-text of chapter 1 is published as a review article:

Authors: Emanuel C. Marques, Zoltán Paluch, Jana Hercogová

Title: The use of biologic agents in the therapy of psoriasis vulgaris – an overview

Journal: Česká dermatovenerologie

Abstract

Psoriasis is a global disease affecting up to 4,8% across the globe and causing significant impairment of quality of life, disfiguring morbidity, and even mortality. The first therapies consisted only of old natural oitments, but with time, these have been substituted by advanced potent drugs. In the last decades, as the immunological pathways of the disease are being unveiled, the development of powerful but selective biologic drugs targeting these immune pathways became possible. These have raised hopes that complete remission may be possible, even when all other previous therapies have failed. In this review, we will shortly present some of the latest data available on the treatment of psoriasis by biologic agents.

Psoriasis

It was only in the 18th century that Willan first described psoriasis. At first, lepra and psoriasis were poorly differentiated but was Hebra that in 1863 finally defined it as a distinct entity, as we know it today (Khachemoune and Guillen 2006). Derived from the Greek "psora" which means "itch", this chronic, non-infectious inflammatory skin disorder affects about 0,6% to 4,8% of the world's population. Variatons in prevalence are seen according to countries' latitude, studies have shown that psoriasis is significantly less prevalent in countries closer to the equator line (Smith and Barker 2006), (Parisi et al. 2013). Limited epidemiological studies pertaining to psoriais and races have been carried out, nevertheless data suggests an higher prevalence of the disease among Caucasians, when compared to non-Caucasians (Alexis and Blackcloud 2014). No clear gender predilection has been observed among sexes (Parisi et al. 2013), (Michalek, Loring, and John 2017), (Rachakonda, Schupp, and Armstrong 2014). Regarding the age of onset, psoriasis can literally begin at any age; it is known, however, that children are less commonly affected. There seem to be two peaks for the age of onset of the disease: the early one between 30 and 39 years and the later one between the ages of 50 and 69 years of age (Parisi et al. 2013).

Despite the fact that it is rarely life-threatning, psoriasis can severily impairs one's quality of life: concomitant anxiety and depression are not uncommon, treatments are costly, long-lasting and time-consuming. Evidently, the severity of the disease is directly proportional to its economical and social impact, and without a doubt, these are undissociable. Patients who have higher severity indexes perceive more interferences with work activities and therefore are more likely to generate lower incomes (S. R. Feldman et al. 1997). This economical impact is not, however, restricted to families themselves, it is also costly to the health care systems of each country – a recent study in the United States of America have concluded that, all summed up, annual expenses with psoriasis can reach up to $25796/patient per year or a total of $135 billion for everyone with the disease (Steven R. Feldman et al. 2017).

Psoriasis is considered to be a multifactorial disease, with an unquestionable genetic component interacting with some environmental factors (Parisi et al. 2013). Studies including families in which either one or both parents had the disease have shown that if one

parent has psoriasis, there is a 28% chance for the child to develop this condition; if both parents are affected, then the chance rises up to 65%; contrastingly, if none of the child's parents have this skin disease, there is only a 4% chance of developing psoriasis. Genetic researches have established strong associations between the disease and those who are HLA (human leukocyte antigen) B13, -B13, -B17, -B39, -B57, -Cw6, or -DR7 positive (Rahman and Elder 2005). From those seven HLA types, patients who are HLA-Cw6 positive have a worse prognosis: HLA-Cw6 positivity is associated with early onset of the disease, guttate eruptions, and increased severity (yet, such associations are sometimes seen in Cw6 negative patients) (Guojónsson et al. 2002). Environmental factors are various and can trigger the disease at any time; these include physical trauma (Koebner phenomenom), meaning that an injury to the epidermis may trigger a cytokine cascade and cause psoriatic lesions: examples of trauma include bites, tatoos, excoriations, and others (S. P. Raychaudhuri, Jiang, and Raychaudhuri 2008). Also, the association between B-hemolytic streptococcus infections and the guttate form of the disease is nowadays well-known (Prinz 2001). Nevertheless, other organisms such as Malassezia Furfur, Staphylococcus aureaus, Candida albicans, Pityrosporum orbiculare and several viruses have also been described to be implicated as playing an etiological role in the development of psoriasis (Baroni et al. 2004), (Balci et al. 2009), (Waldman et al. 2001), (Kirby et al. 2000). Although difficult to quantify, stress can undoubtedly aggravate the disease: the mechanisms behind this process are not fully known, however it is thought that either stress hormones affect one's immune and autonomic nervous system or that people with psoriasis have their nerve endings secreting neuropeptides which influence skin immune cells and keratinocyte function (Chapman and Moynihan 2009). Certain drugs such as antibiotics, lithium, antihypertensive agents (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors), and NSAIDs (non-steroidal anti-inflammatory drugs) have been reported to induce or aggravate the disease - again, the mechanisms by which they do so are not fully understood. Other than these, it is also well-documented that those who have high intakes of alcohol, smoke or have a vitamin D deficiency have a worse prognosis of the disease (Huerta, Rivero, and García Rodríguez 2007), (Orgaz-Molina et al. 2012).

When it comes to the ethiopathogenesis of the disease, psoriasis is nowadays considered a T cell mediated disease (Kirby et al. 2000). Involvement of both innate and adaptive immune systems are both believed to play a vital role in the pathophysiology of the disease –scientific evidence points to a theory of a "dysregulated immune system". The characteristic psoriatic plaques we are used to see are not more than the result of a complex interaction between dendritic cells, T cells, keratinocytes, neutrophils and cytokines realeased from immune cells (Frank Nestle, Kaplan, and Barker 2009). Essentially, we may say that it all starts with a response from our innate immune system: first, an antigen activates our plasmacytoid dendritic cells and other innate immune cells. Plasmacytoid dendritic cells are primary producers of INF-alpha, a crucial cytokine involved in the initiation of autoimmune responses and antiviral immunity. INF-alpha, together with other proinflammatory cytokines produced by these other innate immune cells, then stimulate the activation of myeloid dendritic cells in the skin (Frank Nestle, Kaplan, and Barker 2009), (Schafer et al. 2014), (Papp et al. 2012), (Papp et al. 2016) (Fig. 1). Myeloid dendritic cells are potent antigen presenting cells that influence T-cell activity. They do so by producing 2 cytokines: IL-23 that causes differentiation of precursor $CD4^+$ cells into Th17 cells and IL-12 that stimulates the development of Th1 cells and effector $CD8^+$ T cells (McKenzie, Kastelein, and Cua 2006). Myeloid dendritic cells have also been found to be responsible for the production of IL-20 and nitric oxide, the first involved in alterations of the epidermal thickness, maturation defects and upregulation of antimicrobial peptides, the second contributing to the attraction and migration of leukocytes by vasculature activation (Blumberg et al. 2001), (Wolk et al. 2009), (Costa, Incio, and Soares 2007). T cells, recruited by myeloid dendritic cells, mediate this all inflammatory process by producing even more cytokines. Among others, these T cells produce IL-17A which stimulate keratinocytes to proliferate. Activated proliferative keratinocytes and consequent permanent cytokine activation perpetuates this inflammatory process via participation in positive feedback loops (Frank Nestle, Kaplan, and Barker 2009).

In summary, psoriasis is a challenging immune-mediated disorder caused by diverse dysregulations and alterations of our immune system. Regulated by T cells, cytokines play a key role in this process, activating and stimulating components of our innate and adaptive immune systems, resulting in a cascade of events. The identification of such cytokines was

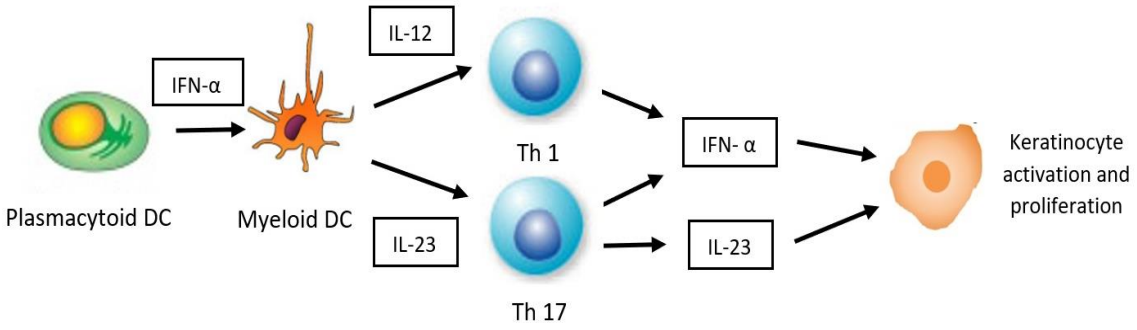

Fig. 1 Pathogenesis of psoriasis vulgaris

a great step towards the control of the most severe forms of the disease, as they enabled the creation of the first biologic agents.

Psoriasis can be classified according to the different features: age of onset (age of onset before or after 40 years of age), degree of severity (mild, moderate, severe), pattern of distribution (inverse, seborrheic, vulgaris), morphology (plaque, guttate, erythrodermic, localized pustular and generalized pustular), anatomical site (scalp, palmoplantar, vulgaris, anogenital and nail psoriasis) and stage of development (stable plaque or unstable eruptive forms of the disease) (table 1). Sometimes, in clinical practice, these classifications are combined for a better characterization of the status of the patient (ex: psoriasis vulgaris – chronic plaque form). The most used classifications are the ones based on the degree of severity, pattern of distribution of the disease, morphology of the lesions and affected anatomical site. According to the degree of severity, psoriasis is considered to be mild when BSA<5, moderate when BSA 5-10% and severe when BSA≥10 (BSA=body surface area affected by the disease). Plaque psoriasis or psoriasis vulgaris, represents 90% of all cases: characterized by minimally changing sharply marginated dull-red plaques, with lamellar silvery/white scales, it usually persists from months to many years. These plaques may fuse between each other creating big geographic, polycyclic shapes, are typically bilateral and symmetrical, localized to one or more predilection sites: elbows, knees, sacralgluteal region, scalp, palms and soles. Sometimes, however, in contrast to its preferred external surfaces, psoriasis may manifest itself only on the flexor surfaces and skin folds (perineum, axillas,

inguinal and intergluteal areas) – in such cases, dermatologists name it inverse psoriasis. Besides the localization, also the aspect of the lesions differs from the plaque form: standardly, because these areas are moist, plaques do not present as many scales. The guttate form of the disease typically follows an upper respiratory infection or a streptococcal infection. It occurs more commonly among children, adolescents and young adults, and is characterized by the rapid appearance of diffuse drop-like or nummular (coin-shaped) papules with little scale all over one's body, predominantly on the trunk. Characteristically, new lesions keep rising for about a month, persist for 2 to 3 months and then resolve spontaneously; sometimes, however, these lesions may persist and enlarge taking on the characteristics of the chronic stable plaque type. Typically, pustular psoriasis exhibits itself as tender deep-seated sterile pustules on an erythematous base. Most patients have a localized form – meaning that these pustules only affect a specific part of the body – however, some suffer from or develop a rare generalized form of the disease. The localized form of pustular psoriasis is either manifested on one's fingers, dorsal aspects of the hands and toes (acrodermatitis continua of Hallopeau) or it is limited to palms and soles (palmoplantar psoriasis). The generalized form, also called von Zumbusch pustular psoriasis, is often associated with fever, myalgia, nausea, leukocytosis and generalized erythematous tender skin. These patients are usually severely sick and require hospitalization for close monitoring. Erythrodermic psoriasis consists of generalized erythema involving the majority of one's body. Since other diseases (atopic dermatitis, drug eruptions, pityriasis rubra pilaris, etc) may present themselves as erythroderma, determining the exact diagnosis can sometimes be tricky: examining possible nail changes may prove helpful, in case of doubt a skin biopsy should be performed. Just like von Zumbusch pustular psoriasis, this disease phenotype can be life threatning, therefore, identifying the possible trigger can only benefit the patient's outcome: abrupt withdrawal of systemic medications (eg. corticosteroids), drug reaction responses (eg. lithium) or underlying systemic infections are all described as possible leading causes to erythrodermic psoriasis. Not rarely, patients suffering from psoriasis have their nails affected – nail psoriasis. The most characteristic feature of nail psoriasis is pitting of the nails, whereas the most commonly seen feature is onycholysis (detachment of the distal portion of nail from the nail bed). Besides these, psoriatic nails may present dystrophy and dyscoloration, extra thickness can also be seen especially when there

is accumulation of keratinous material under the nail bed – subungual hyperkeratosis (S. K. Raychaudhuri, Maverakis, and Raychaudhuri 2014), (Hercogová 2011). Even though these classifications prove useful in patient referral and disease surveillance, they can be somehow tricky in clinical practice, since many patients suffer from several types of the disease combined.

Today we know that symptoms of psoriasis are very often underated – most dermatologists do not include these in the evaluation of the severity of the disease, PASI (psoriasis area severity index) classification is a good example of a widely used method that excudes patient's feelings. Symptoms may represent a serious disabling factor, especially in those who are already psychologically distressed by the disease. There are a variety of forms to measure patient's quality of life, but commonly this is accessed by the Dermatology Life Quality Index (DLQI) (Gisondi et al. 2017). If we sort symptoms descending, itching clearly comes as the most common complain, followed by irritation, burning/stinging, sensitivity and last, but not least, pain (Sampogna et al. 2004). Current drugs to alleviate these provide somehow unsatisfactory results, pruritus for example is practically nonrespondent to oral antihistamines, unless they cause sedation. Moisturizers, phototherapy, oral antidepressants, topical kinase inhibitors, and lately biologic agents, are among the most beneficial current treatment modalities (Szepietowski and Reich 2016).

Tab. 1 Clinical classification of psoriasis vulgaris

Classification criteria	Clinical phenotypes
Age of onset	Type I (onset before 40 years of age)
	Type II (onset after 40 years of age)
Degree of severity	Mild (<5% BSA)
	Moderate (5%-10% BSA)
	Severe (>5% BSA)
Pattern of distribution	Inverse
	Seborrheic
	Vulgaris/Plaque
Morphology	Vulgaris/Plaque
	Guttate
	Erythrodermic
	Pustular (localized or generalized)
Anatomical site	Scalp
	Palmoplantar
	Nail
	Vulgaris/Plaque
Stage of development	Stable plaque
	Unstable eruptive

The diagnosis of psoriasis is mostly clinical, as lesions usually have a classical appearance. Other characteristics supportive of the diagnosis is positive family history, Koebner phenomenom evidence or Auspitz sign positivity. When these reveal themselves insufficient, a skin biopsy is sometimes performed to confirm the diagnosis (S. K. Raychaudhuri, Maverakis, and Raychaudhuri 2014). Other than this, antistreptolysin tests and streptococcal throat extracts from patient's throats can also be carried out, especially if there there was an antecedent streptococcal infection (Dupire et al. 2019).

Unfortunately, nowadays it is well known that psoriasis is not an isolated disease. Just like other systemic inflammatory diseases, it is highly associated with the development of several comorbidities. These have been lately classified as classic, emerging, related to lifestyle and related to the treatment of the disease. Classic comorbidities include psoriatic arthritis, Chron's disease, psychological/psychiatric disorders and uveitis. Emerging comborbidities refer to a number of underdiagnosed conditions that only lately have been associated with psoriasis, which include metabolic syndrome, coeliac and inflammatory bowel diseases, non-alcoholic fat liver disease, lymphomas and other neoplasms, obstructive sleep apnea/hypopnea syndrome, chronic obstructive pulmonary disease, osteoporosis, erectile dysfunction and Parkinson's disease (Juzlova et al. 2016), (Votrubova et al. 2014). Unsurprisingly, associated with higher levels of anxiety and depression, psoriatic patients have an higher frequency of smoking and drinking habits which alone lead to increased risk of hepatic steatosis, cirrhosis, depression, anxiety and decreased response to psoriasis treatments – these are considered to be comorbidities related to patients' lifestyle. The last category accounts for comorbidities related to the treatment of the disease: patients who undergo many sessions of phototherapy have an higher risk of developing skin cancers (eg. squamous-cell carcinoma), and generally, methotrexate and ciclosporine in high-doses can also be associated with carcinogenesis. Ciclosporine is, moreover, nephrotoxic, and may cause hypertension and dyslipidemia; methotrexate may lead to bone marrow and liver toxicity and so does acitretin that, besides nephrotoxicity, can also cause dyslipidemia (de Oliveira, Rocha, and Duarte 2015).

Presently, there is no cure for psoriasis (Nickoloff and Nestle 2004). Patients with a mild form of the disease are treated with topical agents: there are a variety of options from topical corticosteroids, vitamin D analogues, coal tar preparations, tazarotene, tacrolimus, pimecrolimus, emollients, anthralin and salicylic acid (Menter et al. 2009). A common problem found with this form of treatment is patients' compliance, which tend to decrease over time (Devaux et al. 2012). Systemic therapy is indicated when topical agents fail to control patients' symptoms, PASI≥10 (unless involvement of sensitive of areas such as hands, soles, genitals, scalp, face or nails), BSA<5 with disseminated lesions, BSA≥5 resistant to topical therapy, active psoriatic arthritis or when patients are severily distressed

by the disease (e.g. DLQI≥10). Short sessions of ultraviolet radiation can be combined with topical preparations, or if preferred, oral antipsoriatic drugs, also known as conventional systemic agents, can be started (Gisondi et al. 2017). Current options include acitretin, fumaric acid esters, methotrexate or ciclosporine. Besides these, the most recent class of antipsoriatic drugs are biologic agents and recently, Apremilast (an oral agent that inhibits the enzyme phosphodiesterase 4). This new class of drugs represent a second-line form of therapy if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated (Nast et al. 2015a), (Nast et al. 2017). Not all patients are suitable to these forms of therapy: these agents are extremely expensive, they are administered parenterically (with the exception of Apremilast), and involve, as any other drug, a variety of side-effects that should be pondered (Nast et al. 2017), (Pichler 2006).

Biologic agents

According to the The US Food and Drug Administration (USFDA), biologic products or biologics, are broadly defined as medical products. They are made from a variety of natural sources (human, animal or microorganism), often produced by biotechnology methods and other cutting-edge technologies. These can include any therapeutic serum, toxin, antitoxin, vaccine, virus, blood, blood component or derivatives, allergenic product, etc. Like drugs, some are intended to treat diseases and medical conditions, while others can be used for prevention and diagnosis. However, unlike most traditional therapeutic approaches, directed to symptom control and clinical improvement, biologic agents target specific points of the immunopathogenesis of a disease. They are produced by recombinant DNA technology, aiming at specific targets without interfering with rest of the pathogenetic pathways (Hassan et al. 2013). Nevertheless, truth is, biologics are not new: the development of molecules such as the human growth hormone, insulin, and red-blood cell stimulating agents occurred decades ago, but with time, targets have increased exponentially as our knowledge of genetics and subcellular cascades and disease processes develops (Coondoo 2009). Biologics are generally divided into three major groups: monoclonal antibodies, fusion antibody proteins and recombinant human cytokines and growth factors (Hassan et al. 2013) (Fig. 2).

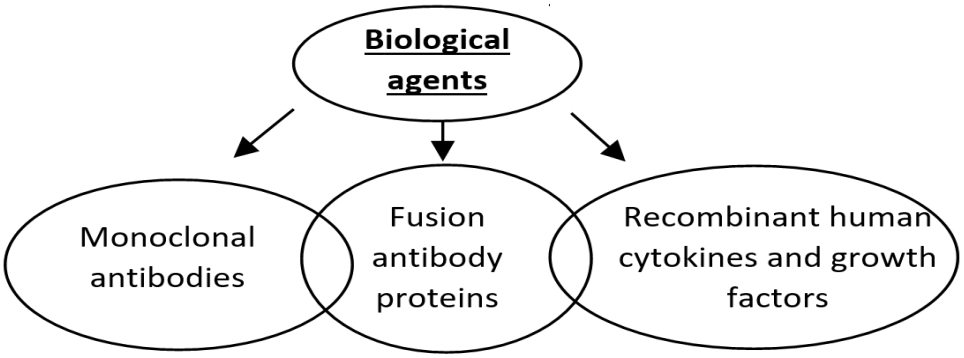

Fig. 2 Classification of biologic agents

Antibodies are proteins produced by a single clone of the B lymphocytes of the immune system in response to foreign proteins, called antigens. Antibodies function as markers, binding to the antigen so that the antigen molecules can be recognized and destroyed by cells of our immune system with those functions (ex: phagocytes). The part of the antigen that the antibody binds to is called the epitope. When antigents present many epitopes, they may activate many lymphocytes. Each of these these lymphocytes may then differentiate to plasma cells, resulting in a polyclonal antibody response. Contrastingly, monoclonal antibodies (mAbs) recognize only one chemical structure, meaning they are directed against a single epitope of the antigenic substance used to raise the antibody: it is this exquisite specificity of mAbs that allows them to be used for disease diagnosis and targeted therapies (Lipman et al. 2005). Fusion antibody proteins, also known as chimeric proteins, are proteins which are created by the fusion of the receptor domain of a human protein with the constant region of human IgG. The point being that the fused partner will be soluble in plasma (such as native IgG) and at the same time specifically bind to a particular ligand or co-receptor of interest (such as the variable region of an antibody) (Krueger 2002). The main reason this bound was created is half-life extension: due to fast renal clearance, many biologically active proteins and peptides have very short half-lives, which limits their exposure in the target tissue. However, by adding the Fc domain, fusion proteins enjoy a longer plasma half-life, resulting in a drug with advanced efficacy and pharmacokinetical properties (Beck and Reichert 2011). The last major group includes cytokines, which are non-immunoglobulin

proteins and glycoproteins produced by a wide variety of cells in the human body and released in response to any immune stimulus (Nikas and Drosos 2003), (Holman and Kalaaji 2006). Recombinant cytokines or cytokine antagonists have been used as immunomodulators (Oppenheim 2001) - interferons and interleukins are a good example of a variety of protein drugs that alter the activity of cytokines modifying the host response to a disease (Trefzer et al. 2003). Others, such as polypeptide growth factors (GFs) - a cluster of multifunctional peptides - play fundamental roles in processes such as stimulation of cellular differentiation and chemotaxis, signalling among cells of the same and different type, control of extracellular matrix formation and angiogenesis, regulation of the contraction process and reestablishment of tissue integrity during tissue repair (Chandler and Bewley 2013), (Lawrence 1998), (Werner and Grose 2003). From these 3 major groups of biologic agents, only monoclonal antibodies and fusion proteins are available for the treatment of psoriasis.

The first biologic to be approved in the field of dermatology was alefacept in 2003 for the treatment of moderate to severe forms of psoriasis (Sehgal, Pandhi, and Khurana 2014). Nowadays, however, the number of indications grow incessantly and new drugs appear yearly: besides psoriasis, biologic agents are today used in conditions such as malignant melanoma, cutaneous lymphoma, chronic spontaneous urticaria, hidradenitis suppurativa, granulomatosis with polyangiitis, microscopic polyangiits, chronic wounds and others (Hassan et al. 2013) (Fig. 3).

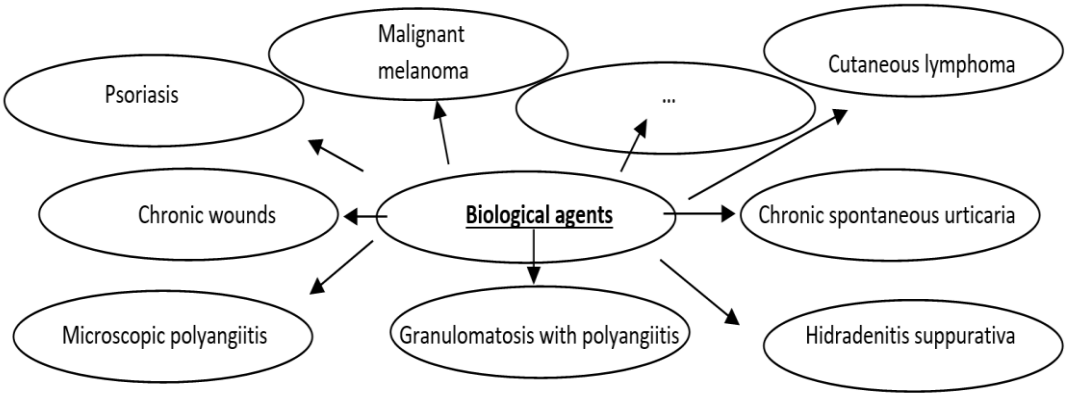

Fig. 3 Indications for biologic therapy in the field of dermatology

According to the latest European guidelines (October of 2015 and June of 2017), two big groups of agents are available for the treatment of psoriasis: inhibitors of TNFα and interleukin inhibitors. Adalimumab, etarnecept and infliximab all inhibit TNFα, ustekinumab inhibits IL-12 and IL-23 and secukinumab inhibits IL-17A (Nast et al. 2015b), (Thaçi et al. 2015). Since the publication of the latest guidelines, however, a few other biologic agents have already been approved by the EMA (European Medicines Agency): certolizumab pegol (TNFα inhibitor), ixekizumab (IL-17A inhibitor), brodalumab (IL-17 inhibitor), guselkumab and risankizumab (both IL-23 inhibitors) ("EMA. Committee for Medicinal Products for Human Use (CHMP). (n.d.). Summary of Opinion (Initial Authorization) - Kyntheum, Brodalumab." n.d.), ("EMA. Committee for Medicinal Products for Human Use (CHMP). (n.d.). Summary of Opinion (Initial Authorization) - Taltz, Ixekizumab." n.d.), ("EMA. Committee for Medicinal Products for Human Use (CHMP). (n.d.). Summary of Opinion (Initial Authorization) - Tremfya, Guselkumab." n.d.), ("Summary of Product Information - Cimzia (Certolizumab Pegol). (n.d.)." n.d.), ("Summary of Product Information - Skyrizi (Risankizumab). (n.d.)." n.d.) (Fig. 4 and 5). Of notice is also itolizumab, another effective biologic agent available for the treatment of psoriasis that is, so far, to our knowledge, only available in India (for this reason, this drug will not be reviewed in detail in this article) (Krupashankar et al. 2014).

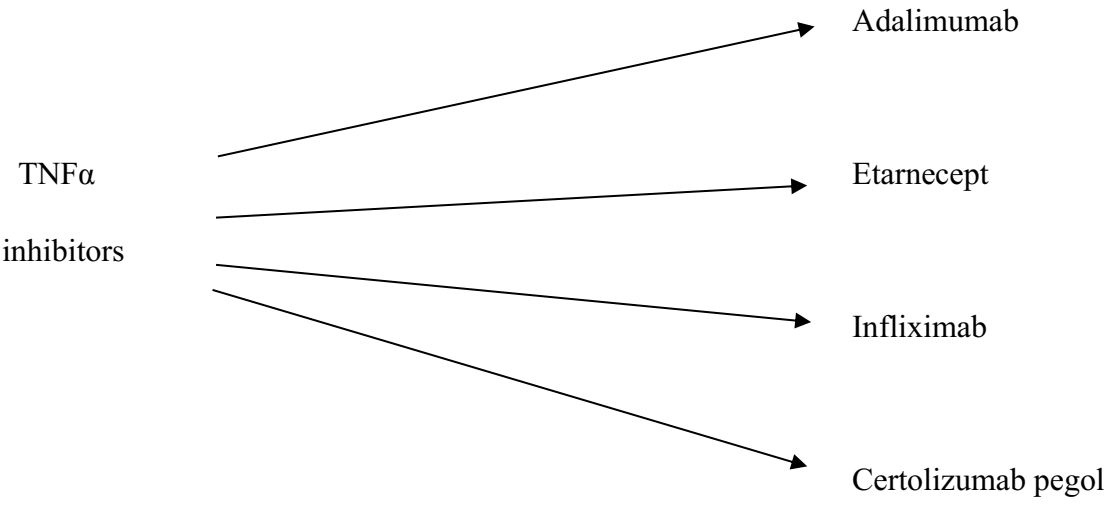

Fig. 4 Types of TNFα inhibitors

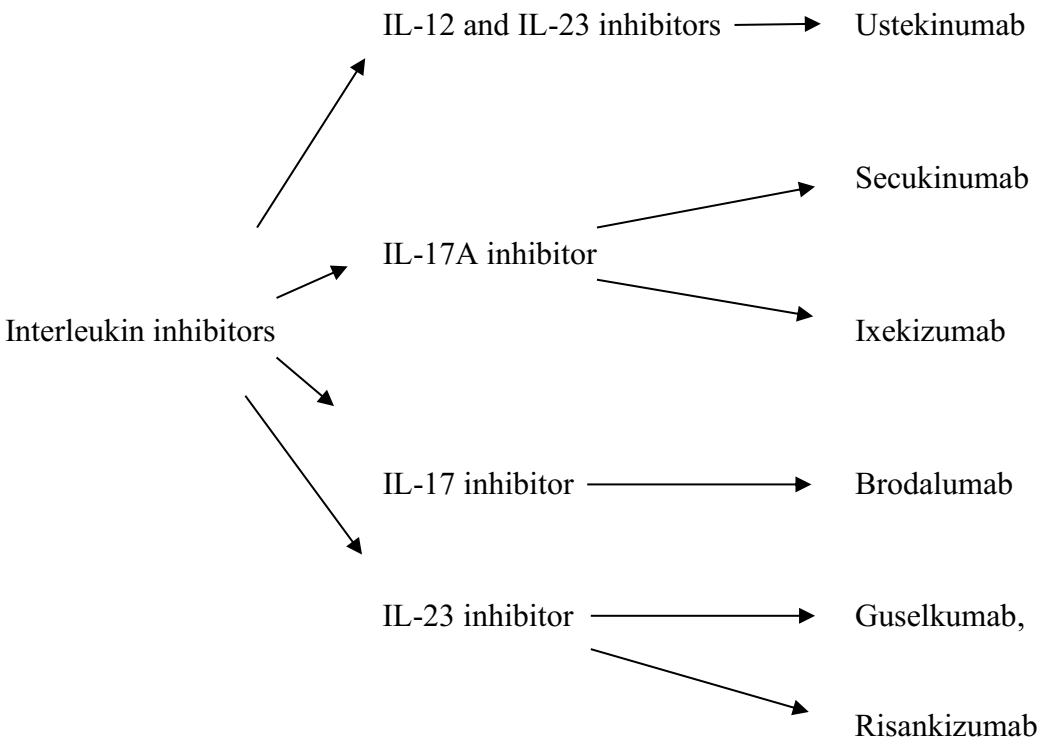

Fig. 5 Types of interleukin inhibitors

As mentioned before, psoriatic patients are only entitled to systemic therapy if they meet certain criteria. Biologic agents, specifically, should only be considered as a second-line form of therapy if phototherapy and conventional systemic agents were inadequate in response or if they are contraindicated or not tolerated. Biologics are not explicitly contraindicated to certain groups of patients, however it is consensually not recommended to prescribe TNF-inhibitors to patients suffering from multiple sclerosis or other demyelinating diseases, as well as to those suffering from ischaemic heart diseases or congenital heart failure NYHA III or IV (according to the New York Heart Association classification). Apart from these, a variety of precautions should be taken while prescribing biologics to special patient populations: children and elderly, women who are pregnant or lactating, those being treated with imunosupressants, patients who suffered or suffer from

chronic hepatitis B or C, or have an active infectious process (including tuberculosis). Special prudence is also necessary with those who were recently vaccinated with live vaccines, known hypersensitive reactions to these agents or who have or had a malignant tumour less than 5 years ago. Therefore, logically, it is recommended that when initiating these drugs, a dermatologist should objectively and subjectively access the severity of the disease (by using PASI and DLQI for example), take a good medical history and perform a complete clinical physical examination focusing on: prior antipsoriatic drugs taken, congestive heart failure, lymphadenopathy, neurological disease signs and symptoms, past malignancies (including skin cancer), eventual infections (including tuberculosis infections) and possible arthritis. Furthermore, if the patient is a female of reproductive age, then using contraception is recommended. Still prior to commencing such therapy, the clinician should request a panel of laboratory tests: these include a complete blood cell count (including haemoglobin, hematocrit, leucocytes and platelets), liver enzymes (including AST, ALP, AP and γGT), serum creatinine, urine status, urine pregnancy test, CRP, hepatitis B and C panel and HIV. Of note is the fact that not all laboratory tests may be of exact need, the patient's medical history, risk exposure and clinical signs during physical examination dictates the need for more or less specific testing (Nast et al. 2015b), (Nast et al. 2017) (table 2).

After starting the treatment, patients should be objectively and subjectively accessed every 3-6 months (by using PASI and DLQI for example) and physical examinations should be continuously performed with special focus on malignancies (including skin cancer), lymphadenopathy, active infections, congestive heart failure and neurological symptoms. To make sure the therapy carries on without complications, some basic routine laboratory tests including a complete blood cell count, liver enzymes, serum creatinine and urine status are recommended to be repeated within this interval (Nast et al. 2015b), (Nast et al. 2017).

When stopping a biologic agent, dermatologists are advised to continue following-up their patients. Physical examinations and medical history taking should be periodically repeated, moreover, depending on the specific biologic, females of reproductive age should keep using contraception up to 5 months after withdrawal of the drug (Nast et al. 2015b).

Tab. 2 Intructions before commencing biologic therapies

1. Enrol patients in a registry (if available)
2. Objectively assess the disease
3. Estimate patient's mental and physical health
4. Take patient's detailed medical history and perform a full physical examination
5. Send the patient for some basic laboratory tests
6. Recommend using contraception

Unfortunately, there is not yet a drug which is totally safe or innocuous, all have some sort of adverse reactions, the same apllies to biologic agents. An adverse drug reaction is, by definition, "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (Edwards and Aronson 2000). Generally, biologic agents are well tolerated, self-limited, and seldom reason to require discontinuation of therapy. Most adverse reactions are quite mild, all described serious/life-threatning adverse reactions are rather rare or very rare. Among the most common adverse reactions are injection site reactions, mild respiratory tract infections and general flu-like symptoms; nowithstanding, specific adverse reactions are inevitable as each drug have their own mechanisms of action (tables 3 and 4). Sparated in two tables (TNFα inhibitors and interleukin inhibitors), we address very common (≥1/10) and common (≥1/100 to <1/10) adverse reactions of each biologic agent.

Tab. 3 Most common adverse events associated with TNFα inhibitors ("Summary of Product Information - Cimzia (Certolizumab Pegol). (n.d.)." n.d.), ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.)

	Adalimumab		Etarnecept		Infliximab		Certolizumab pegol	
	Very common	Common	Very common	Common	Very common	Common	Very common	Common
Infections and infestations	•		•		•			•
Neoplasms (benign, malignant and unspecified)		•						
Blood and lymphatic system disorders	•					•		•
Immune system disorders		•		•		•		
Psychiatric disorders		•				•		
Nervous system disorders	•				•			•
Eye disorders		•				•		
Cardiac and vascular disorders		•				•		•
Respiratory disorders		•		•				
Gastrointestinal disorders/ hepatobiliary disorders	•				•			•
Skin and subcutaneous disorders	•			•		•		•
Musculoskeletal and connective tissue disorders	•					•		
Renal and urinary disorders		•				•		
General disorders and administration site conditions	•		•		•			•

Tab. 4 Most common adverse events associated with interleukin inhibitors ("Summary of Product Information - Skyrizi (Risankizumab). (n.d.)." n.d.), ("Summary of Product Information - Stelara (Ustekinumab)." n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.), ("Summary of Product Information - Taltz (Ixekizumab). (n.d.)." n.d.), ("Summary of Product Information - Kyntheum (Brodalumab). (n.d.)." n.d.), ("Summary of Product Information - Tremfya (Guselkumab)." n.d.)

	Ustekinumab		Secukinumab		Ixekizumab		Brodalumab		Guselkumab		Risankizumab	
	Very	Common	Very	Common	Very	Common	Very	Common	Very	Common	Very	Common
Infections and infestations		•	•		•			•	•		•	
Blood and lymphatic system disorders								•				
Nervous system disorders		•						•		•	•	
Respiratory disorders		•		•		•		•				
Gastrointestinal disorders		•		•		•		•		•		
Skin and subcutaneous disorders		•								•	•	
Musculoskeletal and connective tissue disorders		•						•		•		
General disorders and administration site conditions		•			•			•		•	•	

Conclusion

Today, more and more biologics are found each year. In fields like rheumatology and dermatology, these have gained a remarkable importance, considered by some as the therapies of the future. Empowered by most trial's success on drug efficacy and patient outcomes, these drugs are nowadays prescribed more and earlier in the disease process. However, one must keep in mind that these agents are relatively recent, some still lack consistent and solid data from long-lasting studies. Expectedly, with time, reports of serious adverse reactions are slowly starting to appear in the literature with the conduction of more studies and longer follow-ups; it is imperative, therefore, to be familiar with the benefits as well as the possible serious adverse reactions associated with these agents. For this reason, it is strictly recommended that physicians prescribing such agents remain vigilant and prudent, safety of the patient will always come first (Scheinfeld 2004).

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CHAPTER 2

Epidemiology of moderate-to-severe psoriasis: a comparison between psoriasis patients treated with biologic agents, conventional systemic drugs and topical agents

Full-text of chapter 2 is published as an original study:

Authors: Emanuel C. Marques, Zoltán Paluch, Petr Boháč, Ondřej Slanař, Jaromír Běláček, Jana Hercogová

Title: Epidemiology of moderate-to-severe psoriasis: a comparison between psoriasis patients treated with biologic agents, conventional systemic drugs and topical agents

Journal: Journal of Dermatological treatment

Abstract

Introduction: Understanding how different comorbidities and epidemiological factors are related to psoriasis severity can help us estimating patients' clinical outcome.

Aim: Establish possible prognostic factors of severe psoriasis.

Methods: Three groups of patients were included: 118 were on topical therapy, 83 used conventional systemic drugs and 112 were treated with biologic agents. Based on the fact that patients on topical therapy have a lower grade of disease severity than patients treated systemically, we compared a variety of comorbidities and epidemiological parameters between the three groups.

Results: Patients treated more aggressively have an increased risk of cardiovascular disease ($p=0.044$), suffer more from depression ($p=0.020$), hyperuricemia ($p=0.031$) and nonspecific non-infectious liver disease ($p=0.005$). Male gender ($p<0.001$), increased height ($p<0.001$), early age of disease onset ($p<0.001$), viral upper respiratory infections ($p=0.049$) and periods of hormonal changes ($p=0.045$) are associated with these therapies.

Conclusion: Psoriasis severity is directly related to an increased risk of cardiovascular disease, depression, hyperuricemia and nonspecific non-infectious liver disease. Male gender, increased height, early age of disease onset, viral upper respiratory infections and periods of hormonal changes seem to be prognostic of higher degrees of psoriasis severity. We are pioneering the use of increased height and puberty, menopause/andropause as independent prognostic factors of psoriasis severity.

Keywords: high-need psoriasis; psoriasis; psoriasis prognostic factors; psoriasis trigger factors

Introduction

Psoriasis is a global disease affecting up to 4.8% across the globe and causing significant impairment of quality of life, disfiguring morbidity, and even mortality (Smith and Barker 2006), (Parisi et al. 2013), (S. R. Feldman et al. 1997). Concomitant anxiety and depression are not uncommon, treatments are costly, long-lasting and time-consuming (Steven R. Feldman et al. 2017). Evidently, the severity of the disease is directly proportional to its economical and social impact, and these are undissociable (S. R. Feldman et al. 1997), (Steven R. Feldman et al. 2017). High-need psoriatic patients, meaning those for whom at least two systemic treatments are unsuitable due to lack of efficacy, intolerance or contraindication, are therefore at higher risk (Dubertret et al. 2006). Understanding how different comorbidities and epidemiological factors affect psoriasis severity grades can therefore be of great help for both patients themselves and countries' health care systems.

Materials and Methods

This is a cross-sectional observational study incorporated in a prospective study, where a population of 289 psoriatic patients was followed for 29 months (table 1).

Tab. 1 Brief epidemiological data of study population

Total number of patients in our study		289
	men	156 (54%)
	women	133 (46%)
Age (mean in years)		48 ± 80
BMI (mean)		28.3 ± 52.2

The objective was to study and compare a variety of comorbidities and epidemiological factors between 3 groups of psoriatic patients treated differently (table 2 and 3).
Data was obtained by means of a questionnaire. During our study some patients were forced to rotate different agents within their stratum/type of therapy, while others had to be shifted to a different therapy type. The most common reasons were drug intolerance or loss of treatment efficacy. Concretely, 24 (8.3%) of our patients used both conventional systemic agents and biologics during our research period – from these 9 (3.1%) individuals used acitretin and methotrexate concomitantly with biologic agents, the remaining 15 (5.2%) were treated with only one systemic agent at a time. For this reason, patients were included in as many groups as many therapy(ies) they had – that is, if a patient was on conventional systemic agents, but was later forced to initiate biologic therapy, then he/she was included in both group 2 and 3. Patients using any form of therapy/agent for less than 8 weeks were not included in our research study. All patients were treated according to the recommendations of the Summary of Product Characteristics of each drug.

We defined alternative topical therapies as those not mentioned in the European recommendantions (Nast et al. 2015), (Nast et al. 2017). Puberty and perimenopausal/periandropausal periods were considered as times of hormonal variations.

Nonspecific noninfectious liver disease was defined as history of elevated liver tests/enzymes or ultrasound verified liver disease (fatty liver disease, steatosis, steatohepatitis or cirrhosis) of noninfectious ethiology in the past 2.5 years.

Tab. 2 Study population therapies

Group of patients	Type of therapy	Specific agent	Number of patients
1	Topical therapy	Corticosteroids	118
		Keratolytics	
		Vitamin D derivates	
		Tacrolimus/pimecrolimus*)	
		Coal tar and its derivates	
2	Conventional systemic agents	Acitretin	34
		Cyclosporine	13
		Methotrexate	51
3	Biologic agents	Infliximab	11
		Secukinumab	17
		Etanercept	21
		Ustekinumab	33
		Adalimumab	41

Results were statistically processed in STATISTICA SW by means of standard ANOVA analysis with one fixed factor (type of therapy). Fischer least significance difference (LSD) post-hoc tests were then applied to all statistically significant results. Chi-squared tests were performed for all parameters to check whether there was a statistically significant difference between expected and observed frequencies.

Tab. 3 Tested epidemiological factors

Personal information	Personal history	Professional history and habits	Pharmacological history	Disease related history	Possible trigger factors	Treatment history
Age	History of skin diseases	Education level	Beta-blockers	Familiy history of psoriasis	Drugs	General practisioner
Gender	Thyroid disease	Profession	ACE inhibitors	Age of psoriasis onset	Hormonal changes	Dermatologist
Fototype	Gastroenterological diseases	Smoking	Diuretics		Stress	Psychological support
Height	Other autoimmune diseases	Alcohol	Acetyl salicylic acid		Trauma	Alternat. topical compounds
Weight	Oncological disease		Statins		Infection	Spa/wells
BMI	HIV		Proton pump inhibitors		Food	Heliotherapy
	Organ transplants		Lithium		Alcohol	Use of topical corticosteroids
	Osteoporosis		Antimalarials		Weather changes	Use of topical tar
	Rheumatological diseases		NSAIDs		Weight changes	Use of topical vit.D derivates
	Hyperuricemia		Interferon			Use of topical cignolin
	Depression		Benzodiazepines			Localized phototherapy
	Chronic heart failure					Systemic phototherapy
	Hypertension					Use of conv. syst. agents
	Dyslipidemia					
	Diabetes mellitus					

			Antidepressants			Use of BA Hospitalizations due to psoriasis

Ethics

This study was approved by our Faculty's ethical commission, and patients were recruited into the study after informed consent had been obtained.

Results

We noted that the type of therapy used was somehow age-related. Older patients were rather kept on topical therapy, while younger patients were tendentiously initiated on systemic agents more often. This became evident not only when studying our populations´age ($p<0.001$, fig. 1), but also when inspecting their professional situation - pensioners tend to be treated topically and kept away from biologic agents ($p<0.001$, table 4).

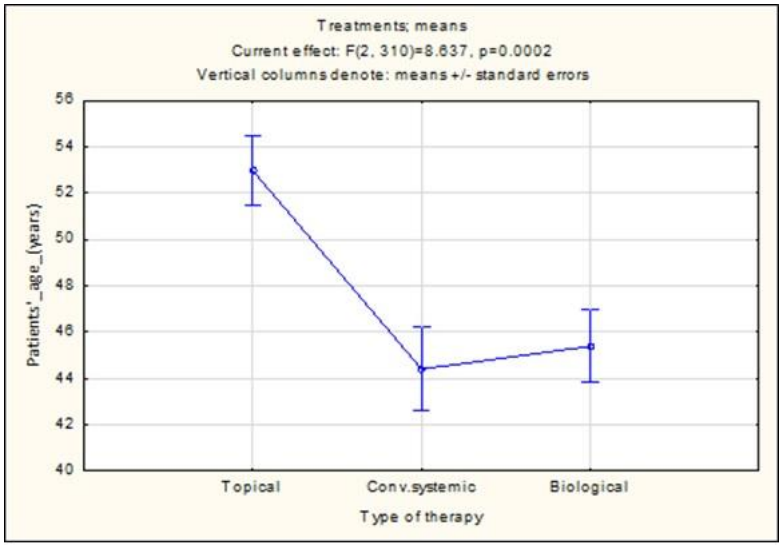

Fig. 1 Patients' age ($p<0.001$)

Tab.4 Profession ($p<0.001$)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Students	3.4%	4	10.8%	9	7.1%	8	6.7%	21
Manual workers	**22.0%**	26	**47.0%**	39	34.8%	39	33.2%	104
Intelectual workers	36.4%	43	**25.3%**	21	39.3%	44	34.5%	108
Pensioners	**35.6%**	42	14.5%	12	**13.4%**	15	22.0%	69
Pensioners for invalidity	2.5%	3	2.4%	2	5.4%	6	3.5%	11
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

We observed that more women were treated topically than men. This difference was even more evident in the group of patients treated with biologic agents, which clearly have the highest percentage of men (p=0.001, fig. 2 and table 5).

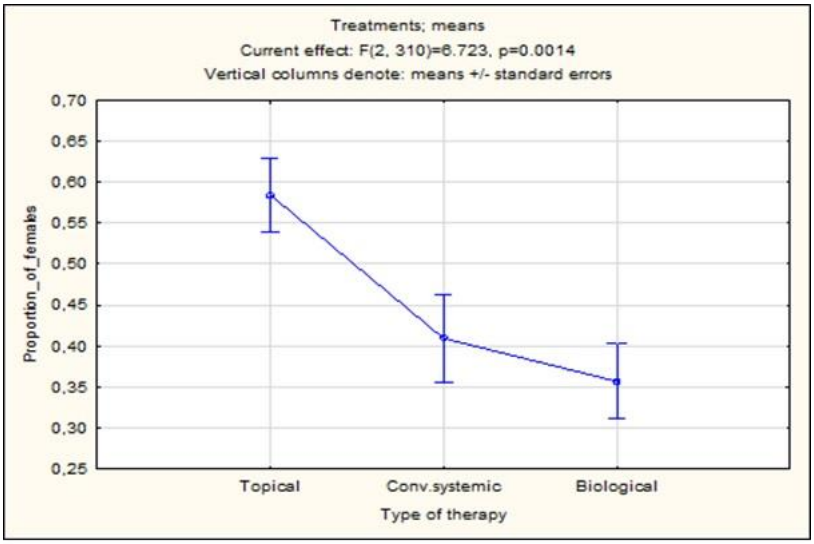

Fig. 2 Proportion of females (p=0.001)

Tab. 5 Proportion of females (p=0.001)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Men	**41.5%**	49	59.0%	49	**64.3%**	72	54.3%	170
Women	**58.5%**	69	41.0%	34	**35.7%**	40	45.7%	143
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

Patients´ height also statistically differed depending on how they were tre1ated. We found taller patients to be treated with more more aggessive forms of therapy than shorter patients (p<0.001, fig. 3).

Furthermore, we realized that patients treated systemically showed a statistically significant earlier disease onset than the group treated with topical agents ($p<0.001$, fig. 4).

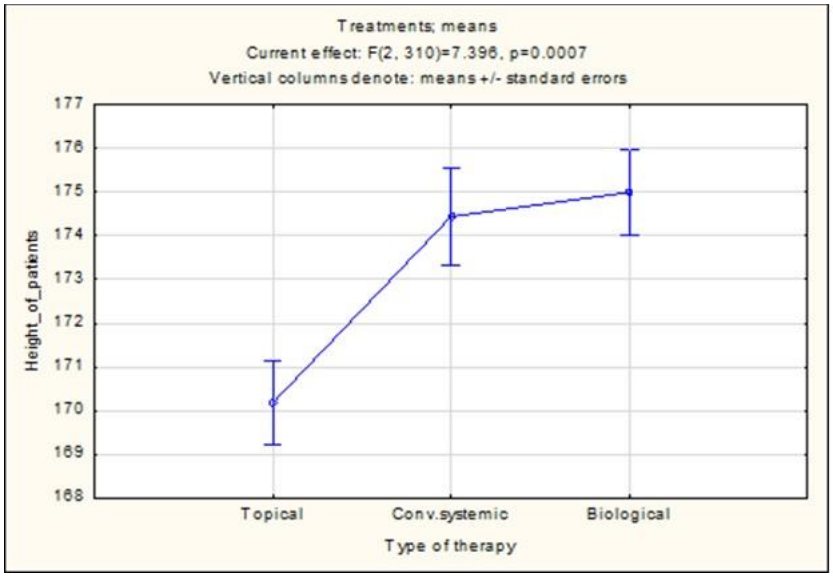

Fig. 3 Height of patients ($p<0.001$)

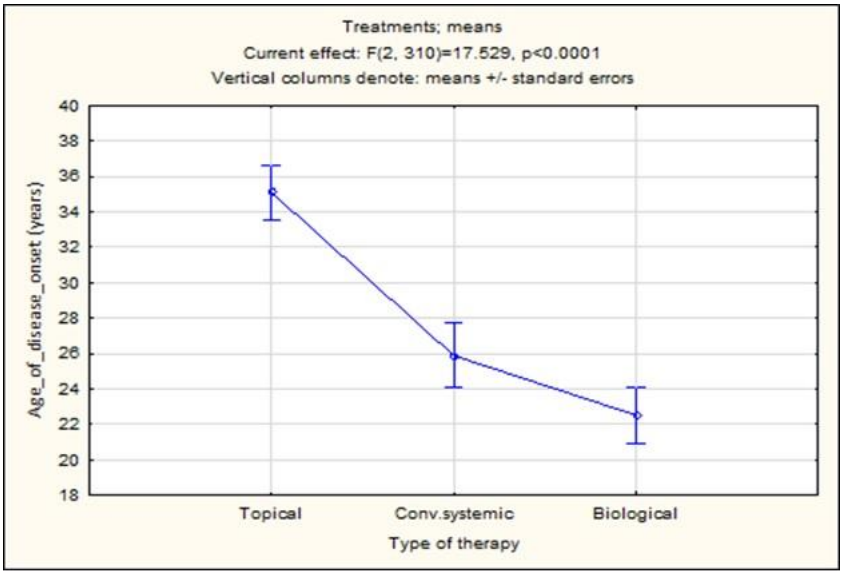

Fig. 4 Age of disease onset (years) ($p<0.001$)

The vast majority of patients treated with topical agents did not refer infections as a disease trigger factor. This difference was significantly different when compared to the two other groups of patients, where plenty more patients indicated infections as a trigger factor of psoriasis (p=0.047, fig. 5 and table 6). We found the same relationship regarding viral upper respiratory tract infections: again, patients treated topically described viral upper respiratory tract infections as a disease trigger factor way less often than the other two groups (p=0.049, fig. 6 and table 7).

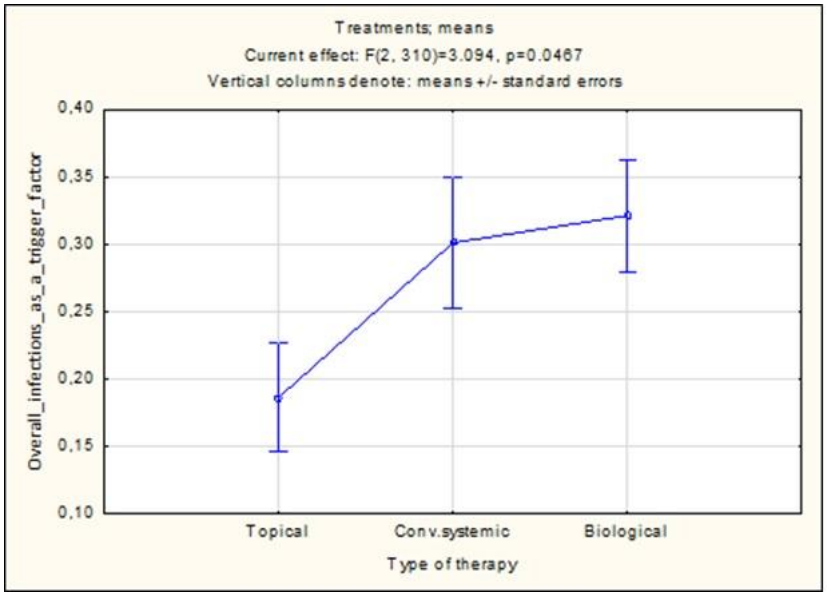

Fig. 5 Overall infections as a trigger factor (p=0.047)

Tab. 6 Overall infections as a trigger factor (p=0.047)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Not present	**81.4%**	96	69.9%	58	67.9%	76	73.5%	230
Present	**18.6%**	22	30.1%	25	32.1%	36	26.5%	83
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

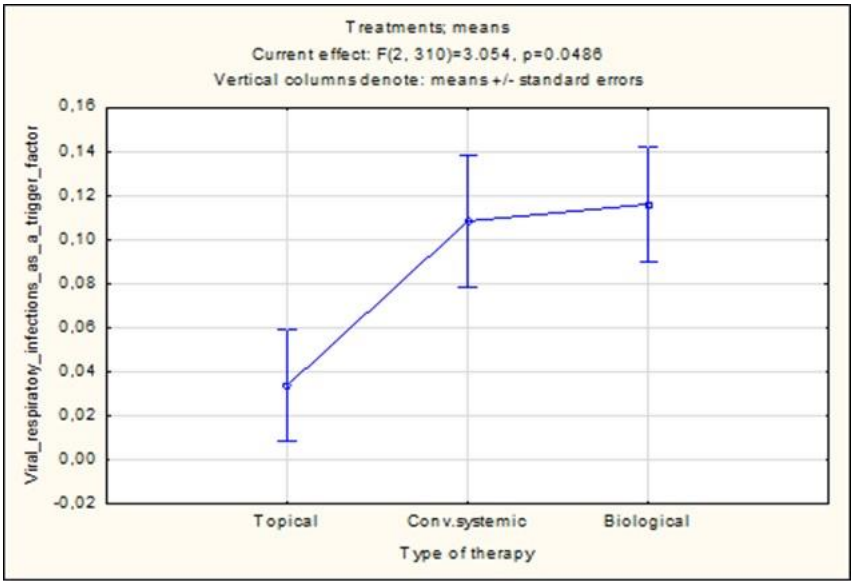

Fig. 6 Viral respiratory infections as a trigger factor (p=0.049)

Tab. 7 Viral respiratory infections as a trigger factor (p=0.049)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Not present	**96.6%**	114	89.2%	74	88.4%	99	91.7%	287
Present	**3.4%**	4	10.8%	9	11.6%	13	8.3%	26
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

Patients treated with biologic agents also pointed hormonal changes such as puberty and perimenopausal/periandropausal periods more often as a possible trigger factor of their disease. There was a statistically significant difference between group 3 and the remaining groups (p=0.045, fig. 7 and table 8).

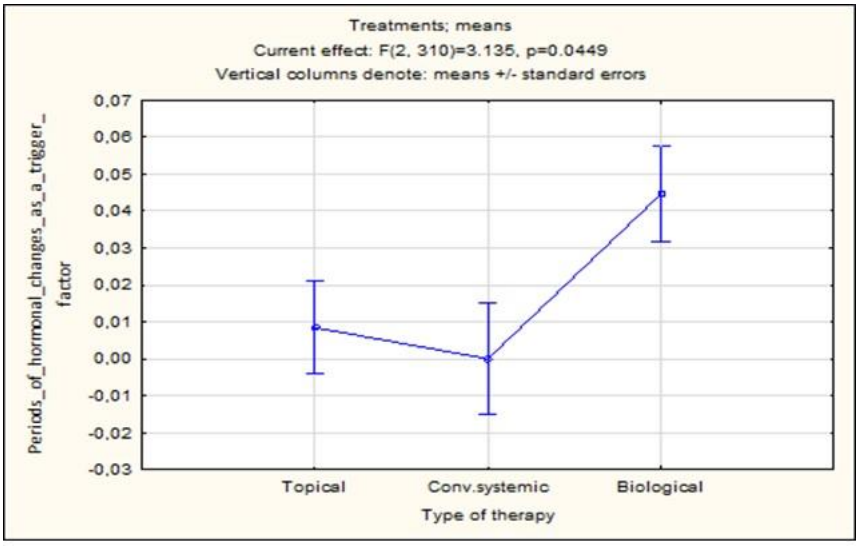

Fig. 7 Periods of hormonal changes as a trigger factor (p=0.045)

Tab. 8 Periods of hormonal changes as a trigger factor (p=0.045)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Not present	99.2%	117	100.0%	83	**95.5%**	107	98.1%	307
Present	0.8%	1	0%	0	**4.5%**	5	1.9%	6
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

A number of conditions also seem to differ according to patients´ therapy. Psoriatics treated systemically suffer more from depression, hyperuricemia, noninfectious nonspecific liver disease and are more often treated with statins. In addition, the prevalence of hyperuricemia and nonspecific liver disease significantly differ between the groups treated with topical agents and biologic agents. We observed the same p-values for the constant depression (fig. 8, table 9), hyperuricemia (fig. 9, table 10) and statin usage (fig. 10, table 11) (p=0.020, p=0.031 and p=0.044 respectively), while for the constant nonspecific liver disease p=0.005 (table 12).

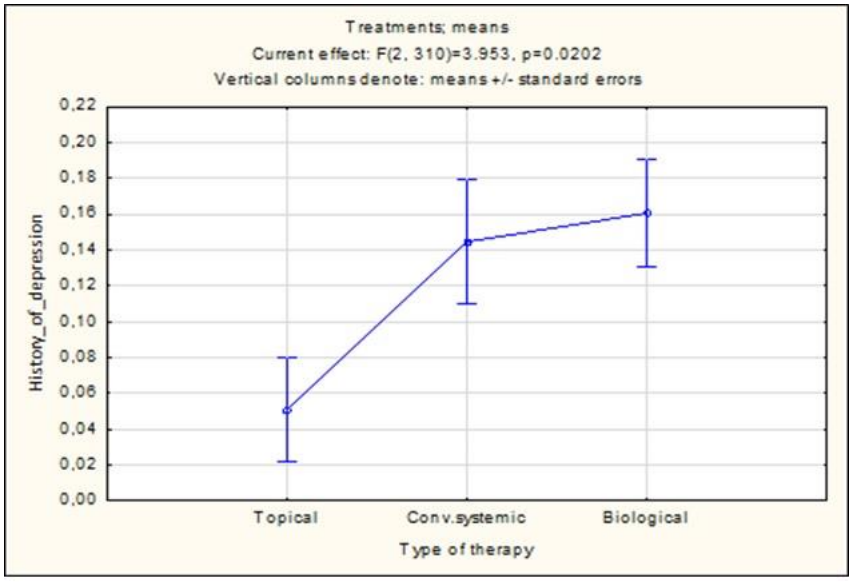

Fig. 8 History of depression (p=0.020)

Tab. 9 History of depression (p=0.020)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Not present	**94.9%**	112	85.5%	71	83.9%	94	88.5%	277
Present	**5.1%**	6	14.5%	12	16.1%	18	11.5%	36
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

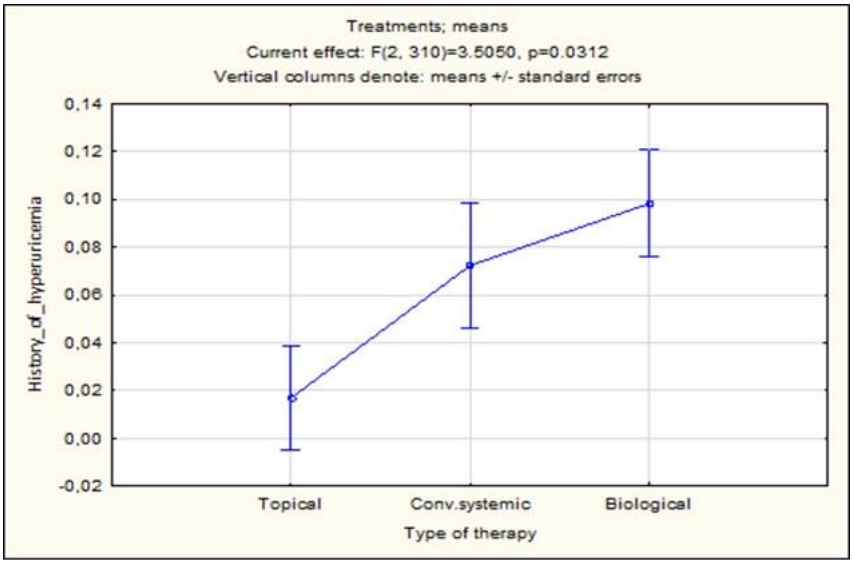

Fig. 9 History of hyperuricemia (p=0.031)

Tab. 10 History of hyperuricemia (p=0.031)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Not present	**98.3%**	116	92.8%	77	**90.2%**	101	93.9%	294
Present	**1.7%**	2	7.2%	6	**9.8%**	11	6.1%	19
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

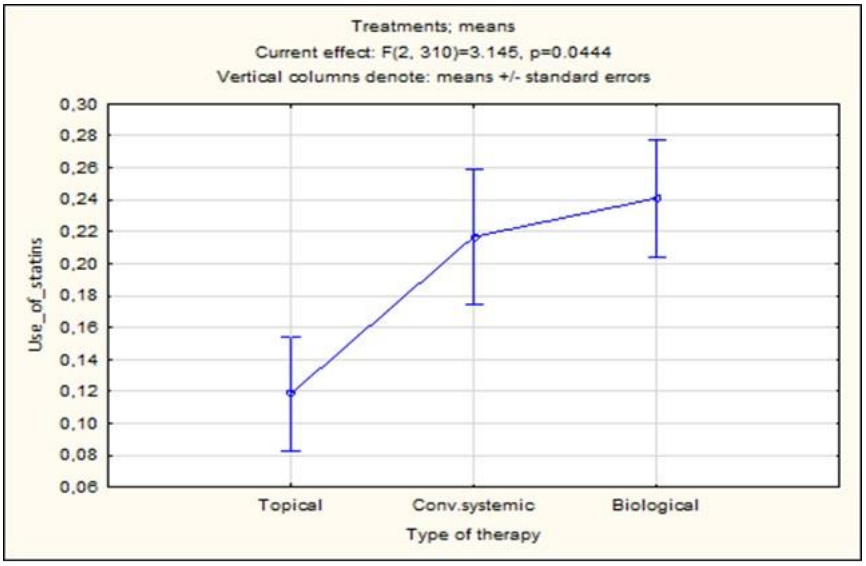

Fig. 10 History of usage of statins (p=0.044)

Tab. 11 History of usage of statins (p=0.044)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Not present	**88.1%**	104	78.3%	65	75.9%	85	81.2%	254
Present	**11.9%**	14	21.7%	18	24.1%	27	18.8%	59
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

Tab. 12 History of liver disease (p=0.005)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Not present	**98.3%**	116	96.4%	80	**91.1%**	102	95.2%	298
Nonspecific noninfectious	0%	0	3.6%	3	**8.9%**	10	4.2%	13
Infectious	1.7%	2	0%	0	0%	0	0.6%	2
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

Psoriatics treated with biologic agents also require more psychological help than patients treated with topical therapy (p=0.010, fig. 11, table 13).

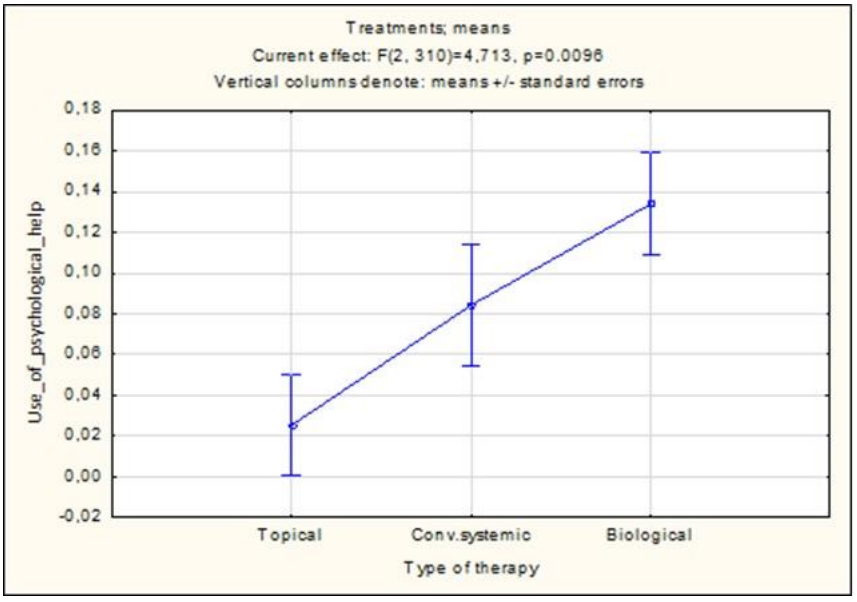

Fig. 11 History of psychological help (p=0.010)

Tab. 13 History of psychological help (p=0.010)

	Type of therapy						(total)	
	Topical		**Conv. systemic**		**Biologic**			
	%	n	%	n	%	n	%	n
Not present	**97.5%**	115	91.6%	76	**86.6%**	97	92.0%	288
Present	**2.5%**	3	8.4%	7	**13.4%**	15	8.0%	25
(total)	100.0%	118	100.0%	83	100.0%	112	100.0%	313

Patients treated topically have a considerably less number of past hospitalizations due to psoriasis than the other groups of patients treated systemically, namely with biologic agents (p<0.001, fig. 12).

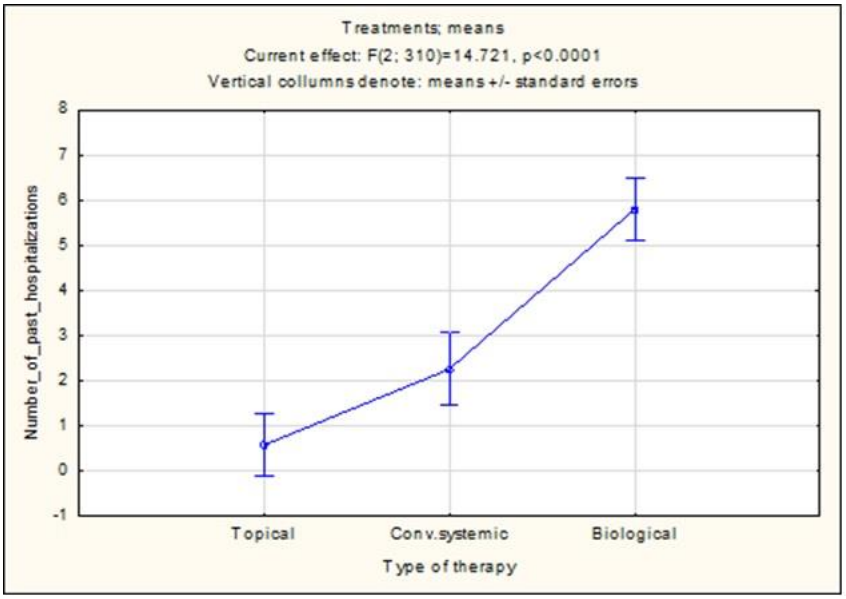

Fig. 12 Number of past hospitalizations ($p<0.001$)

Discussion

Biologic agents represent the latest step in the therapy of psoriasis (Nast et al. 2015), (Nast et al. 2017). Thus, we may assume that patients on topical therapy have a lower grade of disease severity than patients treated with systemic drugs, namely biologic agents. This is unquestionably supported by our patients' history – patients under biologic therapies have been more intensively treated in the past than those treated topically (table 14). We studied a variety of epidemiological parameters aiming for any possible links with psoriasis severity.

Tab. 14 History of past treatments

Specific factor	ANOVA	Chi-square test
Usage of topical tar	**p<0.001***	**p<0.001***
Usage of topical cignolin	**p<0.001***	**p<0.001***
Usage of topical vitamin D derivates	0.554	0.552
Usage of topical corticosteroids	0.439	0.437
Usage of topical alternative compounds	**p=0.005***	**p=0.005***
Number of focal phototherapy sessions	-	**p=0.005***
Number of systemic phototherapy sessions	-	**p=0.016**
Heliotherapy	**p<0.001***	**p<0.001***
Spas/Wells	**p<0.001***	**p<0.001***
Number of hospitalizations	-	**p=0.409**

To start with, we observed that older patients were clearly treated less aggressively than younger patients ($p<0.001$, fig. 1, table 4). Patients treated with topical therapy aged an average of 53 years old, those treated with conventional systemic agents and biologic agents aged an average 44.4 ± 70 and 45.4 ± 70 yearls old respectively. This is likely to be related with a certain tendency of excluding elderly patients from more aggressive forms of therapy,

as these are often described as a high-risk group for adverse events, namely infectious complications (Strangfeld et al. 2011). Furthermore, this group of patients often suffers from multiple comorbidities, are polymedicated, and therefore at higher risk of drug interactions (Phan et al. 2016). Despite this, Ricceri et al. concluded that age alone should not be limit therapeutic options (Grozdev et al. 2011), (Ricceri et al. 2019). In addition, we observed a linkage between gender and type of therapy. Women were treated topically more often than men, and that more men had a history of biologic therapy than women. Within the group treated with topical agents 58.5% of patients are women and 41.5% are men. Contrarily, only 35.7% of patients treated with biologics are women, while 64.3% are men (statistical results from group 1 and 3 significantly differed from group 2, $p<0.001$, fig. 2, table 5). Such results support Hägg´s and Colombo´s studies (Colombo et al. 2014). Hägg concluded that women enjoy lower PASI scores than men, hence men tend to be treated systemically more often than women (Hägg et al. 2017), (Hägg et al. 2013). Therapy adherence is associated with improvement of disease severity (C. L. Carroll et al. 2004), (Christie L. Carroll et al. 2004), (Steven R. Feldman et al. 2007), (Evers et al. 2010), (Lecha et al. 2005), (Lynde et al. 2012). Storm reported higher rates of therapy adherence among men (Storm et al. 2008), Zaghloul and Goodfield described women as the most compliant (Zaghloul and Goodfield 2004), Gokdemir could not establish any association between sex and therapy adherence (Gokdemir, Ari, and Köşlü 2008). Literature is not consensual, therefore we tend to conclude that men are indeed more severily affected by psoriasis than women.

Patients' height also differed according to therapy type (statistical results from group 1 significantly differed from group 2 and 3, $p<0.001$, fig. 3). Other related measures such as weight and BMI did not reveal statistically significant values ($p=0.190$ and $p=0.930$). To our knowledge, a relationship between height alone and psoriasis severity has never been hypothesized before, while direct associations between overweight and psoriasis have been widely presented (Hercogová et al. 2010), (Duarte and da Silva 2014), (Huang et al. 2010), (Sterry, Strober, and Menter 2007). Nonetheless, such results must be interpreted with caution, since more males were treated systemically in our research study (in the Czech Republic men are substantially taller than women: 181± cm vs 169± cm) (Grasgruber and Hrazdíra 2013).

Psoriasis severity also seems to be directly related to the age of onset of the disease. We observed that patients treated systemically, therefore more aggressively, had an earlier disease onset (statistical results from group 1 significantly differed from group 2 and 3, $p<0.001$, fig. 4). Averagely, patients treated topically had their first lesions appearing around the age of 35.1 years old, those treated with conventional systemic drugs at the age of 25.9± years old and, finally, patients on biologics at the age of 22.5± years old. Our results confirm those of Na and García-Diez (Na, Jo, and Youn 2013), (García-Diez et al. 2008).

In addition, we observed that patients treated with more aggressive forms of therapy are more likely to refer infections as a trigger of psoriasis. While only 18.6% of patients treated with topical agents invoked infections as a disease trigger factor, 30.1% of those treated with conventional systemic drugs and 32.1% of patients on biologic agents indicated infections as a trigger factor of their disease (statistical results from group 1 significantly differed from group 2 and 3, $p=0.047$, fig. 5, table 6). Concretely, a clear and statistically significant difference was observed between patients treated topically and systemically for "viral upper respiratory tract infections" (statistical results from group 1 significantly differed from group 2 and 3, $p=0.049$, fig. 6, table 7). In this case, 3.4% of those treated topically refered a viral upper respiratory tract infection as a trigger factor of psoriasis, while 10,8% of patients on conventional systemic agents and 11.6% of those treated with biologic agents described the same type of infection as a trigger factor of their skin disease. The fact that psoriasis can be triggered by upper respiratory tract infections is not new (Sbidian et al. 2019), (Weisenseel et al. 2002), (Raychaudhuri, Maverakis, and Raychaudhuri 2014), though, our study suggests a relationship between psoriasis severity and these trigger factors. We also verified a possible association between patients' therapy, and disease onset life stage, concretely periods of possible hormonal variations. While no patients on conventional systemic drugs and only 0.8% of patients on topical therapy invoked hormonal variations as a possible disease trigger factor, 4.5% of patients on biologic therapy referred worsening of their condition during these periods (this difference between group 3 and the remaining groups revealed to be statistically significant, $p=0.045$, fig. 7, table 8). Ceovic (Ceovic et al. 2013), Islam (Islam et al. 2011) and Murase (Murase et al. 2005) already wrote about how puberty,

premenstrual states and menopause can lead to psoriasis flare-ups in women. We found no studies suggesting periods of hormonal variations as an independent prognostic factor of the disease; our results suggest that patients in which psoriasis is triggered by periods of hormonal variations might suffer from a more severe form of the disease.

Tab. 15 Psoriasis trigger factors and type of therapy

Specific factor	**ANOVA**	**Chi-square test**
Pregnancy	p=0.051	p=0.051
Stress	p=0.267	p=0.265
New drugs	-	p=0.395
Onset of atopic eczema	-	-
Trauma	p=0.405	p=0.403
Any infection	**p=0.047***	**p=0.047***
Infections of the respiratory tract	**p=0.026***	**p=0.026***
Viral upper respiratory tract infections	**p=0.049***	**p=0.049***
Bacterial tonsillitis	p=0.411	p=0.409
Pneumonitis	p=0.527	p=0.524
Mycotic infections	p=0.439	p=0.437
Unknown infections	p=0.134	p=0.134
Hormonal changes	**p=0.045***	**p=0.045***
Exotic/irritant foods	p=0.226	p=0.224
Weather changes	p=0.469	p=0.466
Alcohol	p=0.397	p=0.394
Significant weight changes	p=0.251	p=0.249
Other factors	p=0.515	p=0.513

Psoriatic patients are at higher risk of suffering from anxiety and depression (Nelson et al. 2013), (Mattei, Corey, and Kimball 2013), (Tsai et al. 2011), (Wade et al. 2016), (M. A.

Gupta and Gupta 1998). Psoriasis severity also seems to be directly proportional to depression severity (M. Gupta et al. 1993). Our study supports such results: while only 5.1% of patients on topical therapy suffer from depression, 14.5% of those treated with conventional systemic drugs and 16.1% of patients treated with biologic agents are depressed (statistical results obtained from group 1 significantly differed from group 2 and 3, p=0.020, fig. 8, table 9). Besides, 2.5% of patients on topical therapy refered they are followed by a psychologist, while 8.4% of those on conventional systemic drugs and 13.4% of patients on biologic therapy revealed having psychotherapy (values obtained for group 1 and 3 statistically differ from group 2, p=0.010, fig. 11, table 13).

We noticed that patients treated systemically use statins more than those treated topically. Concretely, while only 11.9% of those treated with topical drugs use statins, 21.7% of patients on conventional systemic drugs and 24.1% of those treated with biologic agents use statins (statistical values revealed by group 1 were significantly different than group 2 and 3, p=0.044, fig. 10, table 11). The European Cardiology Society and European Atherosclerosis Society recommend maitaining a certain LDL-c (low-density lipoprotein cholesterol) based on the patient's CVD (Mach et al. 2020). Thus, we may conclude that patients on systemic agents do have a higher CVD because they use statins more than the group treated with topical drugs. This link has already been demonstrated (Chiriac, Podoleanu, and Azoicai 2017), (Abuabara et al. 2010), (Gelfand et al. 2007), (Gelfand et al. 2006).

Hyperuricemia was also found to be associated with more agressive psoriasis therapy. While only 1.7% of the patients on topical therapy had a history of high serum uric acid concentrations (SUAC), 7.2% patients on conventional systemic drugs and 9.8% of patients on biologics revealed suffering from hyperuricemia (statistical results from groups 1 and 3 significantly differed from group 2, p=0.031, fig. 9, table 10). Multiple authors have already described about how psoriasis is associated with hyperuricemia (Gisondi et al. 2014), (Alpsoy et al. 2014), (Zhou Z et al. 2013), (Zhang et al. 2012), (Ibrahim et al. 2012), (Isha, Jain, and Lal 2011), (Severin et al. 1999), (Merola et al. 2015), (Gui et al. 2018), however studies trying to establish linear correlations between SUAC and psoriasis severity have

reported inconsistent results. Gisondi and others have described a linear relationship between SUAC and PASI (Sterry, Strober, and Menter 2007), (Gisondi et al. 2014), (Gelfand et al. 2006), (Kwon et al. 2011), (Eisen and Seegmiller 1961), (Baumann and Jillson 1961), (Tickner and Mier 1960), (Sommer et al. 2006), (Neimann et al. 2006), (Murray et al. 2009), (Shiraishi and Une 2009), however a meta-analysis including 29416 patients have failed to show a direct association between SUAC and psoriasis severity (Li et al. 2016). Our results rather follow Gisondi's: it seems like the more severe psoriasis a patient suffers from, the highest his/her chance of having high SUAC – nevertheless, this topic remains controversial, further research is needed. A direct correlation between psoriasis severity and nonspecific noninfectious liver disease was also observed. Regarding possible infectious hepatopathies, only 1.7% of patients on topical therapy answered positively, no patients treated systemically revealed recent infectious hepatopathies, and these results were ultimately not statistically significant. Regarding nonspecific noninfectious liver diseases, results revealed a direct correlation between psoriasis severity and this group of hepatopaties: while no patients on topical therapy refered suffering from liver diseases, 3.6% of those on conventional systemic agents and 8.9% of patients treated with biologics invoked history of nonspecific noninfectious liver disease (statistical results from groups 1 and 3 significantly differed from group 2, p=0.005, table 12). Alcohol consumption and BMI did not statistically vary according to therapy type, however we cannot 100% exclude their presence in the past. Gisondi and Miele were already able to prove a link between psoriasis and nonalcoholic fatty liver disease independent of alcohol intake, obesity, and hepatotoxic medications (Gisondi et al. 2009), (Miele et al. 2009). Regarding psoriasis severity, Gisondi described a strong linear correlation between psoriasis severity and NAFLD (Gisondi et al. 2009), while Miele and Van der Voort rejected this hypothesis (Miele et al. 2009), (van der Voort et al. 2014). Most authors seem to agree that this link does exist (Yeung et al. 2013), (Madanagobalane and Anandan 2012), (Narayanasamy et al. 2016), (Barak et al. 2009), (Harada et al. 2009), (Ogdie et al. 2018). The fact that NAFLD and NASH are associated with an increased likelihood of developing CVD could help explaining why some of our patients suffer from a higher risk of CVD (Villanova et al. 2005).

Tab. 16 Suggested psoriasis prognostic factors

Male gender	Increased height	Early age of onset	Viral upper respiratory infections as a trigger factor	Hormonal changes as a trigger factor
p<0.001*	p<0.001*	p<0.001*	p=0.049*	p=0.045*

Tab. 17 Conditions associated with moderate-to-severe psoriasis

Depression	Increased cardiovascular risk	Hyperuricemia	Nonspecific noninfectious liver disease
p=0.020*	p=0.044*	p=0.031*	p=0.005*

We also faced several limitations. To start with, we acknowlegde that our study population is relatively small. Besides, the fact that 9 (3.1%) patients were treated with both conventional systemic agents and biologics concomitantly was not optimal; nevertheless, these patients represent a very small proportion of our study group, hence it is unlikely that this has affected our results. Another limitation was the fact that patiens were already being treated for some time when our study started: in this fashion, we cannot exclude that some of the diseases that we assumed being related to psoriasis severity were, in fact, adverse events of those same therapies (ex. liver disease due to methotrexate hepatoxicity). We also recognize that the ideal conditions were if psoriasis severity scores were followed in untreated patients; however, we also aknowlegde that such conditions are unrealistic because a patient with severe psoriasis eventually needs to be treated systemically.

Conclusion

We verified that psoriasis severity is directly related to an increased risk of cardiovascular disease, depression, hyperuricemia and nonspecific non-infectious liver disease. Moreover, male gender, increased height, early age of disease onset (till 25.9 years), and trigger factors such as puberty, menopause/andropause and viral upper respiratory infections seem to be prognostic of higher degrees of psoriasis severity. Although, some of the above-mentioned comorbidities and epidemiological characteristics have already been associated with psoriasis, it is the first time, to our knowledge, that increased height and puberty, menopause/andropause are considered independent prognostic factors of psoriasis severity. Our study proposes a series of prognostic factors and conditions that can help one estimating patient's clinical outcome. Long-term studies comparing the evolution of psoriasis severity scores in untreated patients are needed to confirm this theory.

Conflicts of Interest

Jana Hercogová has received honoraria as a speaker and/or consultant for AbbVie, Celgene, Eli Lilly, Frankl Pharma, Janssen, Leo Pharma, Novartis, Novartis Global, Sanofi Aventis and Sanofi Genzyme. Other co-authors (Emanuel Marques, Zoltán Paluch, Petr Boháč, Ondřej Slanař, Jaromír Běláček) declare no conflicts of interest.

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List of Abbreviations

*	Statistical significant p-values
ACE	Angiotensin converting enzyme
BMI	Body mass index
BSA	Body surface area
CVD	Cardiovascular risk of death
DM	Diabetis mellitus
HIV	Immunodefiency virus
N	Number of patients
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
NSAID	Nonsteroidal anti-inflammatory drugs
P	p-value (probability significance)

PASI	Psoriasis area severity index
SUAC	Serum uric acid concentrations
Syst.	Systemic

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CHAPTER 3

The safety profile of biologic agents in comparison with non-biologic systemic agents, and topical compounds in the management of psoriasis

Full-text of chapter 3 is published as an original study:

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Title: The safety profile of biologic agents in comparison with non-biologic systemic agents, and topical compounds in the management of psoriasis - a 30-month prospective, observational cohort study

Journal: International Journal of Clinical Practice

Abstract

Background: Although biologic agents are very effective, solid data proving they are safer than other therapies in psoriasis are still lacking.

Methods: A total of 289 psoriatic patients were followed for 30 months; of which number 118 were treated with topical agents alone, 112 received biologic agents, and the remaining 59 patients were on non-biologic systemic agents. The rates of adverse events in these groups were recorded and statistically analyzed.

Results: Patients treated with biologic agents had higher rates of adverse events ($p=0.017$), including overall infections ($p=0.003$), respiratory infections ($p<0.001$), renal, urinary ($p<0.001$), musculoskeletal, connective tissue ($p<0.001$, and $p=0.021$) and oral cavity-related ($p=0.046$) disorders. Except for the incidence of infections, all the above adverse events occurred more often in our study than in clinical trials. The occurrence of serious adverse events was $p=0.066$, with the incidence of serious infections being $p=0.164$. Unlike patients on topical therapy and non-biologic systemic agents, patients treated with biologic agents were forced to discontinue their therapies ($p=0.001$). The Psoriasis Area Severity Index (PASI) and Body Surface Area (BSA) scores were the lowest among patients on biologic agents.

Conclusion: While biologic agents were the most effective therapies, they were associated with higher rates of treatment discontinuation and adverse events in comparison with other forms of therapy.

Keywords

adverse events; biologic agents; drug safety; psoriasis; non-biologic systemic agents; psoriasis treatment

Introduction

Psoriasis is an immune-mediated skin disease with a prevalence of 1-3% in adults (Luigi Naldi 2004). Not only does it impair one's quality of life, it is tightly linked to several comorbidities (Smith and Barker 2006), (Parisi et al. 2013), (Feldman et al. 1997), (Hercogová et al. 2010). Until 2003, topical therapy, phototherapy and use of non-biologic systemic agents (NBSAs) were the only possible therapeutic options in psoriasis. With evolving knowledge of the immunopathogenesis of the disease process, a new and revolutionary form of therapy called biologic agents (BAs), otherwise known as biologics, has emerged (Hassan et al. 2013). These have proved to be the most effective therapies (Gisondi et al. 2008) (Piaserico et al. 2014) (Barker et al. 2011) (Saurat et al. 2008) (Au SC, Madani A, Alhaddad M, Alkofide M 2013) (Schmitt et al. 2008); however, consistent and solid data from long-term studies on the safety of these agents are still lacking when compared with the other forms of therapy. Unsurprisingly, with the implementation of longer follow-ups, reports of serious adverse events (SAEs) are slowly emerging (Schwab et al. 2012). It is therefore imperative to explore the safety profile of biologic agents.

The objective of our study was to compare the occurrence of AEs in three groups of psoriatic patients on different therapeutic regimens: topical therapy, non-biologic systemic drugs and biologic agents.

Materials and methods

We performed a prospective, observational cohort study with a total of 289 psoriatic patients followed for 30 months: 156 (54%) were men, 133 (46%) were women, their mean age was 48 (6–86) years and their mean BMI (body mass index) 28.3 (14.5–66.7) (Fig. 1). A total of 118 were treated with topical agents alone, 83 used non-biologic systemic drugs, and 122 received biologic agents (Table 1). Patients suffered from different forms of the disease: 227 (78.5%) patients had plaque psoriasis, 130 (45.0%) scalp, 112 (38.7%) nail, 23 (8.0%) palmoplantar, 9 (3.1%) inverse and 1 (0.3%) the guttate form of the disease.

During our study, some patients were forced to switch to other agents within their stratum/type of therapy, while others had to be switched to another type of therapy. The most common reasons for this included drug intolerance or loss of efficacy. Specifically, 24 (8.3%) of our patients used both non-biologic systemic drugs and BAs during the research period; of these, nine (3.1%) individuals used acitretin and methotrexate concomitantly with a BA, the remaining 15 (5.2%) were receiving only one systemic agent at a time. For this reason, patients were included in as many groups as many therapy(ies) they had, that is, if a patient was on a NBSA, but was later forced to initiate a BA, they were included in both groups (NSBA and BA). Patients using any form of therapy/agent for less than eight weeks were not included in our study. The only exclusion criterion was unwillingness to participate in the study. All patients were treated according to the recommendations of the Summary of Product Characteristics (SPC) of each drug.

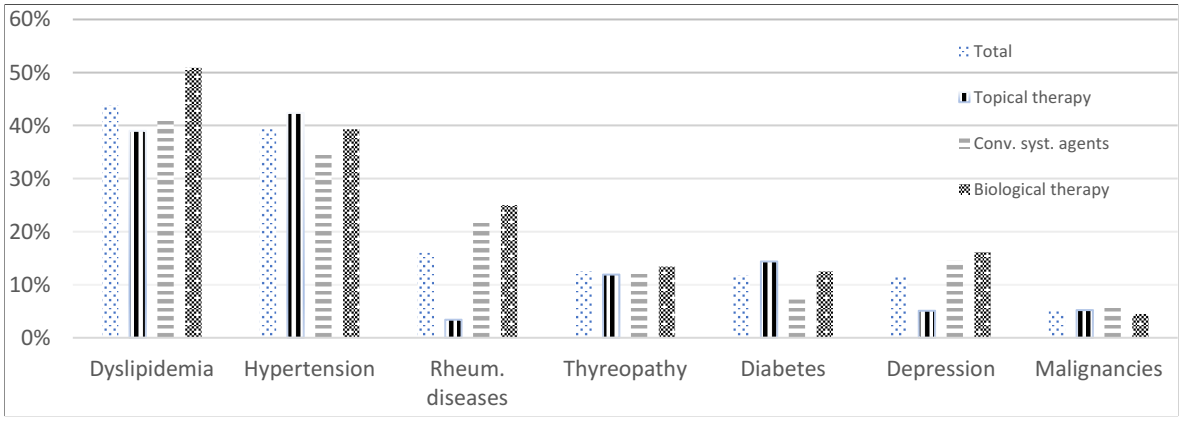

Fig.1 Population comorbidities - comparison of the prevalence of the most common comorbidities found among all treated groups (the three treated groups include patients on topical therapy, non-biologic systemic agents, and biologic agents)

Tab. 1 Study population therapies

†) off-label

Group of patients	Type of therapy	Class of drugs/ Specific agent	Number of patients
1	Topical therapy	Corticosteroids	118
		Keratolytics	
		Vitamin D derivatives	
		Tacrolimus/pimecrolimus†)	
		Coal tar and its derivates	
2	Non-biologic systemic agents	Acitretin	34
		Cyclosporine	13
		Methotrexate	51
3	Biologic agents	Infliximab	11
		Secukinumab	17
		Etanercept	21
		Ustekinumab	33
		Adalimumab	41
Total			289

Once our study started, all patients were requested to attend regular follow-up visits every three months. During these visits, detailed records of each patient's status, disease progression, and possible AEs were obtained. Complete physical examinations were performed, and BSA (body surface area) plus PASI (Psoriasis Area Severity Index) scores recorded at each visit. Furthermore, five ml of urine (U) and 12 ml of serum (S) and plasma (P) were collected for basic laboratory tests. Patients treated with a BA were also tested for auto-antibodies and Quanti-FERON-TB Gold, followed by annual lung function tests.

We used Edwards‘ definition of AEs (Edwards and Aronson 2000) and European Medicines Agency’s (EMA) definition of serious AEs (“No Title,” n.d.). Serious infections were defined as all serious AEs classified as “infections and infestations” according to the System Organ Class of the Medical Dictionary for Regulatory Activities (version 16.0) (SAS 2013). Based on this system (SAS 2013), we grouped the AEs according to the affected system with two minor adaptations. The first one consisted of all corresponding infections and infestations to each affected system, with the exception of dermatological, respiratory and urinary infections. The second one was the creation of a separate category for all oral cavity-related disorders. For systemic antibiotics (ATBs) that patients failed to identify, a separate category designated as “unknown antibiotics” was created.

As some patients used more than one type of therapy during our study period, all AEs and lab results corresponding to each six-month interval were carefully paired with the type of therapy used during the very same time interval. Results were then statistically processed using standard ANOVA with one fixed factor (type of therapy) and one repeated factor (six-month interval). Fischer’s least significant difference (LSD) post-hoc tests were then applied to all statistically significant results. Lastly, chi-squared tests were performed for all parameters to check whether there was a statistically significant difference between the expected versus observed frequencies.

This study was approved by the Ethics Committee of Charles University, Second Faculty of Medicine in Prague, and patients were recruited into the study after informed written consent had been obtained.

Results

During the 30 months of follow-up, AEs were reported in 116 cases in patients receiving topical agents, 121 cases in patients treated with NBSAs and in 260 cases in patients on BAs. We observed a higher occurrence of all AEs combined in the group treated with biologic agents (BAs) compared with patients using topical agents (p=0.017) (Figs. 2 and 3, Table 2). No significant difference was observed between the groups treated with topical versus non-biologic systemic agents but, also, between patients receiving non-biologic systemic versus biologic therapy.

Patients on BAs were more likely to develop more non-infectious renal and urinary disorders, whereas no cases of AEs suggestive of non-infectious renal and urinary disorders occurred in those treated with topical agents and/or NBSAs (p<0.001) (Table 2). Higher incidence rates of non-infectious renal and urinary disorders were reported in BA-treated patients, with the numbers being four (4.1%) patients (p=0.032) after 1.5 years of therapy, and five (5.2%) patients at two years of therapy (p=0.013) (Table 2).

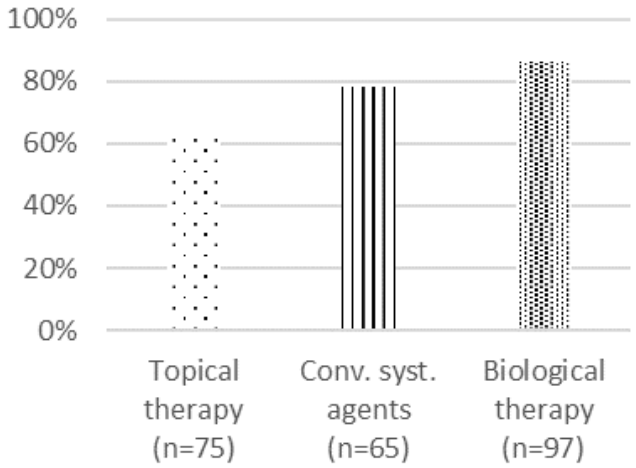

Fig. 2 Overall rates of adverse events throughout the study (p=0.017) - comparison of the overall incidence of adverse events between all treated groups (p=0.017) (the three treated groups include patients on topical therapy, non-biologic systemic agents, and biologic agents)

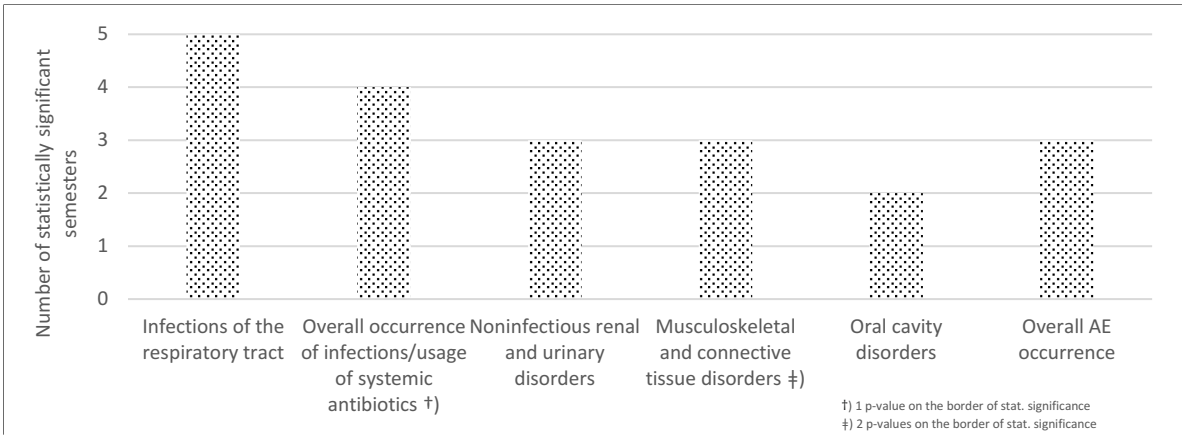

Fig. 3 Biologic agents' most frequent adverse events - comparison of the most frequent types of adverse events experienced by patients treated with biologic agents throughout our study (the y-axis represents time and is divided into five 6-month-periods)

Adverse events related to musculoskeletal and connective tissue disorders in the first six months (after study initiation) were reported in 15 (16.5%) psoriasis patients treated with BAs, in four (8.9%) on non-biologic systemic therapy, and in none receiving topical therapy. At one year of follow-up, AEs were documented in ten (10.3%), four (9.5%) and two (1.7%) patients receiving BAs, NBSAs, and topical agents, respectively. Compared with patients on topical agents, AEs in patients on BAs and NBSAs at six months ($p<0.001$) and one year of treatment ($p=0.021$) occurred more often in BA-treated patients (Table 2).

Patients on BAs also experienced more oral cavity-related AEs than the remaining groups. Over the 30 months of follow-up, patients receiving BAs had more oral cavity-related events in the first ($p=0.035$) and second years ($p=0.032$); four patients (4.1%) compared with none in the other groups (Table 2).

Higher rates of respiratory tract infections among patients treated with BAs were also noted throughout the study ($p<0.001$), (Fig. 4; Table 2). On average, 3.9% of patients on topical therapy were diagnosed to have a respiratory tract infection, while the respective figures in those on NBSAs and BAs were 20.3% and 25.1%, with 93.3% of the infections involving

the upper respiratory tract. Whilst, after one year of therapy, occurrence of these infections differed significantly between all treated groups, the rates of topically and BA-treated patients differed significantly from those treated with non-biologic systemic agents in the remaining six-month periods.

Tab. 2 Occurrence of AEs arranged by system organ class

System organ classes and other parameters	Therapy	6-month periods										Average (all 6-month periods)
		1		2		3		4		5		
		n (%)	χ^2; ANOVA	n (%)	χ^2; ANOVA	n (%)	χ^2; ANOVA	n (%)	χ^2; ANOVA	n (%)	χ^2; ANOVA	ANOVA
Respiratory, thoracic and mediastinal disorders	TT	5 (4.2%)	**0.001*; 0.001***	4 (3.4%)	**<0.001*; <0.001***	2 (1.7%)	**<0.001*; <0.001***	11 (9.3%)	**<0.001*; <0.001***	4 (3.4%)	**<0.001*; <0.001***	**<0.001***
	NBSA	10 (22.2%)		12 (28.6%)		9 (19.1%)		14 (29.8%)		8 (14.8%)		
	BA	16 (17.6%)		28 (28.9%)		25 (25.8%)		32 (33.0%)		30 (28.6%)		
Skin and subcutaneous tissue disorders	TT	6 (5.1%)	0.085; 0.085	13 (11.0%)	0.589; 0.592	10 (8.5%)	0.076; 0.076	20 (16.9%)	0.745; 0.747	8 (6.8%)	**0.015*; 0.015***	**0.038***
	NBSA	7 (15.6%)		7 (16.7%)		10 (21.3%)		8 (17.0%)		12 (22.2%)		
	BA	7 (7.7%)		14 (14.4%)		14 (14.4%)		13 (13.4%)		15 (14.3%)		
Non-infectious renal and urinary disorders	TT	2 (1.7%)	0.667; 0.670	0 (0.0%)	0.170; 0.171	0 (0.0%)	**0.032*; 0.031***	0 (0.0%)	**0.013*; 0.013***	1 (0.8%)	0.278; 0.280	**<0.001***
	NBSA	0 (0.0%)		1 (2.4%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		
	BA	1 (1.1%)		3 (3.1%)		4 (4.1%)		5 (5.2%)		3 (2.9%)		
Oral cavity-related disorders	TT	0 (0.0%)	0.327; 0.330	0 (0.0%)	**0.035*; 0.035***	1 (0.8%)	0.542; 0.545	0 (0.0%)	**0.032*; 0.031***	1 (0.8%)	0.773; 0.775	**0.046***
	NBSA	1 (2.2%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		1 (1.9%)		
	BA	1 (1.1%)		4 (4.1%)		0 (0.0%)		4 (4.1%)		2 (1.9%)		
Hepatobiliary disorders	TT	0 (0.0%)	0.327; 0.330	0 (0.0%)	**0.045*; 0.045***	0 (0.0%)	0.426; 0.429	0 (0.0%)	0.088; 0.089	1 (0.8%)	0.509; 0.511	**0.002***
	NBSA	1 (2.2%)		1 (2.4%)		0 (0.0%)		1 (2.1%)		0 (0.0%)		
	BA	1 (1.1%)		5 (5.2%)		1 (1.0%)		4 (4.1%)		0 (0.0%)		
Gastrointestinal disorders	TT	0 (0.0%)	**0.010*; 0.010***	1 (0.8%)	0.287; 0.289	0 (0.0%)	**0.032*; 0.031***	0 (0.0%)	**0.014*; 0.014***	1 (0.8%)	**0.001*; <0.001***	**0.002***
	NBSA	4 (8.9%)		2 (4.8%)		0 (0.0%)		2 (4.3%)		8 (14.8%)		
	BA	4 (4.4%)		2 (2.1%)		4 (4.1%)		7 (7.2%)		5 (4.8%)		
Musculoskeletal and connective tissue disorders	TT	0 (0.0%)	**<0.001*; <0.001***	2 (1.7%)	**0.021*; 0.021***	5 (4.2%)	0.054; 0.054	9 (7.6%)	0.977; 0.977	11 (9.3%)	0.759; 0.761	**0.002***
	NBSA	4 (8.9%)		4 (9.5%)		5 (10.6%)		4 (8.5%)		6 (11.1%)		
	BA	15 (16.5%)		10 (10.3%)		13 (13.4%)		8 (8.2%)		8 (7.6%)		
Infections and infestations	TT	4 (9.8%)	0.344; 0.199	6 (13.3%)	0.067; **0.006***	2 (3.9%)	0.056; 0.120	23 (23.0%)	0.095; **0.026***	11 (12.6%)	**0.001*; <0.001***	**0.010***
	NBSA	11 (26.2%)		12 (31.6%)		10 (22.2%)		17 (37.8%)		14 (26.4%)		

	B A	15 (16.7%)		24 (25.0%)		25 (26.0%)		26 (26.8%)		25 (24.0%)		
Infections (respiratory)	TT	3 (2.5%)	**0.005*; 0.005***	4 (3.4%)	**<0.001* ; <0.001***	1 (0.8%)	**<0.001* ; <0.001***	11 (9.3%)	**<0.001* ; <0.001***	4 (3.4%)	**<0.001*; <0.001***	**<0.001***
	N BS A	6 (13.3%)		12 (28.6%)		8 (17.0%)		13 (27.7%)		8 (14.8%)		
	B A	13 (14.3%)		28 (28.9%)		22 (22.7%)		32 (33%)		28 (26.7%)		
Use of syst. antibiotics	TT	2 (4.9%)	0.517; 0.419	4 (8.9%)	0.611; 0.193	1 (2.0%)	0.283; 0.053	3 (3.1%)	**0.031*; 0.011***	2 (2.3%)	**0.002*; 0.002***	**0.003***
	N BS A	5 (11.9%)		3 (7.9%)		2 (4.4%)		4 (8.9%)		4 (7.7%)		
	B A	9 (10.0%)		14 (14.6%)		11 (11.5%)		12 (12.4%)		18 (17.3%)		
Overall occurrence of AEs	TT	13 (31.0%)	0.123 ; 0.125	19 (42.2%)	0.131; 0.132	15 (29.4%)	**0.038*; 0.038***	40 (40.4%)	**0.003*; 0.003***	29 (33.0%)	**0.017*; 0.016***	**0.017***
	N BS A	22 (52.4%)		24 (63.2%)		23 (52.3%)		27 (60.0%)		25 (47.2%)		
	B A	41 (45.6%)		55 (56.7%)		47 (49.0%)		62 (63.9%)		55 (53.4%)		

Note. n = absolute number of patients; TT = topical therapy; NBSA = non-biologic systemic agent; BA = biologic agent

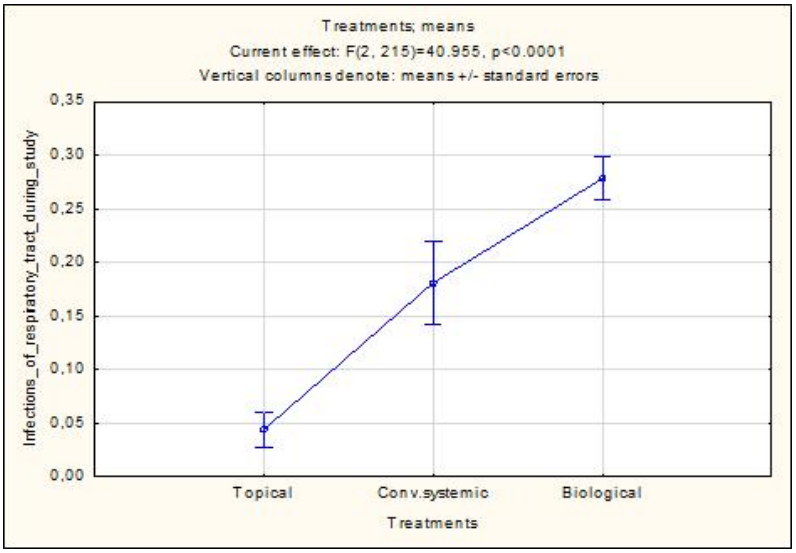

Fig. 4 Overall rates of respiratory tract infections (p<0.001) - comparison of the overall incidence of respiratory tract infections between all treated groups during our study (p<0.001) (the three treated groups include patients on topical therapy, non-biologic systemic agents, and biologic agents)

Besides, patients treated with BAs used, and required treatment with systemic antibiotics more often than the other two groups (Table 2). By the end of our study, 18 (17.3%) BA-treated patients were taking at least one antibiotic and three (3.1%) patients were on dual antibiotic therapy, whereas only four (7.7%) patients were receiving NBSA and two (2.3%) topical agents concomitantly with one systemic antibiotic (p=0.020) (Table 2). Similar differences were also noted after the two-year period (p=0.011 [ANOVA]; p=0.031 [chi-squared tests]), hence p=0.003 (ANOVA) was obtained for the overall usage of systemic antibiotics (Fig. 5) (Table 2).

We report 8 cases (7.2%) of patients on BAs who were forced to discontinue, either temporarily or permanently, their treatment due to AEs, with some of the latter classified as serious AEs (Table 4). When compared with patients on BAs, no patients treated topically or with NBSAs discontinued their treatment (p=0.001). Throughout the study, three patients on BAs developed a serious AE (two malignancies and one case of systemic lupus erythematosus) (p=0.066) (Table 4). The rates of malignancies in our study were p=0.164. The incidence of serious infections between the three groups was p=0.164. No deaths occurred during follow-up.

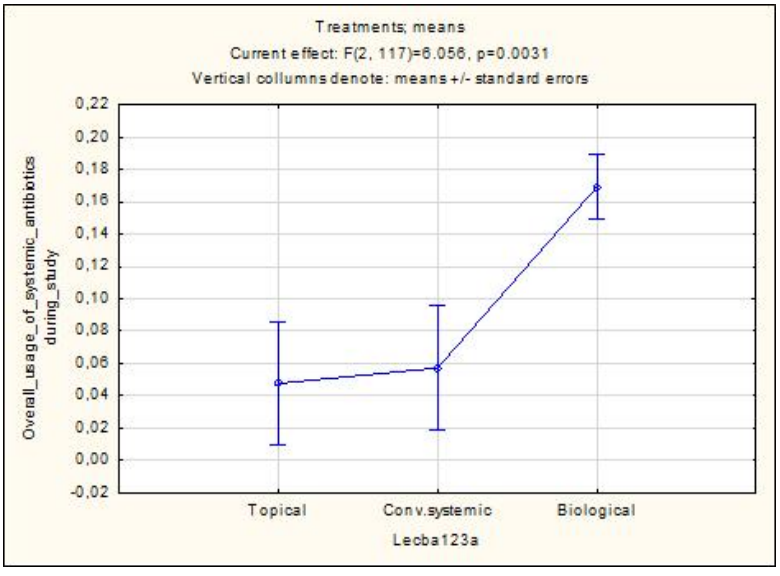

Fig. 5 Overall usage of systemic antibiotics (p=0.003) - comparison of the overall usage of systemic antibiotics between all treated groups during our study (p=0.003) (the three treated groups include patients on topical therapy, non-biologic systemic agents, and biologic agents)

Despite the various above AEs, BAs seem to be the most effective form of therapy. Compared with patients treated with NBSAs and/or topical agents, individuals on BAs were the closest to disease remission for 60% of the time of our study – PASI scores (p=0.001), (Fig. 6); BSA (p<0.001), (Fig. 7), (Table 3).

Tab. 3 PASI and BSA scores throughout the study

Type of score	Type of treatment	6-month periods										Average (all 6-month periods)
		1		2		3		4		5		
		Score	ANOVA	Score	ANOVA	Score	ANOVA	Score	ANOVA	Score	ANOVA	ANOVA
PASI	TT	3.7	**0.002***	2.4	0.899	2.8	**0.003***	4.8	**<0.001***	3.6	0.441	0.385
	NBSA	8.2		2.9		4.8		4.6		3.9		
	BA	2.8		3.0		1.8		1.8		2.8		
BSA	TT	5.5	**0.003***	3.4	0.755	3.5	**<0.001***	6.0	**<0.001***	4.1	0.607	0.114
	NBSA	12		4.5		6.7		5.3		4.3		
	BA	4.8		4.6		2.3		2.2		3.3		

Note. TT = topical therapy; NBSA = non-biologic systemic agent; BA = biologic agent; PASI = Psoriasis Area Severity Index; BSA = Body Surface Area

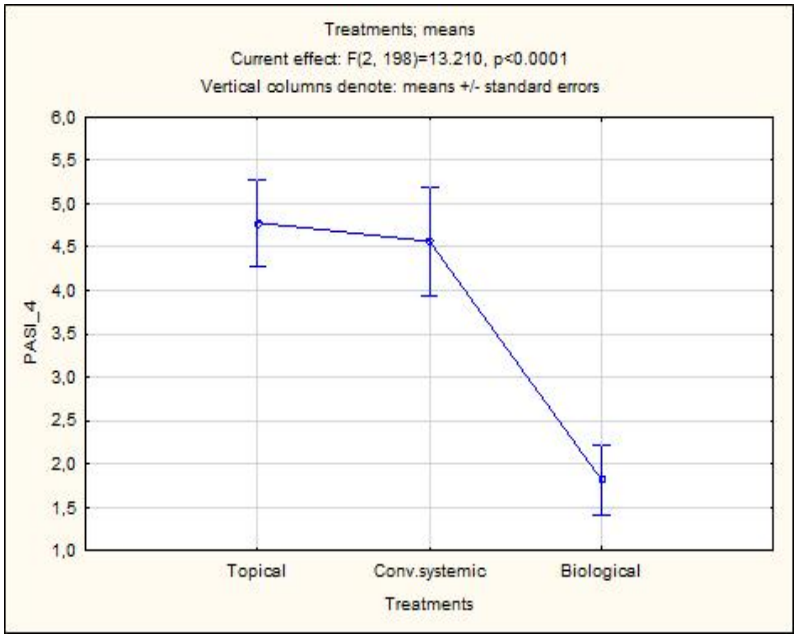

Fig. 6 PASI scores (fourth 6-month period) ($p<0.001$) - comparison of the average PASI score among patients in each treated group in the fourth 6-month period of our study ($p<0.001$) (the three treated groups include patients on topical therapy, non-biologic systemic agents, and biologic agents)

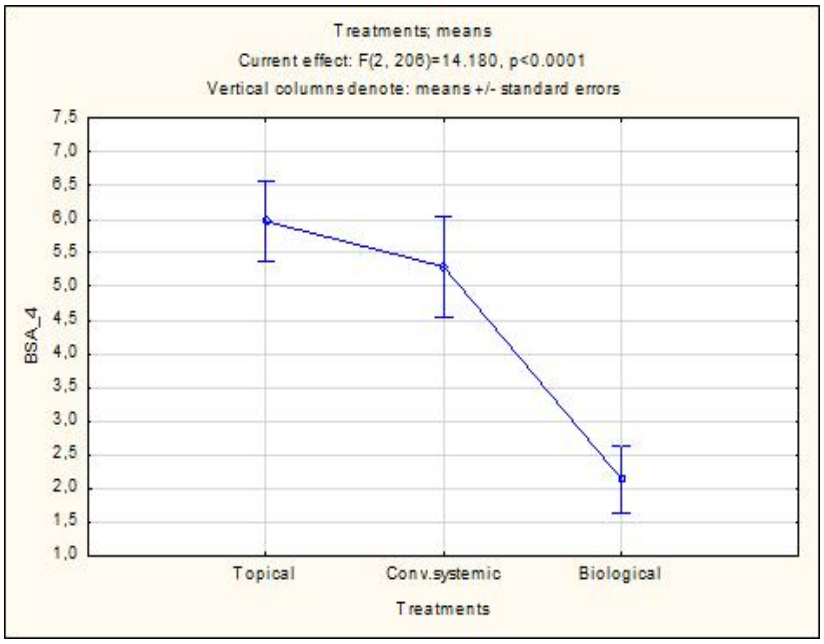

Fig. 7 BSA scores (fourth 6-month period) ($p<0.001$) - comparison of the average BSA score among patients in each treated group in the fourth 6-month period of our study ($p<0.001$) (the three treated groups include patients on topical therapy, non-biologic systemic agents, and biologic agents)

Tab. 4 Discontinuation of biologic agents

		Adalimumab	Etanercept	Infliximab	Ustekinumab	Secukinumab
Pregnancy		0	1 pause	0	0	0
Infections	Erysipelas	1 pause	0	0	0	0
	Urinary tract infection		1 pause			
Malignancy (breast cancer)		1 end	0	0	1 end	0
Positive QNF-TB Gold		1 end	0	0	0	0
Surgery (total knee replacement)		1 pause	0	0	0	0
Autoimmune diseases (SLE)		1 pause	0	0	0	0
Total		5 (4.5%)	2 (1.8%)	0	1 (0.9%)	0

Note. Percentages are based on the total number of patients treated with biologic agents; QNF-TB = QuantiFERON-TB (tuberculosis); SLE = systemic lupus erythematosus

No significant differences in the incidence rates of cardiovascular, eye, endocrine, psychiatric, nervous system, blood and lymphatic system, ear and labyrinth, metabolic and nutrition, reproductive system and breast disorders, benign and malignant cancers, sexually transmitted diseases, use of topical antibiotics and hospitalizations were seen between the three groups during follow-up.

Discussion

The incidence rates of all AEs combined were higher for patients who received BAs than for other patients throughout the 2.5-year study period. Only few studies have directly compared the former with NBSAs. The vast majority of these studies either put BAs at the same level of safety or even labeled them as the safer alternative (Garber C, Plotnikova N, Au SC, Sorensen EP 2015), (K. Reich et al. 2015), (Carretero et al. 2015), (Medina et al. 2015), (Montes-Torres et al. 2019), (Kristian Reich et al. 2010), as confirmed by a meta-analysis of randomized controlled trials (Schmitt et al. 2008) We did not find any studies similar to ours demonstrating an overall higher incidence of AEs among patients treated with a BA than with NBSAs. Our research also suggests no incidence of delayed AEs: although there was a significant increase in the occurrence of AEs after 1.5 years (49.0%) and two years (63.9%) of therapy, we did notice a decrease of AEs after 2.5 years (53.4%).

Patients treated with BAs developed non-infectious renal and urinary disorders. While urinary tract infections were the most common AEs, our results were not statistically significant throughout the study. Other fairly frequent AEs included dysmenorrhea/amenorrhea and prostate hypertrophy. Taking into consideration all five six-month periods together, the overall occurrence of these AEs was 3.3%, outcomes comparable with those reported in clinical trials with infliximab and adalimumab, where renal and urinary disorders were classified as common AEs (incidence ≥1% to <10%) (“Summary of Product Information - Humira (Adalimumab),” n.d.), (“Summary of Product Information - Remicade (Infliximab),” n.d.). The SPCs of the remaining BAs do not give the occurrence of these AEs (“Summary of Product Information - Enbrel (Etanercept),” n.d.), (“Summary of Product Information - Stelara (Ustekinumab),” n.d.), (“Summary of Product Information - Consentyx (Secukinumab),” n.d.).

Musculoskeletal and connective tissue disorders seem to occur more often among patients treated with BAs. While, in the first year of our study, an average 0.85% of those treated with topical agents developed musculoskeletal and connective tissue disorders, these AEs were reported in 9.2% and 13.4% of patients treated with NBSAs and BAs, respectively. It

is not quite clear why these AEs were only experienced in the early period of our study, but BAs have been suggested to neutralize nociceptive joint pain even before starting to exert their anti-inflammatory effect (Hess et al. 2011). The most common AEs included general arthralgia, enthesopathy and new-onset osteoarthritis (involving mostly the spine). With an overall occurrence of 11.2% in the group on BAs during our study period, our results are comparable with those obtained in clinical trials with adalimumab, but substantially superior to those reported for other BAs ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)," n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.).

Also, oral cavity-related AEs seem to affect particularly psoriatics treated with BAs more frequently than patients receiving other therapies. The most common AEs included dry mouth and gingivitis. We investigated whether these AEs were not related to a recent switch from a NBSA to a BA (acitretin causes such an AE ("Summary of Product Information - Neotigason (Acitretine)," n.d.)): however, we excluded this hypothesis since all patients experiencing these AEs had been on a BA for many years prior to enrolment into our study; we are unable to establish whether these AEs were of infectious or non-infectious etiology. We are also unaware of any other studies explicitly comparing this type of AEs. The overall incidence of oral cavity-related disorders in our BA-treated patients was 2.2%, and the SPCs of all tested BAs do not list any AEs ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)," n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.).

Patients on BAs had higher rates of respiratory tract infections than the other groups throughout the study. Our results are consistent with those obtained in other clinical trials ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information - Enbrel

(Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)," n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.). The body of clinical data comparing the AEs experienced during therapy with biologic agents versus other types of therapy in psoriasis patients is small. Besides Yan, who found no significant differences in the incidence of these AEs (Yan et al. 2011), we are unaware of any other comparisons of BAs and NBSAs.

The last year of our study period was marked by more frequent usage of systemic antibiotics by the group treated with BAs. We may conclude with a relatively high level of confidence that the BA-treated group had overall higher rates of infections than the remaining groups throughout the study. Generally, the SPCs of BAs label infections and infestations as a more common AE compared with the other types of therapy ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)," n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.), ("Summary of Product Information - Neotigason (Acitretine)," n.d.), ("Summary of Product Information - Sandimmun (Ciclosporin)," n.d.), ("Summary of Product Information – Jylamvo (Methotrexate)," n.d.). In similar studies comparing the infection rates between BAs and NBSAs, Piaserico reported data identical to ours (Piaserico et al. 2014), whereas Garber failed to obtain significant results (Garber et al. 2015).

Although statistically significant results were found for the rates of gastrointestinal AEs, we cannot draw any conclusions based on our data, since NBSAs were the class of drugs associated with the highest rates of AEs at one year whereas, in the last year of the study, most AEs occurred in BA-treated patients.

A total of 7.2% of patients on BAs discontinued their treatment due to adverse events. During our study, we identified a total of five patients presenting with positive QNF-TB tests: three were on a BA (two on adalimumab, one on infliximab), and two were using a NBSA (cyclosporine). Similar to other studies (Gómez-Reino et al. 2003), we did not classify these patients as tuberculosis (TB) cases, since they did not present the typical clinical picture.

Nevertheless, both TNF-α inhibitors and cyclosporine have been commonly associated with mycobacterial infections (Fonseca et al. 2006), (Brassard, Kezouh, and Suissa 2006), (Wallis et al. 2004), (Wallis et al. 2004), (Askling et al. 2005), (Dixon et al. 2006), (Tubach et al. 2009), (Winthrop et al. 2013), (John et al. 1994). Regarding malignancies, our results are consistent with those of a systematic review (Dommasch et al. 2011), three placebo-controlled studies (Leonardi et al. 2008), (Papp et al. 2008), (Igarashi et al. 2012), and a study by Gottlieb (Gottlieb et al. 2014). TNF-α inhibitors have been associated with autoimmune disordes (Pirowska et al. 2015), but, apart from a single case of systemic lupus erythematosus (SLE), no other patients in our study developed clinical pictures or presented laboratory results consistent with this type of diagnosis. Lastly, except for ustekinumab (Leonardi et al. 2008), (Papp et al. 2008), and secukinumab (Thaçi et al. 2015), BAs (specifically TNF-α inhibitors) have been reported to be associated with serious AEs as compared with non-biologic agents (Garcia-Doval et al. 2012), (Barker et al. 2011), (Kimball et al. 2015), (Kalb et al. 2015), (Galloway et al. 2011), in our study, serious AE were of borderline statistical significance.

Nevertheless, BAs seem to be currently the most effective class of drugs: lower PASI scores and BSA values were obtained during 60% of our study period. Despite the slightly higher baseline PASI and BSA scores for NBSAs (average baseline PASI score: 8.2 vs 2.8; average baseline BSA score: 12.0 vs 4.8), statistically significant results were also obtained throughout the study. The relevant literature is again scarce in such comparative studies: Zweegers reported a few studies in a systematic review (Zweegers et al. 2016).

Our study has several limitations:

1. The study period was not long, and our patient sample was relatively small – facts that can theoretically limit the detection rates of delayed and/or rare AEs. Nevertheless, most of our patients were already being treated for some time at the time of their enrolment, which can considerably compensate for this limitation;
2. The fact that nine (3.1%) patients were treated concomitantly with both a NBSA and a BA was not optimal. However, it is quite unlikely that such a small proportion of our study group may have biased our results;

3. We did not consider dose-dependent AEs; NBSAs are toxic when given at higher doses ("Summary of Product Information - Sandimmun (Ciclosporin)," n.d.), ("Summary of Product Information – Jylamvo (Methotrexate)," n.d.), (L. Naldi and Griffiths 2005), (Ho 2004), (Pathirana et al. 2009), (Bissonnette, Ho, and Langley 2009).
4. The group of patients on NBSAs included substantially fewer patients than groups treated with topical therapy or BAs, which may have resulted in wider confidence intervals.

It is unlikely that information bias has influenced our results since all records were completed in the presence of the same doctor.

Conclusion

In our study, BAs were associated with the lowest safety profile when compared with the other forms of treatment. Patients treated with BAs showed higher overall rates of AEs, overall rates of infections, respiratory tract infections, renal, urinary, musculoskeletal, connective tissue, oral cavity-related disorders, and treatment discontinuation. With the exception of infections, all the above biologic agent-related AEs occurred more often in our study than in clinical trials. While the rates of serious AEs were of borderline statistical significance, those of serious infections were not statistically significant.

Still, biologic agents were the most effective form of therapy when compared with topical agents and non-biologic systemic agents.

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Author contributions

All authors had full access to all of the data of the study and take responsibility for the integrity of the data and accuracy of data analysis. All authors contributed equally to the study concept and design, data acquisition, analysis and interpretation, drafting and critical revision of the manuscript, statistical analysis and study supervision.

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Conflicts of interest

Jana Hercogová has received honoraria as a speaker and/or consultant for AbbVie, Celgene, Eli Lilly, Frankl Pharma, Janssen, Leo Pharma, Novartis, Novartis Global, Sanofi Aventis and Sanofi Genzyme. The other co-authors (Emanuel Marques, Zoltán Paluch, Petr Boháč, Ondřej Slanař, Jaromír Běláček) declare no conflicts of interest.

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CHAPTER 4

The safety profiles of adalimumab, infliximab, etanercept, secukinumab and ustekinumab in psoriasis

Full-text of chapter 4 has been submitted as an original study:

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Title: Adverse events of adalimumab, infliximab, etanercept, secukinumab and ustekinumab in psoriasis

Journal: Journal of Cutaneous Medicine and Surgery

Abstract

Background: Although biologic agents are very effective, long-term comparative studies assessing their safety are lacking.

Objectives: To compare and evaluate any potential differences in the occurrence of adverse events in individual groups of psoriatic patients treated with different biologic agents.

Methods: A total of 124 psoriatic patients were followed up for 30 months; 74 received anti-TNF-alpha inhibitors (adalimumab, etanercept, infliximab), 33 were on ustekinumab, and 17 were treated with secukinumab. The rates of adverse events in these groups were recorded and statistically analyzed.

Results: Infliximab-treated patients showed a high occurrence of asymptomatic, yet increased liver enzymes, fatigue, and respiratory as well as skin infections. Adalimumab-treated patients were more often affected by musculoskeletal disorders and infections of all types. Patients treated with secukinumab presented with higher rates of cardiovascular disorders as well as respiratory and skin infections. The group receiving etanercept was diagnosed more often to have musculoskeletal and reproductive (specifically menstrual) disorders. The rates of therapy discontinuation and serious adverse events did not reach statistically significant values.

Conclusion: A higher incidence of adverse events was observed among adalimumab- and infliximab-treated patients, with ustekinumab found to have the safest profile. Our results demonstrate that a personalized approach, including evaluation of a patient's risk profile, is necessary before commencing a biologic. Further research is warranted to confirm the findings of our study.

Keywords

psoriasis; biologic agents; safety of biologic agents; adverse events caused by biologic agents

Introduction

Psoriasis is a chronic inflammatory skin disease with a prevalence of 1–3% among adults (Hassan et al. 2013). Its pathogenesis is based on T-cell dysregulation. Biologic agents (BAs) opened a new era in terms of pharmacotherapy: with an outstanding effect on symptom control and prognosis of the disease, they have fundamentally changed the treatment of psoriasis (Hassan et al. 2013; Smith et al. 2020).

Biologic agents have been shown to have remarkable short and long-term clinical effects. Currently, TNF-alpha inhibitors and interleukins IL-12, IL-17, and IL-23 (etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, risankizumab, certolizumab pegol) are available for the treatment of psoriasis. Despite their beneficial actions (Piaserico et al. 2014; Barker et al. 2011; Au et al. 2013; Schmitt et al. 2008), adverse events (AEs) such as infections, and malignancies, or immune-mediated complications may occur. These molecules and their properties differ, hence they can cause different AEs (Schwab et al. 2012; Sbidian et al. 2017).

The aim of this study was to compare and evaluate any potential differences in the occurrence of AEs in individual groups of psoriatic patients treated with different BAs.

Materials and methods

This is a substudy of a 30-month observational cohort prospective study including a total of 289 patients with psoriasis vulgaris and designed to compare the incidence of AEs in a group of patients (n=124) treated with 5 different BAs (etanercept, adalimumab, infliximab, ustekinumab, secukinumab) (Tables 1 and 2).

The only two pre-defined exclusion criteria were (1) unwillingness to participate and (2) therapy with any of the 5 BAs for less than 8 weeks while strictly adhering to the information about the respective BA's Summary of Product Characteristics (SPC). Upon therapy initiation, all study participants were asked to attend regular follow-up visits at a 2–3-month interval to check their health status, disease activity, and drug AEs should there be any.

Table 1 Study population characteristics

	Adalimumab	Etanercept	Infliximab	Secukinumab	Ustekinumab	Total
Number of patients, n (%)	41 (33.1%)	22 (17.7%)	11 (8.9%)	17 (13.7%)	33 (26.6%)	124 (100.0 %)
Men, n (%)	24 (58.5%)	15 (68.2%)	10 (90.9%)	9 (52.9%)	19 (57.6%)	77 (62.1%)
Women, n (%)	17 (41.5%)	7 (31.8%)	1 (9.1%)	8 (47.1%)	14 (42.4%)	47 (37.9%)
Smokers, n (%)	8 (19.5%)	6 (27.3%)	8 (72.7%)	6 (35.3%)	15 (45.5%)	43 (34.7%)
Age, years (mean)	43.0 ± 17.8	47.9 ± 17.3	46.6 ± 8.9	44.3 ± 15.8	44.8 ± 14.2	-
BMI, kg/m^2 (mean)	27.6 ± 6.0	29.0 ± 5.78	27.2 ± 4.5	29.8 ± 7.2	27.7 ± 5.9	-

BMI=Body Mass Index; n=number of patients

Table 2 Characteristics of study population with regard to their comorbidities

	Adalimumab n=41 (100%)	Etanercept n=22 (100%)	Infliximab n=11 (100%)	Secukinumab n=17 (100%)	Ustekinumab n=33 (100%)
Hypertension	13 (31.7%)	13 (59.1%)	2 (18.2%)	7 (41.2%)	13 (39.4%)
Dyslipidaemia	19 (46.3%)	13 (59.1%)	5 (45.5%)	7 (41.2%)	16 (48.5%)
Depression	5 (12.2%)	3 (13.6%)	3 (27.3%)	2 (11.8%)	7 (21.2%)
Hyperuricemia	4 (9.8%)	3 (13.6%)	1 (9.1%)	2 (11.8%)	2 (6.1%)
Diabetes mellitus	7 (17.1%)	0 (0.0%)	1 (9.1%)	3 (17.6%)	4 (12.1%)
Rheumatologic diseases	13 (31.7%)	3 (13.6%)	5 (45.5%)	7 (41.2%)	4 (12.1%)
History of skin diseases	5 (12.2%)	2 (9.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
Thyroid disease	4 (9.6%)	5 (22.7%)	1 (9.1%)	3 (17.6%)	4 (12.1%)
Gastrointestinal disease	4 (9.6%)	0 (0.0%)	2 (18.2%)	0 (0.0%)	1 (3.0%)
Other autoimmune diseases	5 (12.2%)	1 (4.5%)	3 (27.3%)	2 (11.8%)	3 (9.1%)
Malignancy	2 (4.9%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	2 (6.1%)
Organ transplants	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Osteoporosis	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.1%)
Chronic heart failure	1 (2.4%)	1 (4.5%)	0 (0.0%)	2 (11.8%)	0 (0.0%)

n=number of patients

We grouped the AEs according to the system of organ classes in the Medical Dictionary for Regulatory Activities (version 16.0) (Garber et al. 2015) with one minor adaptation: except for skin, respiratory and urinary infections, infections and infestations were included in each affected system. We used Edwards' definition of AEs (Edwards and Aronson 2000), and that of the European Medicines Agency's (EMA) of serious AEs ("Https://Www.Ema.Europa.Eu/En/Glossary/Serious-Adverse-Reaction" n.d.).

Complete physical examinations were performed at each follow-up visit. Furthermore, 5 ml of urine, and 12 ml of serum and plasma were collected for basic laboratory tests. Patients were also tested for auto-antibodies and Quanti-FERON-TB Gold, with annual lung examinations. All AEs, and lab results for each 6-month interval were carefully paired with the agent being used during that very same time interval. Results were then analysed using standard ANOVA with one fixed factor (type of therapy), and one repeated factor (6-month intervals). Fischer's least significant difference (LSD) post hoc tests were subsequently applied to all statistically significant results. Lastly, chi-square tests were performed for all parameters to check whether there was a significant difference between the expected versus observed frequencies.

The present study was approved by the Ethics Committee of the Second Faculty of Medicine, Charles University, Prague, Czech Republic. Patients were recruited into the study after informed consent had been obtained.

Results

The most common AEs registered in our study were infections (143 cases in total). Two years into our study, infliximab-, and secukinumab-treated patients were more prone to experience these AEs (chi-square test p=0.001) (Table 3). Regarding respiratory infections, whereas adalimumab performed the worst in the first semester (n=10, 31.3%, chi-square test p=0.016), it was infliximab- and secukinumab-treated patients who tended to report more of these AEs toward the end of the study (infliximab: n=5, 50.0%; secukinumab: n=4, 36.4%; ANOVA, and chi-square test p<0.001) (Table 3). Skin infections were more frequent in the last year of follow-up in patients treated with adalimumab, infliximab, and secukinumab (4th semester: chi-square test p=0.037; ANOVA p=0.035, 5th semester: chi-square test p=0.042; ANOVA p=0.030) (Table 3). Patients treated with adalimumab were more often affected by urogenital infections at the end of the follow-up (chi-square test p=0.004; ANOVA p=0.005) (Table 3).

Reproductive system disorders were more frequent among patients treated with etanercept during the first year of our study (chi-square test p=0.050; ANOVA p=0.048) (Table 3). After two years of treatment, this group showed a higher incidence of menstrual disorders (chi-square test p=0.004; ANOVA p=0.005) (Table 3).

We also recorded a higher incidence of cardiovascular disorders among the study groups. Cardiovascular disorders occurred more often in the group of patients treated with secukinumab (ANOVA p=0.028) (Fig. 1).

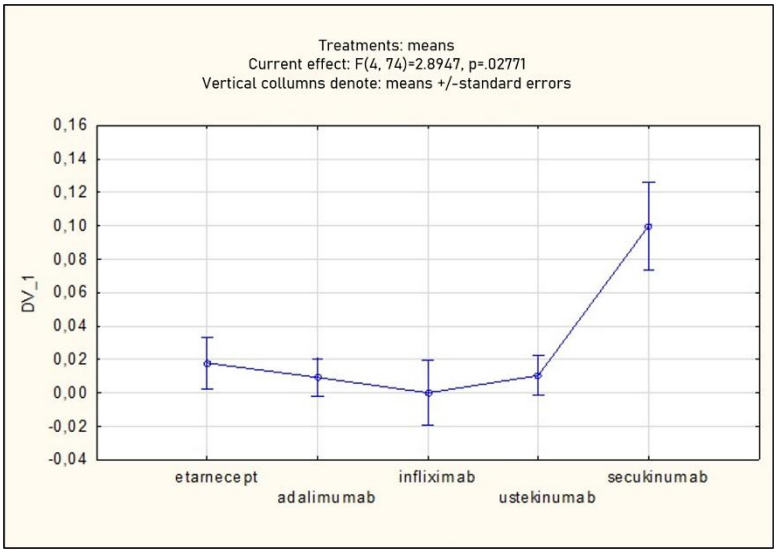

Fig. 1 Incidence of cardiovascular disorders throughout the study

A higher incidence of musculoskeletal disorders was noted throughout the study period among patients treated with etanercept and adalimumab (ANOVA p=0.031) (Table 3).

Within the category of general disorders and administration site reactions, a higher incidence of fatigue was reported by patients receiving infliximab in the early follow-up period (chi-square test, and ANOVA p=0.001) (Table 3). However, these AEs did not occur at statistically significant rates during the rest of the study period.

Patients treated with infliximab showed higher levels of liver enzymes than the remaining groups. Throughout the entire study period, infliximab-treated patients presented with alanine transaminase (ALT), and gamma-glutamyltransferase (GGT) levels above the reference range (ALT: 0.1–0.78 μkat/L; GGT: 0.14–0.68 μkat/L for women, 0.14–0.84 μkat/L for men) (Průša R 2019), (ANOVA p=0.031 and ANOVA p=0.035, respectively).

Table 3 Occurrence of AEs arranged by organ class

System organ class and other parameters	Therapy	6-month intervals										Average (all 6-month intervals)
		1		2		3		4		5		
		n (%)	χ^2; ANOVA	n (%)	χ^2; ANOVA	n (%)	χ^2; ANOVA	n (%)	χ^2; ANOVA	n (%)	χ^2; ANOVA	ANOVA
Reproductive system disorders	ETN	1 (5.9%)	0.326; 0.338	2 (11.8%)	**0.050*; 0.048***	1 (5.9%)	0.320; 0.329	1 (6.8%)	0.238; 0.244	5 (27.8%	**0.004*; 0.005***	0.059
	ADA	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		9 (25.0%)		
	IFX	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		
	UST	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		
	SEC	0 (0.0%)		0 (0.0%)		1 (1.0%)		0 (0.0%)		0 (0.0%)		
Cardiovascular disorders	ETN	0 (0.0%)	-:-	0 (0.0%)	0.099; 0.099	0 (0.0%)	0.132; 0.134	0 (0.0%)	0.884; 0.890	1 (5.6%)	0.271; 0.278	**0.028***
	ADA	0 (0.0%)		0 (0.0%)		0 (0.0%)		1 (3.0%)		0 (0.0%)		
	IFX	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		
	UST	0 (0.0%)		0 (0.0%)		0 (0.0%)		1 (3.4%)		0 (0.0%)		
	SEC	0 (0.0%)		1 (9.1%)		1 (8.3%)		0 (0.0%)		0 (0.0%)		
Musculoskeletal and connective tissue disorders	ETN	2 (11.8%)	0.283; 0.292	2 (11.8%)	0.618; 0.631	5 (29.4%)	0.241; 0.247	2 (13.3%)	0.817; 0.826	7 (38.9%)	**0.001*; 0.001***	**0.031***
	ADA	8 (25.0%)		4 (12.5%)		3 (9.4%)		3 (9.1%)		13 (37.1%)		
	IFX	0 (0.0%)		2 (20.0%)		1 (11.1%)		0 (0.0%)		0 (0.0%)		
	UST	4 (16,7%)		2 (7.7%)		2 (7.7%)		2 (6.9%)		2 (6.7%)		
	SEC	0 (0.0%)		0 (0.0%)		1 (8.3%)		1 (10.0%)		0 (0.0%)		
Infections and infestations	ETN	3 (17.7%)	0.396; -	10 (58.8%)	0.776; -	8 (47.1%)	0.411; -	5 (33.4%)	0.782	1 (5.6%)	**0.001***	**-**
	ADA	12 (38.7%)		12 (38.7%)		12 (38.7%)		13 (39.3%)		1 (2.8%)		
	IFX	1 (11.1%)		5 (50.0%)		3 (33.3%)		3 (30.0%)		5 (50.0%		
	UST	2 (8.3%)		8 (30.8%)		5 (19.2%)		14 (48.3%)		7 (23.4%		
	SEC	0 (0.0%)		3 (27.3%)		2 (16.6%)		2 (20.0%)		6 (54.6%		
Skin and subcutaneous tissue infections	ETN	1 (5.9%)	0.649; 0.663	1 (5.9%)	0.492; 0.792	0 (0.0%)	0.594; 0.269	0 (0.0%)	**0.037*; 0.035***	0 (0.0%)	**0.042*; 0.030***	0.287
	ADA	2 (6.3%)		2 (6.3%)		4 (12.5%)		5 (15.2%)		1 (2.8%)		
	IFX	0 (0.0%)		0 (0.0%)		1 (11.1%)		0 (0.0%)		2 (20.0%		
	UST	0 (0.0%)		2 (7.7%)		0 (0.0%)		0 (0.0%)		1 (3.3%)		
	SEC	0 (0.0%)		0 (0.0%)		1 (8.3%)		0 (0.0%)		2 (18.2%		
Respiratory infections	ETN	2 (11.8%)	0.132; **0.016***	8 (47.1%)	0.094; 0.087	7 (41.2%)	0.259; 0.556	5 (33.3%)	0.204; 0.907	0 (0.0%)	**0.000*; 0.000**	0.289
	ADA	10 (31.3%)		7 (21.9%)		6 (18.8%)		9 (27.3%)		0 (0.0%)		

	IFX	0 (0.0%)		5 (50.0%)		2 (22.2%)		3 (30.0%)		5 (50.0%		
	UST	1 (4.2%)		4 (15.4%)		5 (19.2%)		13 (44.8%)		5 (16.7%		
	SEC	0 (0.0%)		3 (27.3%)		2 (16.7%)		2 (20.0%)		4 (36.4%		
General disorders and administration site reactions	ETN	0 (0.0%)	**0.001*; 0.001***	0 (0.0%)	0.367; 0.378	0 (0.0%)	**-;-**	1 (6.7%)	0.599; 0.612	1 (5.6%)	0.872 ; 0.879	0.988
	ADA	0 (0.0%)		0 (0.0%)		0 (0.0%)		1 (3.0%)		1 (2.8%)		
	IFX	2 (22.2%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		
	UST	0 (0.0%)		1 (3.8%)		0 (0.0%)		0 (0.0%)		1 (3.1%)		
	SEC	0 (0.0%)		1 (9.1%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		
Neoplasms benign, malignant and unspecified (including cysts and polyps)	ETN	0 (0.0%)	0.778; 0.789	0 (0.0%)	0.732; 0.744	0 (0.0%)	0.732; 0.744	0 (0.0%)	**-;-**	0 (0.0%)	**-;-**	0.267
	ADA	1 (3.1%)		1 (3.1%)		1 (3.1%)		0 (0.0%)		0 (0.0%)		
	IFX	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		
	UST	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		
	SEC	0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		

ADA=adalimumab; ANOVA=analysis of variance; ETN=etanercept; IFX=infliximab; n=number of patients; SEC=secukinumab; UST=ustekinumab

A total of 8 patients (6.4%) discontinued therapy: 5 patients (4.0%) temporarily interrupted their treatment, 3 (2.4%) definitively stopped their therapies (Table 4). Our data suggest that, apart from a case of pregnancy and one total knee replacement, a total of 6 patients (4.8%) discontinued their therapies due to possible AEs directly related to treatment with BAs.

Table 4 Reasons for discontinuation of therapy with biologic agents

		Adalimumab (n=41)	Etanercept (n=22)	Infliximab (n=11)	Secukinumab (n=17)	Ustekinumab (n=33)
Autoimmune diseases		1 temp. discont.	0	0	0	0
Infections	Skin	1 temp. discont.	0	0	0	0
	Urinary	0	1 temp. discont.	0	0	0
Malignancy		1 perman. discont.	0	0	0	1 perman. discont.
Positive QNF-TB		1 perman. discont.	0	0	0	0
Pregnancy		0	1 temp. discont.	0	0	0
Surgical intervention		1 temp. discont.	0	0	0	0
Total		5 (12.2%)	2 (9.1%)	0	0	1 (3.0%)

discont=discontinuation; n=number of patients; perman=permanent; QNF-TB=QuantiFERON-TB Gold temp=temporary

The most common reason for therapy discontinuation were malignancies (2 cases of breast cancer) in patients treated with adalimumab or ustekinumab; their incidence, however, did not reach significance in any of the semesters (chi-square test p=0.7; ANOVA p=0.267). The group of patients most often discontinuing their therapy was that on adalimumab (12.2%, chi-square test p=0.281); it was also the group experiencing the highest incidence of serious AEs (7.3%, chi-square test p=0.183).

No significant differences between the individual treatment groups, and their associated diseases were found (Table 2).

Discussion

Biologic agents are used to modulate pathological immune reactions involving T and B lymphocytes, and their respective cytokines. Based on their mechanism of action, they can be divided into tumour necrosis factor (TNF) alpha-inhibiting monoclonal antibodies (etanercept, infliximab, adalimumab), IL-17 inhibitors (secukimumab), and IL-12/23 inhibitors (ustekinumab).

Individual subtypes of T-lymphocytes produce specific cytokines that are important in the pathogenesis of psoriasis. Th1, Th2, T17 play a crucial role in T-helper lymphocyte (Th)-associated immune reactions. Th1 is important for cell-mediated inflammation and produces interferon gamma, TNF, and IL-2. Th2 lymphocytes stimulate inflammatory eosinophilic reactions, IL-4, IL-5, IL-10, and IL-13 production, and antibody formation by B lymphocytes. Th1 and Th2 interact with each other. Interferon gamma, and IL 2 inhibit Th2 lymphocytes, while IL-10 inhibits Th1 lymphocytes (Bettelli et al. 2006; Leung et al. 2007). Th17 lymphocytes stimulate IL-23 cytokines, keratinocytes, synoviocytes, macrophages, fibroblasts, and neutrophils, and produce IL-17, which plays a key role in autoimmune tissue damage (Bettelli et al. 2006; Waite and Skokos 2012; Patel et al. 2013). All the 5 BAs inhibit TNF produced by Th1 lymphocytes.

Again, based on their mechanisms of action, the 5 BAs can be divided into two groups: soluble receptor antagonists, and monoclonal antibodies (mAbs). Soluble receptor antagonists bind to serum cytokinins, thereby blocking their capacity to bind to receptors. Once commenced, their effect sets on within a few days (depending on their plasma concentration); a representative of these BAs in our study was etanercept. mAbs act against cytokinins or their receptors; hence, their mechanism of action is more specific.

Likewise, the 5 BAs differ in their structure. Etanercept is a fusion protein comprised of the p75 tumour necrosis factor (p75 TNF) receptor linked to the Fc portion of human immunoglobulin G_1 (IgG_1). One etanercept molecule binds two TNF molecules (Burmester 2022). Its receptor binds tightly to the IgG-Fc receptor, thus its half-life is longer than that of native soluble receptors. Neutralizing anti-drug antibodies are not often elicited by this class of drugs (Bendtzen et al. 1995). Etanercept is administered subcutaneously once or

twice weekly (Heaney and Golde 1996). The class of monoclonal antibodies includes adalimumab, secukinumab, ustekinumab, and infliximab. These are composed of a fragment antigen-binding (Fab), and an Fc (fragment crystallizable) part of the human immunoglobulin IgG1 or IgG4. The suffix (-umab) indicates fully human mAbs (adalimumab, secukinumab, and ustekinumab) whereas infliximab is a chimeric mAb (with both human and murine components) (Manis 2022). Infliximab is composed of 2 murine variable regions (the kappa chain, and heavy chain variable regions) in the antigen-binding portion of the molecule; the constant Fc domain is human. It is administered intravenously once every six weeks ("Https://Www.Drugs.Com/Infliximab.Html" n.d.) Adalimumab is a recombinant fully human mAb against TNF, and is administered subcutaneously every two weeks. The risk of anti-drug antibody formation is lower in adalimumab patients compared with those treated with infliximab, possibly due to the fact that the former is a fully human mAb. Nonetheless, anti-drug antibody formation can happen (Burmester 2022). Secukinumab is a fully human monoclonal imunoglobulin G1κ antibody administered subcutaneously every month. It acts by selectively targeting the binding of IL-17A to its receptor. In this manner, it prevents the downstream release of pro-inflammatory cytokines and chemokines known to be involved in the pathophysiology of inflammatory and autoimmune diseases (Patel et al. 2013; Rothstein and Gottlieb 2015; Ramiro et al. 2016; Genovese et al. 2013). Ustekinumab is a fully human monoclonal immunoglobulin $G1_K$ antibody that targets IL-12 and IL-23 through the binding of the p40 subunit shared by these two interleukins. It prevents the binding of IL-12 and IL-23 to surface receptors, which leads to the inhibition of natural killer cell activation, CD4+ T-cell differentiation and activation, and expression of monocyte chemotactic protein 1 (MCP-1), TNF-alpha, interferon-inducible protein-10 (IP-10), and IL-8. Ustekinumab is administered subcutaneously at a 12-week interval (Kavanaugh et al. 2014; Burmester 2022).

Information about the potential AEs of these agents is crucial for a safe therapeutic approach ("Https://Www.Ema.Europa.Eu/En/Medicines/Human/EPAR/Stelara" n.d.; Kirkham 2022; Chingcuanco et al. 2016). As it is, there is not yet much robust data on the long-term incidence of infectious complications among patients receiving BAs. While the British Society for Rheumatology Biologics Register claims a similar safety profile for these drugs,

at least among the individual anti-TNF-alpha drugs (Dixon et al. 2007; Rutherford et al. 2018), there have been reports of significantly higher risks of infectious complications among patients treated with different BAs (Kourbeti, Ziakas, and Mylonakis 2014; Morel et al. 2017; García-Doval et al. 2017; Dávila-Seijo et al. 2017). A higher incidence of infections has been associated with treatment with infliximab (5.2-fold) and adalimumab (4.1-fold) compared with etanercept (RR 2.5-fold) (Quartuccio et al. 2019). In our study, significant incidence of these AEs was observed at the end of follow-up among infliximab and secukinumab-treated patients (50.0% and 54.6%, respectively). Just another risk factor for these complications is older age (Quartuccio et al. 2019; Kawashima et al. 2017); in fact, patients above 65 years of age are at a 4 times higher risk of developing infections (Quartuccio et al. 2019). Rigorous screening before and during treatment is thus mandatory to avoid such complications.

Adalimumab-, secukinumab-, and infliximab-treated patients had higher and significant rates of respiratory infections (31.3%, 36.4%, and 50.0%, respectively). Non-tuberculous respiratory infections account for almost half of the infections requiring hospitalization during treatment with biologics (Quartuccio et al. 2019; Sánchez-Moya et al. 2013). Addressing risk factors is essential for preventing respiratory infections, with smoking being a modifiable and very important risk factor (Jiang, Chen, and Xie 2020). Our study population had a high proportion of smokers (34.7%), hence, smoking cessation should be encouraged among BA-treated patients.

An increased incidence of skin infections among patients treated with BAs has been widely reported; in fact, among all infection-related hospitalizations, 6.2% are for dermatologic reasons (Quartuccio et al. 2019; Daudén et al. 2020; Hernández et al. 2013; Pasadyn et al. 2020). In our study, a higher incidence of these infections was noted in adalimumab-, secukinumab-, and infliximab-treated patients in the last year of follow-up. The main complications experienced by our patients included genital, and extragenital warts, parvovirus, and dermatophyte infections. Infliximab is known to increase the risk of bacterial skin infections (cellulitis, erysipelas, impetigo) and herpes zoster infections (Davidson et al. 2022). Long-term observational studies of patients treated with adalimumab, infliximab and

secukinumab reported bacterial (60%), fungal (25%), and viral (13.3%, of which the most common were human papillomavirus [HPV] warts, representing 7%) infections (Fréling et al. 2015). Anti-TNF-alpha drugs practically double the risk of HPV and anogenital wart formation (Georgala et al. 2012; Kane Sunanda, Khatibi Bahar, and Reddy Deepa 2008). Hence, it is important to advise BA-treated patients about high-risk behaviours, and educate them about common clinical manifestations so they can seek professional care in a timely manner.

Overall, urogenital infections were diagnosed in 9 patients (25.0%) treated with adalimumab during our study. Urinary tract infections account for 2.4% of all hospitalizations for infection during treatment with biologics (Quartuccio et al. 2019). Women are at a higher risk when treated with infliximab or anti-IL-17 agents (Sahuquillo-Torralba et al. 2020). Increased surveillance of these patients is mandatory.

Current data suggest rates of 5.51 infections per 100 person-years, and a 30-day risk of serious infection leading to 10% mortality (Dixon et al. 2007; Kourbeti, Ziakas, and Mylonakis 2014; Collins 2018). An increased incidence of serious infections including tuberculosis (TB) was noted with anti-TNF-alpha mAb treatment compared with soluble TNF receptor therapy (Tubach et al. 2009; Sánchez-Moya et al. 2013; Puig et al. 2020). We did not register serious infections (the only reported case of QNF positivity did not present with a typical clinical picture, hence, similar to other studies (Gómez-Reino et al. 2003), it was not classified as a TB case).

The effect of BAs on the development of malignancies is not yet clear. While some evidence suggests a higher incidence of malignancies with anti-TNF-α drugs, a large study including ustekinumab did not. Studies with other agents are lacking (Haynes et al. 2013; Fiorentino et al. 2017). In our study, the incidence of cancer was non-significant. Still, breast cancer was the most common reason for therapy discontinuation in 2 patients receiving adalimumab or ustekinumab. A direct link between anti-TNF-alpha therapies and tumour formation is difficult to prove because of patients' underlying conditions and concomitant use of other drugs (Hyrich 2022; Symmons 1995; Cibere, Sibley, and Haga 1997). The finding of two

malignancies in our study underlines the need for careful age-appropriate cancer screening in patients treated with these agents (Pithadia et al. 2019).

We also observed a higher incidence of menstrual disorders at the end of the follow-up period among etanercept-treated patients (5 patients, 27.8%). These disorders included metrorrhagia, dysmenorrhea, and amenorrhea. To the best of our knowledge, there is no data on the effect of anti-TNF-alpha inhibitors on a women's menstrual cycle. The relevant literature provides only information on their safe use during pregnancy, and possible effects on foetal development (Fasoulakis et al. 2016; Bröms et al. 2016).

Also documented was a higher incidence of cardiovascular disorders. Of note were the newly diagnosed cases of hypertension and arrhythmia. The possible effects of BAs on the cardiovascular system, and the respective risk factors are subject to long-standing debate (Egeberg et al. 2018; Ryberg 2013). Concerns about the impact of TNF-alpha inhibitors on the development of heart failure arose in early post-marketing surveillance (Kwon et al. 2003; Gabriel 2008). Still, anti-TNF-alpha therapy does not seem to increase the risk of cardiovascular events (Rungapiromnan et al. 2017; Papamichail et al. 2022).

Etanercept- and adalimumab-treated patients reported musculoskeletal disorders more often than the other patient groups. These disorders included arthritis, osteoarthritis, arthralgia, ostealgia, muscle spasms, tendinitis, and compression fractures. A rheumatologist excluded the diagnosis of psoriatic arthritis in 14 of the 20 affected patients. Our findings are consistent with those found in other studies, that is, patients receiving etanercept tended to experience musculoskeletal disorders including arthralgia and increased incidence of muscle spasms whereas individuals treated with adalimumab were found to be at an increased risk of fractures (Duarte et al. 2017; Daudén et al. 2020).

Patients receiving infliximab had a higher incidence of fatigue which was, however, significant only at the beginning of the study. This AE is already known from clinical studies ("Summary of Product Information - Remicade (Infliximab)," n.d.).

Abnormally high levels of ALT and GGT were documented among infliximab-treated patients throughout the follow-up. A total of 24 patients presented with asymptomatic high

liver enzymes, one was diagnosed with severe liver steatosis. Reich (Reich et al. 2005) described results similar to ours whereas Poulin (Poulin and Thérien 2010) reported a case of infliximab-induced hepatitis. Aparicion and Shelton also mentioned the hepatotoxic effect of infliximab in patients with spondyloarthropathy and inflammatory bowel disease (García Aparicio et al. 2007; Shelton et al. 2015). Our findings highlight the need for permanent surveillance of BA-treated patients, specifically those treated with infliximab.

An important issue with biologic therapy is treatment discontinuation or nonadherence (Baenas et al. 2016; Doshi et al. 2016; Menter et al. 2019). In our study, a total of 8 patients (6.4%) temporarily or permanently discontinued their treatment, the highest number (5 patients) was in the group receiving adalimumab. Our numbers are significantly lower than those in a 5-year follow-up study of rheumatologic patients on with BAs, where 32.8% discontinued their treatment. Similarly, another study with psoriatic patients reported 46% of their patients discontinuing their treatment after one year (Doshi et al. 2016; Baenas et al. 2016).

It is well known that BA-treated patients are at increased risk of developing serious AEs (Li et al. 2020; Minozzi et al. 2016) (especially those on infliximab and adalimumab) (Penso et al. 2021). In our study, only adalimumab-treated patients experienced serious AEs (two malignancies, and one case of systemic lupus erythematosus) – such results were not statistically significant. No deaths occurred during our study.

Our study was limited by substantial differences in the numbers of patients treated with different BAs, potentially resulting in wider confidence intervals. Another possible limitation is that our study period was not very long, which can theoretically limit the detection rates of delayed and/or rare AEs. Nevertheless, most of our patients were already being treated for some time at the time of enrolment, which can considerably compensate for this limitation; in fact, we cannot exclude that some of the above AEs were of delayed type. It is unlikely that information bias has affected our results since all records were completed in the presence of the same physician.

All references in our article only included adults.

Conclusion

Infliximab-treated patients showed a high incidence of asymptomatic increased liver enzyme levels, fatigue, and respiratory and skin infections. Adalimumab-treated patients were more often affected by musculoskeletal disorders and infections of all types. Patients receiving secukinumab showed higher rates of cardiovascular disorders, respiratory, and skin infections. The group treated with etanercept experienced more musculoskeletal and reproductive (specifically menstrual) disorders. The rates of therapy discontinuation, and serious adverse events did not reach significant values.

A higher incidence of AEs was observed among adalimumab- and infliximab-treated patients, with ustekinumab found to have the safest profile. Our results demonstrate that a personalized approach, including evaluation of a patient's risk profile, is necessary before commencing a biologic. Further research is warranted to confirm the findings of our study.

Author contributions

All authors had full access to all of the data of the study and take responsibility for the integrity of the data and accuracy of data analysis. All authors contributed equally to the study concept and design, data acquisition, analysis and interpretation, drafting, and critical revision of the manuscript, statistical analysis, and study supervision.

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Conflicts of interest

Jana Hercogová has received honoraria as a speaker and/or consultant for AbbVie, Celgene, Eli Lilly, Frankl Pharma, Janssen, Leo Pharma, Novartis, Novartis Global, Sanofi Aventis, and Sanofi Genzyme. The other co-authors (Zoltán Paluch, Emanuel Marques, Petr Boháč, and Kateřina Zemková) declare no conflicts of interest.

List of Abbreviations

*	Statistical significant p-values
ADA	Adalimumab
AE	Adverse event
ALT	Alanine Transaminase
BA	Biologic agent
BMI	Body mass index
Discont.	Discontinuation
EMA	European Medicines Agency
ETN	Etanercept
Fab	Fragment antigen-binding
Fig.	Figure
GGT	Gamma-glutamyltransferase
HPV	Human papilloma virus
IFX	Infliximab
IL	Interleukin
IgG	Immunoglobulin G
IP-10	Interferon-inducible protein-10
LSD	Least significant difference
mAb	Monoclonal antibody
MCP-1	Monocyte chemotactic protein 1
N	Number of patients
P	p-value (probability significance)
Perman.	Permanent
QNF-TB	QuantiFERON-TB GOLD
SEC	Secukinumab
SPC	Summary of Product Characteristics
TB	Tuberculosis
Temp.	Temporary
Th	T helper
TNF	Tumour necrosis factor
UST	Ustekinumab

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OVERALL RESULTS AND DISCUSSION

Discussion

This large prospective, observational cohort study gives a comprehensive evaluation of psoriasis treatment. It reviews all forms of treatment available in the Czech Republic and demonstrates which types of therapy and specific drugs are the safest for the treatment of the disease. Additionally, it investigates possible trigger and prognostic factors of severe psoriatic patients.

Chapter 1

Psoriasis vulgaris is a chronic skin inflammatory disease with high prevalence. It can significantly impair patients‘ quality of life (Votrubova et al. 2014) (Hercogová 2011). Severe psoriasis is associated with a number of comorbidities (Votrubova et al. 2014) (Lotti, Hercogova, and Prignano 2010) (Juzlova et al. 2016) and these are responsible for a shorter life span (de Oliveira, Rocha, and Duarte 2015). Treatment options include topical compounds, phototherapy and non-biologic systemic agents . In cases of intolerance or therapy failure, patients may be candidates to biologic therapy - these are the most modern available form of treatment (Nast et al. 2015). However, just like with any other drug, these may be offset by a number of adverse events (Boháč et al. 2016). It is therefore mandatory to be familiar with the benefits as well as the possible serious adverse events associated with these agents.

Chapter 2

Severe psoriasis is directly proportional to its economical and social impact, and these are undissociable (S. R. Feldman et al. 1997) (Steven R. Feldman et al. 2017). Understanding how different comorbidities and epidemiological factors affect psoriasis severity grades can therefore be of great help for both patients and countries’ health care systems. Our study investigated possible trigger and prognostic factors of severe psoriasis.

A linkage between gender and type of therapy was observed. Women were treated topically more often than men, and that more men had a history of biologic therapy than women. Such results support Hägg´s and Colombo´s (Colombo et al. 2014) studies. Hägg concluded that

women enjoy lower PASI scores than men, hence men tend to be treated systemically more often than women (Hägg et al. 2017) (Hägg et al. 2013). Therapy adherence is associated with improvement of disease severity (C. L. Carroll et al. 2004) (Christie L. Carroll et al. 2004) (Steven R. Feldman et al. 2007) (Evers et al. 2010) (Lecha et al. 2005) (Lynde et al. 2012). Storm reported higher rates of therapy adherence among men (Storm et al. 2008), Zaghloul described women as the most compliant (Zaghloul and Goodfield 2004), Gokdemir could not establish any association between sex and therapy adherence (Gokdemir, Ari, and Köşlü 2008). Literature is not consensual, one may conclude that men are indeed more severily affected by psoriasis than women.

In this study patients' height differed according to therapy type (results from the group treated topically statistically different from the remaining groups). To our knowledge, a relationship between height alone and psoriasis severity has never been hypothesized before. Nonetheless, such results must be interpreted with caution, since more males were treated systemically during this research study (in the Czech Republic men are substantially taller than women: 181± cm vs 169± cm) (Grasgruber and Hrazdíra 2013).

It was observed that patients treated systemically, therefore more aggressively, had an earlier disease onset. Our results confirm those of Na and García-Diez (Na, Jo, and Youn 2013) (García-Diez et al. 2008).

Patients treated with more aggressive forms of therapy are more likely to refer infections as a trigger of psoriasis. The fact that psoriasis can be triggered by upper respiratory tract infections is not new (Sbidian et al. 2019) (Weisenseel et al. 2002) (Raychaudhuri, Maverakis, and Raychaudhuri 2014), though, this study suggests a relationship between psoriasis severity and these trigger factors. Achieved results also suggest that patients in which psoriasis is triggered by periods of hormonal variations might suffer from a more severe form of the disease. Ceovic (Ceovic et al. 2013), Islam (Islam et al. 2011) and Murase (Murase et al. 2005) already wrote about how puberty, premenstrual states and menopause can lead to psoriasis flare-ups in women. No studies suggesting periods of hormonal variations as an independent prognostic factor of the disease were found.

This research study evidenced how patients treated systemically have higher rates of depression history compared to those treated treated topically. This finding is supported by their need of psychotherapy. Thus, this study demonstrated how psoriasis severity seems to be directly proportional to depression severity. Gupta achieved similar results (Gupta et al. 1993).

We noticed that patients treated systemically use statins more than those treated topically. The European Cardiology Society and European Atherosclerosis Society recommend maitaining a certain LDL-c (low-density lipoprotein cholesterol) based on the patient's CVD (Mach et al. 2019). Thus, we may conclude that patients on systemic agents do have a higher CVD because they use statins more than the group treated with topical drugs. This link has already been demonstrated (Chiriac, Podoleanu, and Azoicai 2017) (Abuabara et al. 2010) (Gelfand et al. 2007) (Gelfand et al. 2006).

Hyperuricemia was also found to be associated with more agressive psoriasis therapy. Multiple authors have already described about how psoriasis is associated with hyperuricemia (Gisondi et al. 2014) (Alpsoy et al. 2014) (Zhou Z et al. 2013) (Zhang et al. 2012) (Ibrahim et al. 2012) (Isha, Jain, and Lal 2011) (Severin et al. 1999) (Merola et al. 2015) (Gui et al. 2018), however studies trying to establish linear correlations between SUAC and psoriasis severity have reported inconsistent results. Gisondi and others have described a linear relationship between SUAC and PASI (Sterry, Strober, and Menter 2007) (Gisondi et al. 2014) (Gelfand et al. 2006) (H. H. Kwon et al. 2011) (Eisen and Seegmiller 1961) (H. H. Kwon et al. 2011) (Eisen and Seegmiller 1961) (Baumann and Jillson 1961) (Tickner and Mier 1960) (Sommer et al. 2006) (Neimann et al. 2006) (Murray et al. 2009) (Shiraishi and Une 2009), however a meta-analysis including 29416 patients have failed to show a direct association between SUAC and psoriasis severity (Xin Li et al. 2016). Results of this study rather follow Gisondi's.

A direct correlation between psoriasis severity and nonspecific noninfectious liver disease was also observed. Alcohol consumption and BMI did not statistically vary according to therapy type, however we cannot 100% exclude their presence in the past. Gisondi and Miele were already able to prove a link between psoriasis and nonalcoholic fatty liver disease

independent of alcohol intake, obesity, and hepatotoxic medications (Gisondi et al. 2009) (Miele et al. 2009). Regarding psoriasis severity, Gisondi described a strong linear correlation between psoriasis severity and NAFLD (Gisondi et al. 2009), while Miele and Van der Voort rejected this hypothesis (Miele et al. 2009) (van der Voort et al. 2014). The fact that NAFLD and NASH are associated with an increased likelihood of developing CVD could help explaining why some of our patients suffer from a higher risk of CVD (Villanova et al. 2005).

Chapter 3

Until recently, topical therapy, phototherapy and use of non-biologic systemic agents were the only possible therapeutic options in psoriasis. With evolving knowledge of the immunopathogenesis of the disease process, a new and revolutionary form of therapy called biologic agents has emerged.(Hassan et al. 2013) These have proved to be the most effective therapies (Gisondi et al. 2008) (Piaserico et al. 2014) (Barker et al. 2011) (Saurat et al. 2008) (Au SC, Madani A, Alhaddad M, Alkofide M 2013) (Schmitt et al. 2008). However consistent and solid data from long-term studies on the safety of these agents are still lacking when compared with other forms of therapy. Our research study compared the occurrence of adverse events in three groups of psoriatic patients on different therapeutic regimens (topical therapy, non-biologic systemic drugs and biologic agents) for a period of 30 months.

The incidence rates of all adverse events combined were higher for patients who received biologic agents than for other patients throughout the all study period. Most studies either put biologic agents at the same level of safety or even labeled them as the safer alternative (Garber C, Plotnikova N, Au SC, Sorensen EP 2015), (K. Reich et al. 2015), (Carretero et al. 2015), (Medina et al. 2015), (Montes-Torres et al. 2019), (Kristian Reich et al. 2010), as confirmed by a meta-analysis of randomized controlled trials (Schmitt et al. 2008). No other study demonstrate an overall higher incidence of adverse events among patients treated with a biologic agents than with non-biologic systemic agents. This research also suggested no incidence of delayed adverse events.

Patients treated with biologic agents developed non-infectious renal and urinary disorders. The most common registered adverse events were urinary tract infections,

dysmenorrhea/amenorrhea and prostate hypertrophy. Outcomes were comparable with those reported in clinical trials with infliximab and adalimumab, where renal and urinary disorders were classified as common adverse events (incidence ≥1% to <10%) ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.). The Summary of Product Characteristics (SPC) of the remaining biologics do not give the occurrence of these adverse events ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)." n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.).

Musculoskeletal and connective tissue disorders occurred more often among patients treated with biologic agents. It is not quite clear why these adverse events were only experienced in the early period of the study, but biologics have been suggested to neutralize nociceptive joint pain even before starting to exert their anti-inflammatory effect (Hess et al. 2011). The most common adverse events included general arthralgia, enthesopathy and new-onset osteoarthritis (involving mostly the spine). Obtained results are comparable with those obtained in clinical trials with adalimumab ("Summary of Product Information - Humira (Adalimumab)," n.d.), but substantially superior to those reported for other biologic agents, ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)." n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.).

Oral cavity-related adverse events also seem to affect particularly psoriatics treated with biologic agents more frequently than patients receiving other therapies. The most common AEs included dry mouth and gingivitis. Such adverse events were not related to a recent switch from a non-biologic systemic agent to a biologic (acitretin typically causes such an AE) ("Summary of Product Information - Neotigason (Acitretine)," n.d.); in a matter of fact, all patients experiencing these adverse events had been on a biologic for many years prior to enrolment into the study. It was not possible to establish whether these adverse events were of infectious or non-infectious etiology. Neither other studies, nor the SPCs of all tested biologic agents list this type of adverse events ("Summary of Product Information - Humira

(Adalimumab)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)." n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.).

Patients on biologic agents had higher rates of respiratory tract infections than the other groups throughout the study. Results are consistent with those obtained in other clinical trials ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)." n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.). Apart from Yan, who found no significant differences in the incidence of these adverse events (Yan et al. 2011), no other studies comparing this type of adverse events between biologics and other types of therapy were found.

Considering how the biologic agent-treated group used systemic antibiotics more frequently than the remaining groups, these patients probably had overall higher rates of infections than the remaining groups. SPCs do label infections and infestations as a more common adverse events compared with the other types of therapy ("Summary of Product Information - Humira (Adalimumab)," n.d.), ("Summary of Product Information - Remicade (Infliximab)," n.d.), ("Summary of Product Information - Enbrel (Etanercept)," n.d.), ("Summary of Product Information - Stelara (Ustekinumab)." n.d.), ("Summary of Product Information - Consentyx (Secukinumab)," n.d.), ("Summary of Product Information - Neotigason (Acitretine)," n.d.), ("Summary of Product Information - Sandimmun (Ciclosporin)," n.d.), ("Summary of Product Information – Jylamvo (Methotrexate)," n.d.). Piaserico reported data identical to ours, (Piaserico et al. 2014) whereas Garber failed to obtain significant results (Garber C, Plotnikova N, Au SC, Sorensen EP 2015).

A total of 7.2% of patients on biologic therapy discontinued their treatment due to adverse events. A total of five patients presented with positive QNF-TB tests (two were on adalimumab, one on infliximab, and two were using cyclosporine). Similarly to other studies (Gómez-Reino et al. 2003a), these patients were not classified as tuberculosis cases, since

they did not present the typical clinical picture. Still, both TNF-α inhibitors and cyclosporine have been commonly associated with mycobacterial infections (Fonseca et al. 2006), (Brassard, Kezouh, and Suissa 2006), (Wallis et al. 2004), (Wallis et al. 2004), (Askling et al. 2005), (Dixon et al. 2006), (Tubach et al. 2009a), (Winthrop et al. 2013), (John et al. 1994). Regarding malignancies, our results are consistent with the literature (Dommasch et al. 2011), (Leonardi et al. 2008), (Papp et al. 2008), (Igarashi et al. 2012), (Gottlieb et al. 2014). TNF-α inhibitors have been associated with autoimmune disorders (Pirowska et al. 2015), but, apart from a single case of systemic lupus erythematosus, no other patients in our study developed clinical pictures or presented laboratory results consistent with this type of diagnosis. Lastly, except for ustekinumab (Leonardi et al. 2008) (Papp et al. 2008) and secukinumab (Thaçi et al. 2015), biologics (specifically TNF-α inhibitors) have been reported to be associated with serious adverse events as compared with non-biologic agents (Garcia-Doval et al. 2012), (Barker et al. 2011), (Kimball et al. 2015), (Kalb et al. 2015), (Galloway et al. 2011) – during this study, serious AE were of borderline statistical significance.

Biologic agents were the most effective class of drugs: lower PASI scores and BSA values were obtained during 60% of the study. Literature is scarce in such comparative studies, nevertheless Zweegers resumed a few in a systematic review (Zweegers et al. 2016).

Chapter 4

Information about the potential AEs of each BA is crucial for a safe therapeutic approach ("Https://Www.Ema.Europa.Eu/En/Medicines/Human/EPAR/Stelara" n.d.; Kirkham 2022; Chingcuanco et al. 2016). As it is, there is not yet much robust data on the long-term incidence of infectious complications among patients treated with BAs. While the British Society for Rheumatology Biologics Register claims a similar safety profile for these drugs, at least among the individual anti-TNF-alpha drugs (Dixon et al. 2007; Rutherford et al. 2018), there have been reports of significantly higher risks of infectious complications among patients treated with different BAs (Kourbeti, Ziakas, and Mylonakis 2014; Morel et al. 2017; García-Doval et al. 2017; Dávila-Seijo et al. 2017). A higher incidence of infections

has been associated with treatment with infliximab (5.2-fold), and adalimumab (4.1-fold) compared with etanercept (RR 2.5-fold) (Quartuccio et al. 2019). In our study, a significant incidence of these AEs was observed at the end of follow-up among infliximab, and secukinumab-treated patients (50.0%, and 54.6%, respectively). Just another risk factor for these complications is older age (Quartuccio et al. 2019; Kawashima et al. 2017); in fact, patients above 65 years of age are at a 4 times higher risk of developing infections (Quartuccio et al. 2019).

Adalimumab-, secukinumab-, and infliximab-treated patients had higher, statistically significant, rates of respiratory infections (31.3%, 36.4%, and 50.0%, respectively). Non-tuberculous respiratory infections account for almost half of the infections requiring hospitalization during treatment with biologics (Quartuccio et al. 2019; Sánchez-Moya et al. 2013). Addressing risk factors is essential for preventing respiratory infections, and smoking is a modifiable, and very important risk factor (Jiang, Chen, and Xie 2020). Our study population had a high number of smokers (34.7%).

An increased incidence of skin infections among patients treated with BAs has been widely reported; in fact, among all infection-related hospitalizations, 6.2% are for dermatologic reasons (Quartuccio et al. 2019; Daudén et al. 2020; Hernández et al. 2013; Pasadyn et al. 2020). In our study, a higher incidence of these infections was noted in adalimumab-, secukinumab-, and infliximab-treated patients in the last year of follow-up. The main complications experienced by our patients included genital, and extragenital warts, parvovirus, and dermatophyte infections. Infliximab is known to increase the risk of bacterial skin infections (cellulitis, erysipelas, impetigo), and herpes zoster infections (Davidson et al. 2022). Long-term observational studies of patients treated with adalimumab, infliximab, and secukinumab reported bacterial (60%), fungal (25%), and viral (13.3%, of which the most common were human papillomavirus [HPV] warts, representing 7%) infections (Fréling et al. 2015). Anti-TNF-alpha drugs practically double the risk of HPV¨, and anogenital wart formation (Georgala et al. 2012; Kane Sunanda, Khatibi Bahar, and Reddy Deepa 2008).

Overall, urogenital infections were diagnosed in 9 patients (25.0%) treated with adalimumab during our study. Urinary tract infections account for 2.4% of all hospitalizations for

infection during treatment with biologics (Quartuccio et al. 2019). Women are at higher risk when treated with infliximab or anti-IL-17 agents (Sahuquillo-Torralba et al. 2020).

Current data suggest rates of 5.51 infections per 100 person-years, and a 30-day risk of serious infection leading to 10% mortality (Dixon et al. 2007; Kourbeti, Ziakas, and Mylonakis 2014; Collins 2018). An increased incidence of serious infections including tuberculosis (TB) was noted with anti-TNF-alpha mAb treatment compared with soluble TNF receptor therapy (Tubach et al. 2009b; Sánchez-Moya et al. 2013; Puig et al. 2020). We did not register serious infections (the only reported case of QNF positivity did not present with a typical clinical picture, hence, similar to other studies (Gómez-Reino et al. 2003b), it was not classified as a TB case).

The effect of BAs on the development of oncological disease is not yet clear. While some evidence suggests a higher incidence of malignancies with anti-TNF-α drugs, a large study including ustekinumab did not. Studies with other agents are lacking (Haynes et al. 2013; Fiorentino et al. 2017). In our study, the incidence of cancer was non-significant. Still, breast cancer was the most common reason for therapy discontinuation in 2 patients treated with adalimumab or ustekinumab. A direct link between anti-TNF-alpha therapies, and tumour formation is difficult to prove because of patients' underlying conditions, and concomitant use of other drugs (Hyrich 2022; Symmons 1995; Cibere, Sibley, and Haga 1997). The finding of two malignancies in our study underlines the need for careful age-appropriate cancer screening in patients treated with these agents (Pithadia et al. 2019).

We also observed a higher incidence of menstrual disorders at the end of the follow-up period among etanercept-treated patients (5 patients, 27.8%). These disorders included metrorrhagia, dysmenorrhea, and amenorrhea. To the best of our knowledge, there is no data on the effect of anti-TNF-alpha inhibitors on a women's menstrual cycle. The relevant literature provides only information on their safe use during pregnancy, and possible effects on foetal development (Fasoulakis et al. 2016; Bröms et al. 2016).

Also documented was a higher incidence of cardiovascular disorders. Of note were the newly diagnosed cases of hypertension, and arrhythmia. The possible effects of BAs on the

cardiovascular system, and the respective risk factors are subject to long-standing debate (Egeberg et al. 2018; Ryberg 2013). Initial concerns about the impact of TNF-alpha inhibitors on the development of heart failure arose in the early post-marketing follow-up (H. J. Kwon et al. 2003; Gabriel 2008). Still, anti-TNF-alpha therapy does not seem to increase the risk of cardiovascular events (Rungapiromnan et al. 2017; Papamichail et al. 2022).

Etanercept-, and adalimumab-treated patients reported musculoskeletal disorders more often than the other patient groups. These disorders included arthritis, arthrosis, arthralgia, ostealgia, muscle spasms, tendinitis, and compression fractures. A rheumatologist excluded the diagnosis of psoriatic arthritis in 14 of the 20 affected patients. Our findings are consistent with those found in other studies, that is, patients receiving etanercept tended to experience musculoskeletal disorders including arthralgia, and increased number of muscle cramps whereas individuals treated with adalimumab were found to be at an increased risk of fractures (Duarte et al. 2017; Daudén et al. 2020).

Patients treated with infliximab had a higher incidence of fatigue which was, however, significant only at the beginning of the study. Such AE is already known from clinical studies ("Summary of Product Information - Remicade (Infliximab)," n.d.).

Abnormally high levels of ALT, and GGT were documented among infliximab-treated patients throughout the follow-up. A total of 24 patients presented with asymptomatic high liver enzymes, one was diagnosed with severe liver steatosis. Reich (Kristian Reich et al. 2005) described results similar to ours whereas Poulin (Poulin and Thérien 2010) reported a case of infliximab-induced hepatitis. Aparicion, and Shelton also mentioned the hepatotoxic effect of infliximab in patients with spondyloarthropathy, and inflammatory bowel disease (García Aparicio et al. 2007; Shelton et al. 2015).

It is well known that BA-treated patients are at increased risk of developing serious AEs (Xintong Li et al. 2020; Minozzi et al. 2016) (especially those on infliximab, and adalimumab) (Penso et al. 2021). In our study, only adalimumab-treated patients developed

serious AE (two malignancies, and one case of systemic lupus erythematosus) – such results were not statistically significant. No deaths occurred during our study.

This research study is limited by a small patient sample and a relatively short study period – facts that can theoretically limit the detection rates of delayed and/or rare adverse events. Nevertheless, most patients were already being treated for some time at the time of their enrolment, which can compensate for this limitation. Another limitation was the fact that patiens were already being treated for some time when our study started: in this fashion, diseases assumed to be related to psoriasis severity, can, theoretically, be adverse events of those same therapies (ex. liver disease due to methotrexate hepatoxicity). Also, the fact that nine (3.1%) patients were treated concomitantly with both a non-biologic systemic agent and a biologic was not optimal. However, it is unlikely that such a small proportion of the study group may have biased results. Furthermore, dose-dependent adverse events were not considered (non-biologic systemic agents are toxic when given at higher doses ("Summary of Product Information - Sandimmun (Ciclosporin)," n.d.), ("Summary of Product Information – Jylamvo (Methotrexate)," n.d.), (Naldi and Griffiths 2005), (Ho 2004), (Pathirana et al. 2009), (Bissonnette, Ho, and Langley 2009). The group of patients treated with non-biologic systemic therapies included substantially fewer patients than the remaining groups, which can theoretically result in wider confidence intervals. The same applies to all five groups of patients treated with each one of the BAs. Lastly, ideal conditions were if psoriasis severity scores were followed in untreated patients; however, such conditions are rather unrealistic because a patient with severe psoriasis eventually needs to be treated systemically. It is unlikely that information bias has influenced results of this research, considering the fact that all records were completed in the presence of the same doctor.

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OVERALL CONCLUSION

Conclusion

This study demonstrated that psoriasis severity is directly related to an increased risk of cardiovascular disease, depression, hyperuricemia and nonspecific noninfectious liver disease. Moreover, male gender, increased height, early age at disease onset (up to 25.9 years), and trigger factors such as puberty, menopause/andropause and viral upper respiratory infections seem to be prognostic of higher levels of psoriasis severity. This research pioneers the use of independent prognostic factors such as increased height and trigger factors such as puberty, menopause/andropause as independent prognostic factors of psoriasis severity. A series of prognostic factors and conditions that can help one in estimating patient's clinical outcome are proposed.

Biologic agents were associated with the lowest safety profile when compared with other forms of treatment. Patients treated with biologics showed higher overall rates of adverse events (AEs), overall rates of infections, respiratory tract infections, renal, urinary, musculoskeletal, connective tissue, oral cavity-related disorders, and treatment discontinuation. Except for infections, all the above biologic agent-related AEs occurred more often in our study than in clinical trials. This study pioneers the report of oral cavity-related AEs among users of biological agents. The rates of serious AEs were of borderline statistical significance, those of serious infections were not statistically significant. Still, biologic agents were the most effective form of therapy when compared with topical agents and non-biologic systemic agents.

When comparing BA-treated patients between themselves, infliximab-treated patients showed a high incidence of asymptomatic increased liver enzymes, fatigue, respiratory, and skin infections. Adalimumab-treated patients were more often affected by musculoskeletal disorders and infections of all types. Patients receiving secukinumab showed higher rates of cardiovascular disorders, respiratory, and skin infections. The group treated with etanercept experienced more musculoskeletal and reproductive (specifically menstrual) disorders. The rates of therapy discontinuation and serious AEs did not reach statistical significance. Our results demonstrated a higher incidence of AEs among adalimumab- and infliximab-treated patients, with ustekinumab found to have the safest profile.

To sum up, a personalized approach, including evaluation of a patient's risk profile, is necessary before commencing a biologic. Further research is warranted to confirm the findings of this study.

SUMMARY

Summary

Psoriasis vulgaris is a chronic inflammatory skin disease with a prevalence of 1.5–4.7%. Severe psoriasis is seen as a systemic inflammatory disease associated with an increased risk of complications. Understanding how different comorbidities and epidemiological factors are related to psoriasis severity can help in estimating a patient's clinical outcome.

Severe psoriasis is usually non-responsive to topical agents, phototherapy and, occasionally, to conventional systemic drugs. In such cases, modern immunomodulatory drugs known as biologic agents are prescribed. Still, there are few real-world, consistent and long-term studies on the safety of these agents compared with the other forms of therapy. With the implementation of longer follow-ups, reports of serious adverse events are slowly emerging.

The objectives of this research were to identify the prognostic factors of severe psoriasis, compare the safety profiles of different therapy types (topical compounds, non-biologic systemic agents and biologic agents) and those of biologic agents themselves (adalimumab, etanercept, infliximab, secukinumab, ustekinumab). A total of 289 psoriatic patients were followed up for 30 months; they were divided into 3 groups according to therapy type. Comorbidities, epidemiological parameters, and rates of adverse events were compared between the three groups and, also, between each of the 5 biologic agents. Data was statistically analyzed.

It was concluded that psoriasis severity is directly related to an increased risk of cardiovascular disease, depression, hyperuricemia and nonspecific noninfectious liver disease. Male gender, increased height, early age at disease onset, viral upper respiratory infections and periods of hormonal changes seem to be prognostic of higher levels of psoriasis severity. When comparing therapy types, biologic agents were the most effective therapies; however, they were associated with higher rates of adverse events and treatment discontinuation. A higher incidence of adverse events was observed among adalimumab- and infliximab-treated patients, with ustekinumab found to have the safest profile. Our results demonstrate that a personalized approach, including evaluation of a patient's risk profile, is necessary before commencing a biologic. Further research is warranted to confirm the findings of this study.

Souhrn

Psoriasis vulgaris je chronické zánětlivé kožní onemocnění s prevalencí 1,5–4,7 %. Lupénka je systémové zánětlivé onemocnění se zvýšeným rizikem komplikací. Stratifikace komorbidit a epidemiologických faktorů v souvislosti se závažností psoriázy pomáhají určit prognózu a závažnost formy onemocnění.

U těžkých forem psoriázy topická terapie, fototerapie a konvenční systémová léčba nepřináší dostatečný klinický účinek a je nutná moderní imunomodulační léčba biologickými léčivy. Konzistentních dlouhodobých studií o bezpečnosti biologických léčiv v klinické praxi ve srovnání se studiemi hodnotícími výskyt nežádoucích účinků při tradičním způsobu léčby je výrazně méně. Dlouhodobá sledování pacientů léčených biologickými léčivy naznačují možný výskyt závažných nežádoucích účinků.

Cílem výzkumu bylo stanovit prognostické faktory těžké psoriázy, porovnat bezpečnostní profil různých typů terapií (topická terapie, nebiologická systémová léčiva a biologická léčba) a posoudit účinek jednotlivých biologických léčiv (adalimumab, etarnecept, infliximab, secukinumab a ustekinumab). Výzkum sledoval 289 psoriatických pacientů po dobu 30 měsíců, podle typu terapie byli rozděleni do 3 skupin. Byly porovnávány komorbidity, epidemiologické údaje a četnost nežádoucích účinků mezi jednotlivými skupinami léčenými daným typem terapií a jednotlivá biologická léčiva vzájemně (celkem 5). Údaje byly zpracovány statisticky.

U pacientů se závažnou formou psoriázy byl vyšší výskyt kardiovaskulárních onemocnění, deprese, hyperurikémie, nespecifická neinfekční onemocnění jater. Výsledky výzkumu naznačují, že prognostickými rizikovými faktory závažnější formy psoriázy je mužské pohlaví, vyšší vzrůst, manifestace onemocnění v mladším věku, virová infekce horních cest dýchacích a období hormonálních změn. Ze sledovaných způsobů léčby byla neúčinnější terapie biologickými léčivy, ale spojená s vyšší mírou nežádoucích účinků a nutností přerušit léčbu. Z biologických léčiv byl nejbezpečnější ustekinumab, četnější nežádoucí účinky byly zaznamenány při léčbě adalimumabem a infliximabem. Výsledky výzkumu prokázaly, že personalizovaný přístup hodnotící rizikový profil pacienta je před zahájením terapie biologickými léčivy nezbytný. Zjištěné výsledky vyžadují další studie a ověření.

APPENDICES

List of appendices

1. Statistical analysis of data of patients with psoriasis
2. Occurrence of infectious complications in psoriatic patients treated with biologic agents

STATISTICKÁ ANALÝZA DAT O PACIENTECH S PSORIÁZOU

Jaromír Běláček, Emanuel Marques, Zoltán Paluch

Anotace

Příspěvek pojednává o metodice a výsledcích statistické analýzy dat pořízených při léčbě pacientů s psoriázou na Der- matovenerologické klinice nemocnice Na Bulovce v letech 2015-17. Poměrně velký rozsah datového souboru (čítající K=485 standardních klinických markerů pro N=289 pacientů) vyžaduje aplikovat statistické postupy jako by šlo o hromadné zpracování dat. V příspěvku bude představena logistika tohoto zpracování vycházející z metodik etablovaných v minulosti na oddělení Biostat při 1. LF UK Praha s ukázkou hlavních výsledků. Při zpracování takto poměrně rozsáhlého klinického sou- boru dat můžeme používat zavedené statistické metodologie (One-Way resp. Two-Way ANOVA pro opakovaná měření nebo χ^2-testy nezávislosti v kontingenčních tabulkách), které však musíme redukovat na několik málo nejefektivnějších třídění. Na jejich základě pak analyzujeme výstupní sestavy statisticky významných p-hodnot pro řadu simultánních a odvozených marginálních testů.

Klíčová slova

ANOVA, chí-kvadrát analýza nezávislosti a homogenity v kontingenč- ních tabulkách, testy normality, hromadné zpracování dat, psoriáza, léčba psoriázy, biologika

1 Popis problému – cíle prezentace

Psoriáza neboli lupénka je onemocnění kůže, které postihuje až 4.8% světové populace [1]. Jedná se o neinfekční zánětlivé onemocnění zprostředkované T-buňkami charakterizované dysregulací našeho imunitního systému [2]. Je to multifaktoriál- ní nemoc, kde genetika hraje velkou roli. Postižení obvykle neo- hrožuje pacienty na životě, mnoho splývající odlupovájící

plaky však může i velmi znepříjemňovat nemocným život. Pokožka může být poškozena v malém, ale také velmi velkém rozsahu až do 100% tzv. klinický obraz erytrodermie. Kromě kůže mohou být postiženy také nehty na nohou i na rukou, ale také klouby.

V návaznosti na rozsah poškození jsou pacienti podrobování různým typům léčby. U méně závažných forem psoriázy bývá aplikována *lokální léčba* (masti, gely, tělová mléka apod.). Její výhodou je dobrá tolerance, minimální systémová absorpce a snížení rizika možných systémových nežádoucích účinků. U závažnějších postižení se může zvážit tzv. *konvenční systémo- vá léčba*, která se prostřednictvím tablet nebo injekcí rozvádí krevním oběhem do celého orgamismu (obvykle je podáván methotrexát, cyklosporin nebo acitretin). U pacientů selhávají- cích na takovou léčbu, nebo kteří takové preparáty netolerují či jsou u nich kontraindikovány, se může zvážit eskalace terapie na *biologickou léčbu*, která je zatím považována za nejúčinnější dostupnou terapii [3]. Biologika jsou produkována technologií rekombinantní DNA, zaměřené na specifické cíle imunopa- togenní dráhy nemoci. Jedná se o nejmodernejší formu léčby psoriázy. Vzhledem k jejií vynikající účinnosti, lékaři předepisují více těchto látek a dříve v procesu onemocnění. Bez důsledných a dlouhodobých studií bezpečnosti těchto látek se však začínají objevovat pozdní publikace o závažných nežádoucích účincích [4]. Právě na jejich výskyt při biologické léčbě byl zaměřen vý- zkum MUDr. Marquese a doc. Palucha, Ph.D., MBA na Dermato- logické klinice Nemocnice Na Bulovce, který zde v letech 2015- 17 shromáždil výsledky vyšetření pro soubor N=289 pacientů [5,6].

V rámci tohoto příspěvku jsou shrnuty informace vztažené k metodice a způsobům hromadného zpracování dat o těchto pacientech, které – přestože nejde o typická „big data" – překračují svým rozsahem rámec běžných klinických studií. Soubor o pacientech s psoriázou obsahoval K=489 diagnostických a medicínských markerů různého typu, což vyžaduje aplikaci sofistikovaných zpracovatelských postupů, jejichž finálním účelem musí být oddělení statisticky významných výsledků od těch nevýznamných. Hlavní koncepty a logistika statistického zpracování je shrnuta ve statích 2 a 3. Výsledky pro klinické závěry jsou referenční formou a spíše jen pro ilustraci uvedeny v závěrech (ve stati 4).

2 Pacienti s psoriázou

Data o pacientech s psoriázou byla uspořádána do jedné velké excelovské tabulky: markery ve sloupcích byly nejprve řazeny chronologicky (tak jak byly pořizovány nejprve při vstupních a potom pětkrát s půlroční periodou opakovaných systema- tických prohlídkách); v řádcích tabulky bylo všech N=289 pa- cientů uspořádáno do skupin podle tří základních typů léčby *(1-lokální, 2-systémové a 3-biologické)*, a pro biologickou léčbu dále v členění podle individuálních biologik (tzn. medikací se specifickými názvy: *4-etarnecept; 5-adalimumab; 6-infliximab; 7-ustekinumab; 8-secukinumab*).

V rámci vstupního vyšetření byla u pacientů s psoriázou kromě běžných demo-, fyzio- a anamnestických znaků (jako věk, pohlaví, vzdělání, výška, hmotnost, krevní tlak, fototyp, kožní anamnéza, délka manifestace psoriázy v letech apod.) vyšetřena i řada méně standardních ukazatelů (např. možnost stresových faktorů v rodině i v zaměstnání, rodinná anamnéza výskytu psoriázy, infekce, virózy, hormonální změny, obezita, konzumace alkoholu, koření, kouření a detailní info o minulých a stávajících nemocech pacientů). Sada vstupních 160ti marke- rů dotazovala u pacientů dosavadní užívání řady konkrétních léčebných přípravků (antibiotika, antidepresiva, beta-blokátory, diuretika, statiny, NSA), včetně již výše zmíněných v té době pěti nejvýznamnějších biologik s délkou jejich užívání v měsících. Po zařazení pacientů podle stanoveného typu léčby bylo v rámci pěti pravidelných půlročních prohlídek vedle obligát- ních vyšetření (PASI [Psoriasis Area Severity Index]; BSA [odhad celkového povrchu těla], hmotnost, krevní tlak) ověřováno spektrum přibližně 20ti nežádoucích účinků léčby, včetně nedávných infekcí, užívání specifických antibiotik a na dvacet dalších standardních biochemických markerů. Většina těchto indikátorů byla shledána (a jejich hodnoty naměřeny) v rámci všech opakovaných klinických vyšetření.

3 Logistika hromadného zpracování dat

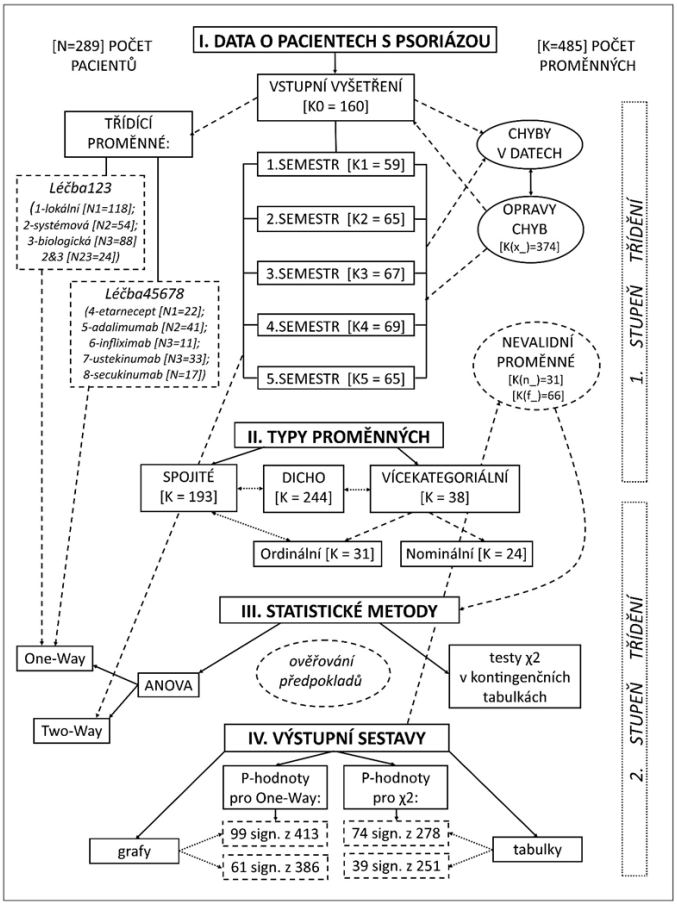
3.1 Verifikace a kontrola dat

První fází statistického zpracování musí být „verifikace a kontro- la dat“. Se zvětšujícím se

rozsahem souboru samozřejmě vzrůstá riziko chyb vzešlých již ze samotného pořizování dat. Nejefek- tivněji lze chyby tohoto typu nalézt načtením do statistického programu a pečlivě prohlédnout výpis hodnot všech sledova- ných markerů. Často se tyto chyby projevují špatně kvalifiko- vaným typem proměnné, než který bychom např. u numerické proměnné očekávali (a program ji mylně interpretuje jako *tex- tovou* nebo *datovou* proměnnou). Anebo se chybové hodnoty identifikují jako odlehlá pozorování (když v uspořádaném vý- pisu hodnot jedné proměnné nalezneme hodnotu např. o řád vyšší nebo nižší než u většiny ostatních pacientů) – obvykle jde o špatně umístěnou desetinnou čárku či tečku. V některých případech mohou být data zatížena měřícími chy- bami diagnostických přístrojů (když je měřící přístroj nevhodně nakalibrován, systematicky usekává např. všechny vysoké nebo nízké naměřené hodnoty). U některých markerů mohou být ale i odlehlá pozorování validně naměřenými hodnotami. Pro tyto situace je vhodné data přeuspořádat tak, aby stejné markery pořízené při opakovaných vyšetřeních byly v datovém souboru umístěny vedle sebe. A někdy je třeba také ohlídat, zda všechny hodnoty v primárním datovém souboru typované jako nuly jsou „skutečně platné-funkční nuly“ anebo zda na jejich místě nemají být spíše vynechané-prázdné hodnoty. (V souboru pacientů s psoriázou může být takovým příkladem proměnná „Počet dosavadních hospitalizací“, která nemá faktický význam u pacientů „s žádnou hospitalizací“ – takže formální nuly by mohly vést ke zkresleným interpretacím.). Někdy jsou data v Excelu pořízena tak, že je zapotřebí un block vyměnit mnoho omylem natypovaných desetinných teček za čárky – některé chyby a překlepy ale nelze na úrovni primárního datového souboru opravit jinak než individuálním překliknutím v rámci každé buňky zvlášť. Pro datovou tabulku obsahující více než 100 000 buněk, jako byla ta pro soubor pso- riatických pacientů, je ale takové řešení nepoužitelné. Kvalitní zpracovatelské pakety mají naštěstí systémové prostředky, kte- ré dokáží převést všechny hodnoty proměnných typu text, kte- ré lze interpretovat jako ‘čísla’, na hodnoty nových *numerických proměnných*. Tímto nástrojem fungujícím pod systémem SPSS muselo být v souboru pacientů s psoriázou opraveno téměř 3/4 markerů, než se podařilo převést vstupní excelovský soubor do standardně zpracovatelného formátu. Tato fáze přípravy dat ob- náší opakovanou kontrolu výpisů základních popisných statistik až po výpis všech individuálních hodnot pro všechny proměnné na úrovni 1. stupně třídění.

3.2 Identifikace typů proměnných

Druhá fáze statistického zpracování se týká „identifikace typů proměnných s ohledem na možnosti budoucího metodického zpracování". Obecně platí, že se zvyšujícím se rozsahem statistického souboru musí zpracovatel-statistik počítat s čím dál tím menším rejstříkem využití dnes již pestrého spektra použi- telných statistických metod. Příprava dat i finální tabulkové vý- stupní sestavy budou totiž vyžadovat spoustu nadstandardního zpracovatelského času. Navíc každá chyba při zpracování (vyne- chání některé proměnné nebo překlepnutí v názvu proměnné při práci s rozsáhlým seznamem systematicky zpracovávaných proměnných) může obnášet velmi nepříjemnou časovou újmu. V rámci souboru pacientů s psoriázou byly postupně identifikovány všechny základní typy proměnných – I/ *spojité* (s po- tenciálně libovolnými hodnotami měřených markerů diskreti- zovaných pouze zaokrouhlovací chybou – v celém souboru bylo těchto proměnných nalezeno 193); - II/ *kategoriální* (nabývající dvou nebo více konečných diskrétních hodnot – těch více než dvoukategoriálních bylo v souboru nalezeno 38). Za speciální případ obou těchto typů můžeme považovat dichotomické proměnné (nabývající právě dvou numerických hodnot – v cel- kovém počtu 244). Přitom vícekategoriální proměnné mohou být dvou typů - IIa) *ordinální* (hodnoty v kategoriích jsou vze- stupně uspořádané a každá vyšší hodnota reprezentuje určitý vyšší stupeň-úroveň daným markerem měřeného kritéria; lze je tedy interpretovat jako spojité i kategoriální proměnné – v sou- boru jsme jich nalezli celkem 31); – IIb) *nominální* (hodnota v ka- ždé jednotlivé kategorii má pouze kvalitativní význam a nijak nesouvisí s hodnotami v ostatních kategoriích – celkově 24). Pro snadnější práci s proměnnými v rozsáhlejších souborech je vhodné připojit před všechny typicky kategoriální proměnné kupř. symbol „c_", před dichotomické symbol „d_" apod. U kategoriálních proměnných vzrůstá pracnost hromadného zpracování ještě tím, že všechny individuální hodnoty kategorií musí být opatřeny popiskami. Tyto informace je nutné natypovat do příslušných segmentů zpracovatelského programu, pro- tože jinak by se výstupní třídící sestavy tabulek staly nepřehled- né. Totéž platí o prezentaci i interpretaci modelů založených na třídění vyšších stupňů. Za úspornější můžeme v tomto smyslu považovat výstupy po spojité proměnné, kde se prostřednictvím již předzpracovaných *průměrů* (nebo také *mediánů*) získá vlastně jedna dimenze formálního třídění navíc. Potom lze efek- tivně prezentovat ještě třídění na dalším stupni (zde např. pro Two-Way ANOVA s faktorem opakovaných měření).



Obrázek 1 – Logistika hromadného zpracování souboru dat o pacientech s psoriázou (distribuce počtů pacientů a počtů proměnných podle nejdů- ležitějších skupin)

3.3 Výběr statistických metod

Správná kvalifikace typů proměnných je zásadní pro třetí fázi zpracování datového souboru, kdy kvalifikujeme jednotlivé proměnné pro„použití specifických statistických metod". V kon- textu typologie proměnných představené výše půjde zjevně buď o aplikaci statistických procedur použitelných – I/ na spo- jitá data; - II/ na data kategoriální. Za standardní pro případ I/ považujeme rozsáhlé spektrum modelů ANOVA (pro normálně rozdělené náhodné veličiny, včetně tzv. generalizovaných ANO- VA pro více speciální spojité distribuce proměnných), v případě velkého množství markerů se a priori omezujeme na One-Way ANOVA. U kategoriálních markerů ad II/ budeme povětšinou vycházet ze standardní metodiky χ^2-testů nezávislosti a ho- mogenity v aplikaci na dvojrozměrné kontingenční tabulky, které statistický program umí vytvořit pro každou vybranou

dvojici kategoriálních proměnných. V rámci obou metodik jsme se u pacientů s psoriázou omezili na třídění podle dvou nejvýznamnějších faktorů – A) podle tří základních *typů léčby* (identifikovaných v rámci proměnné *Léčba123*); - B) podle individuálních *biologik* (pouze při systémové léčbě v rámci pětihod- notové proměnné *Léčba45678*).

Pro dichotomické proměnné můžeme v principu použít obou výše zmíněných přístupů k analýze: pro případ ad I/ interpretu- jeme výsledky u nula-jedničkových proměnných jako„procenta jedniček"; v případě ad II/ interpretujeme testy χ^2-*nezávislosti* spíše jako testy *homogenity řádkových* nebo *sloupcových pro- cent*). Rovněž ordinální proměnné lze obvykle analyzovat meto- dikou ANOVA i prostřednictvím testů χ^2, pro nominální markery lze však použít pouze testy χ^2. V průběhu celého „hromadného zpracování" bychom však měli hlídat, zda nejsou systematicky *porušovány základní teoretické předpoklady, tzn.* – I/ pro ANOVA *normalita* nebo alespoň *středová jednovrcholovost* empirických distribučních rozdělení; - II/ pro testy χ^2 bychom zase měli kon- trolovat, zda máme v tříděných tabulkách *dostatečně velké em- pirické četnosti* (přibližně 95% *četností očekávaných* při hypotéze nezávislosti by mělo být „≥5").

Pro finální statistické zpracování musí být tedy data uspo- řádána tak, aby proměnné podléhající spojité ANOVA byly seskupeny v rámci jednoho samostatně stojícího „seznamu proměnných" a data vstupující do χ^2-analýz do jiného (z výše uvedeného je zřejmé, že některé proměnné se v těchto sezna- mech mohou vyskytovat duplicitně). Na sofistikované testování normality u spojitých proměnných nezbývá u rozsáhlých dato- vých souborů obvykle moc času (pro proměnné, u kterých se hypotéza o normalitě zamítá, by mohla být aplikována ještě specifická „transformace k normalitě" anebo uplatňovány jiné např. *neparametrické* alternativy k ANOVA). Podobně by i tabul- ky s nepostačujícími četnostmi pro legitimní použití *asymptotic- kých* χ^2-testů měly být komprimovány na menší tzn. až třeba na úroveň tabulek čtyřpolních.

3.4 Finalizace výstupních sestav

Pokud by nyní panovala představa, že po úspěšném průchodu navolenými statistickými procedurami stačí jen programem vygenerované výstupní sestavy vyexportovat a poslat konco- vému odběrateli, je bohužel rovněž mylná. Zadavatel analýz se totiž musí především ve výstupních sestavách „vyznat". Za tímto účelem musí tedy zpracovatel-statistik data znovu vyexpor- tovat (obvykte do Excelu) a na úrovni rozsáhlých tabulkových výstupů zvýraznit nejvýznamnější výsledky (nejlépe barevným podbarvením). Ve statistických sestavách lze obvykle nejuni- verzálněji podbarvit *statisticky významné p-hodnoty*, případně testové statistiky, na nichž jsou p-hodnoty založeny. (V Excelu lze pro tyto účely velmi výhodně využít prostředků tzv. *podmí- něného formátování.*) Přitom p-hodnot je ve statistických out- putech celá řada, takže prezentace by měla být přizpůsobena hierarchii významnosti testovaných hypotéz (*od simultánních* F-testů v ANOVA po *mnohonásobná srovnávání* a od *souhrnných* χ^2-testů nezávislosti po analýzu reziduí v jednotlivých buňkách *kontingenčních tabulek*).

Teprve na úrovni výstupních sestav jsme však obvykle schop- ni posoudit i validitu jednotlivých vstupních proměnných. Shle- dáme, že některé výpočty pro některé proměnné ze statistic- kých sestav zcela vypadnou, v jiných sestavách, někdy pro jiné proměnné se nevytiskou např. p-hodnoty. Povětšinou toto sou- visí s tím, že příslušná proměnná má statisticky nepodchytitelný „zdroj měnlivosti" tzn. že příslušná závisle proměnná má již na úrovni primárního souboru identické hodnoty (obvykle samé nuly) nebo obsahuje kromě nul třeba jen jedinou jedničku (což u některých statistických procedur vadí), anebo taková situace nastane při některém základním třídění. V těchto situacích je tedy vhodnější příslušné proměnné ve vstupních seznamech specificky identifikovat: proměnné s konstanstními hodnotami ve sloupcích opatřit třeba předponou „n_" (takových „nulových" markerů bylo v souboru nalezeno 31) a např. nula-jedničkové (dichotomické) proměnné, které obsahují nanejvýš 1-3 jedničky (a ostatní nuly) identifikovat s předponou „f_" (v souboru nale- zeno 66 takových potenciálně „falešných" proměnných). Pak již se bezpečněji zorientujeme ve výstupních sestavách, protože pro všechny tyto proměnné bychom logicky „měli dostávat" nesignifikantní výsledky. Pokud statistický program dokáže systematickým způsobem prezentovat statisticky významné výsledky i prostřednictvím grafů, jsme již téměř u konce. Profesionální statistické pakety vhodné pro

systematické analýzy (SPSS) však obvykle nepro- dukují grafické výstupy v kvalitě vhodné pro prezentační či pu- blikační účely a naopak – softwary vhodné pro finální grafické prezentace (např. program STATISTICA) zase neumožňují plně automatizovat reprezentativní grafické přílohy. Potom se tedy musíme uchýlit k vizuální prezentaci alespoň těch statisticky nejvýznamnějších výsledků, které pořídíme za cenu individuál- ního zaklikávání standardních tlačítkových sestav. Je zajímavé sledovat výsledky One-Way ANOVA na grafech pro markery vzešlé z pololetně se opakujících vyšetření. Pro takováto data (zejména pokud byla úplná) jsme pak ještě využili grafické vý- stupy pro modely Two-Way ANOVA (s fixním faktorem *Léčba123* resp. *Léčba45678* a druhým pro pětici po půlroce opakovaných měření). Ale pokud si přejeme kupř. z programu STATISTICA transformovat do Excelu ještě speciální tabulkové výstupy, mu- síme k tomuto účelu použít speciálně vytvořené makro (!).

4 Diskuse a závěry

Analýza výše popsaného souboru pacientů s psoriázou byla provedena pragmatickými metodickými postupy a nástroji, jak přísluší náležitě a pečlivě zdokumentované kohortní studii založené na vstupním a následně opakovaných vyšetřeních pa- cientů. Rozsah studie přesahuje jiné klinické studie především šíří spektra naměřených markerů, nikoli počtem pacientů, který se pro dané účely jeví jako postačující. Studie byla cílena přede- vším na nežádoucí účinky moderní biologické léčby ve vztahu k tradičným léčbám (lokální a konvenční systémová). Výběr pa- cientů pro jednotlivé typy léčby (identifikace prostřednictvím tříhodnotové proměnné *Léčba123*) byl proveden s ohledem na závažnost postižení pacientů psoriázou – v korespondenci s ty- pem léčby byli pacienti podrobováni odpovídajícím léčebným terapiím, jmenovitě u biolologické léčby aplikaci pěti léčebných přípravků (jejich identifikace v rámci druhé třídící proměnné *Léčba45678*).

Všechny markery obsažené v databázi psoriatických pacientů byly (po pečlivé klasifikaci do dvou obsáhlých seznamů podle svého typu) vytříděny podle obou třídících proměnných v rám- ci One-Way ANOVA (anebo Two-Way pro opakovaná měření) resp. do dvourozměrných kontingenčních tabulek. Na úrovni simultánních testů (F-testů pro One-Way resp. souhrnných tes- tů χ^2-nezávislosti) jsme získali 24,0% resp. 26,6% statisticky vý-

znamných p-hodnot (99 z celkově 413 resp. 74 z 278) pro třídění podle *Léčba123* a 15,8% resp. 15,5% statisticky významných p-hodnot (61/376 resp. 39/251) pro třídění podle *Léčba45678*. Korespondence statistických významností mezi One-Way ANO- VA a testy χ^2 se potvrdila zejména na úrovni dichotomických proměnných, kde nelze předpokládat nesymetrické porušení teoretických vstupních předpokladů pro aplikaci obou princi- piálně odlišných statistických metodik. (Nižší podíl signifikant- ních testů při třídění podle *Léčba45678* si vysvětlujeme jednak nižším vstupním počtem n=112 pacientů léčených pouze biolologickou léčbou; navíc třídění podle pěti typů biologik je kvalitativně na jiné úrovni než podle typů léčby pro pacienty s různě závažným rozsahem postižení.)

Z hlediska zařazení pacientů do skupin podle typu léčby jsme shledali následujícíc statisticky nejvýznamnější rozdíly – a) podle pohlaví, věku a také výšky pacientů; - b) podle vstupní anamnézy (doby manifestace nemoci, frekvence výskytu viróz, infekcí, hormonálních změn, hyperurikémie, depresí apod.); - c) podle častějšího užívání antibiotik (indikace v širším spektru) a dalších speciálních léků proti psoriáze; - d) podle řady nežá- doucích účinků biologické léčby; - e) stopově na úrovni několika biochemických markerů. Povětšinou se indikace ad c)-e) vyskytovaly při pololetních prohlídkách opakovaně. Ale řada jiných se u psoriatických pacientů systematicky nevyskytovaly.

Výsledky studie navazují na klinické zkušenosti a v odborné literatuře již publikované závěry o účincích a bezpečnosti růz- ných typů léčby psoriázy pro různé skupiny pacientů a doplňují je o informace týkající biologické léčby. V tomto příspěvku bylo zejména poukázano na to, že i v rámci víceméně rutinního sta- tistického zpracování dat můžeme verifikovat řadu hodnotných a možná i inovativních výsledků, pokud se zpracování provádí pečlivě a systematicky. Další medicínské zhodnocení těchto vý- sledků je připraveno v podrobnějších studiích [7], kde je věno- ván velký prostor zejména diskusím o zařazení výše nastíněných výsledků do kontextu mezinárodně publikovaných výzkumů.

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Výskyt infekčních komplikací při biologické léčbě psoriázy

Boháč P. Marques E., Jůzlová K., Jirásková-Zákostelská Z., Šmerhovský Z., Hercogová J.

Čes. Dermatovenerol., 2016, 6, č. 4, s. 232–237

SOUHRN

Dermatovenerologická klinika 2. LF UK a Nemocnice Na Bulovce je jedním z 18 center biologické léčby psoriázy v České republice. Zabývá se terapií biologiky nejen těžké, chronicky stacionární psoriázy, ale i jiných kožních onemocně- ní, jako jsou hidradenitis suppurativa a chronická spontánní urtikarie. Pro léč- bu chronicky stacionární psoriázy jsou v ČR v současnosti registrovány biologic- ké a biosimilární přípravky adalimumab, etanercept, infliximab, ustekinumab a secukinumab. Retrospektivní studie shrnuje roční sledování infekčních komplikací u 98 pacientů léčených biologi- ky v porovnání s kontrolní skupinou. Uvedená data ukazují na celkově vyšší podíl pacientů bez infekčních komplikací u pacientů léčených ustekinumabem než u pacientů léčených TNF-α inhibitory. Nebyly zjištěny rozdíly výskytu infekčních komplikací u skupiny pacientů na biologické léčbě a u kontrolní skupiny.

KLÍČOVÁ SLOVA

psoriáza • biologická léčba infekce • komplikace

SUMMARY

Bohac P., Marques E., Juzlova K., Jiraskova-Zakostelska Z., Smerhovsky Z., Hercogova J. Occurrence of infectious complications in bio- logical treatment of proriasis Dermatovenereologic clinic of the 2nd Faculty of Medicine of the Charles University and the Na Bulovce Hospital is one of the 18 centres offering biologi- cal treatment of psoriasis in the Czech Republic. It deals with therapy of not just severe, chronically stationary psoriasis but also of other cutaneous diseases tre- atable by biologics, such as hidradenitis, suppurativa and chronic spontaneous urticarial. There are several biological preparations registered in the Czech Republic for treatment of chronic statio- nary psoriasis: adalimumab, etanercept, infliximab, ustekinumab and secukinu- mab. The retrospective study summari- ses year-long monitoring of infectious complications in 98% of patients treated with biologics, compared to the control group. The data that has been collected shows a higher ratio of patients without infectious complications in patients tre- ated with ustekinumab, compared to pa- tients treated with TNF-alpha inhibitors. There were no differences discovered in occurrence of infectious complications between the group of patients treated with biologics and the control group.

KEY WORDS

biological treatment of psoriasis • biological preparations • infectious complications

PSORIÁZA

Psoriáza je chronické zánětlivé, imunitně podmíněné kožní onemocnění s množ- stvím různých klinických manifestací. Prevalence onemocnění se pro populaci v Evropě i USA udává mezi 1,5–4,7 %.[1, 2] V poslední době se diskutuje vliv kožního mikrobiomu na etiopatogenezi psoriázy. Jak vyplývá z recentních studií, složení kožního mikrobiomu psoriatických lézí se liší od mikrobiomu nepostižené kůže u pacientů s psoriázou i od mikrobiomu zdravých jedinců.[3, 4] Právě odlišnost re- zidentního bakteriálního osídlení kůže by mohla být klíčová v rozvoji psoriázy. Psoriáza je onemocnění nejen kůže a kož- ních adnex, ale mohou být postiženy i klouby ve formě psoriatické artritidy. Kromě toho je těžká forma psoriázy nyní chápána jako systémové zánětlivé one- mocnění se zvýšeným rizikem vzniku kardiovaskulárních a gastrointestinálních chorob, s vyšším rizikem vzniku poruchy glukózového a lipidového metabolismu a vznikem metabolického syndromu.[2, 5, 6] Tyto komorbidity jsou zodpovědné za zdra- votní komplikace a sníženou kvalitu života pacientů. Kvůli psoriáze a následným ko- morbiditám se pacienti dožívají v průměru o 3–4 roky méně než jedinci bez tohoto onemocnění.[7] Z výše uvedeného vyplývá nutnost léčby (zejména) těžkých forem psoriázy.

BIOLOGICKÁ (CÍLENÁ) LÉČBA PSORIÁZY

Podrobné zkoumání intercelulárních sig- nálních molekul a jejich vzájemných in- terakcí dalo možnost vzniku cílených lé- čiv, která působí na subcelulární úrovni. Při patogenezi psoriázy mají klinicky nej- větší význam prozánětlivé cytokiny IL-12, IL-17, IL-23, TNF-α. Proti těmto signálním molekulám jsou namířeny v současnosti v ČR dostupné biologické léky (inhibují jejich biologickou aktivitu).

Díky svému selektivnímu působení vy- kazují biologika nižší riziko vzniku ne- žádoucích účinků než jiné léky indiko- vané k léčbě těžké formy psoriázy, jako jsou metotrexát, acitretin nebo cyklo- sporin A.[8]

Vysoká účinnost biologické léčby těžké formy psoriázy a psoriatické artritidy je ale také doprovázena některými nežádou- cími účinky. Pacienti léčení biologickou léčbou jsou více náchylní k závažným infekcím, mezi další komplikace patří poruchy krvetvorného systému, riziko vzniku neoplazií, poruchy nervového, kardiopulmonálního, gastrointestinál- ního, imunitního systému a psychiat- rické choroby. Z tohoto důvodu musí být pacienti důkladně vyšetřeni před léčbou,

v průběhu léčby i po jejím ukončení (eliminace léčiva z organismu může trvat i několik měsíců).[9, 10, 11, 12, 13] Léčba by neměla být zahájena u pacientů s aktivním, nekontrolovaným infekčním onemocněním a v případě již probíhající léčby by měli být pacienti pečlivě sledová- ni, diagnostikováni a včas léčeni. TNF-α je jedním z mediátorů zánětlivé reakce, hraje roli v buněčné imunitní reakci a je důležitý pro eliminaci intracelulárních patogenů.[9] U pacientů léčených TNF-α inhibitory byly popsány závažné infekce způsobené baktériemi, mykobaktérie- mi, plísněmi či parazity.[10] Při rozvoji těžší infekce je vhodné biologickou léčbu přerušit do doby zvládnutí infekčního onemocnění. U pacientů na biologické léčbě je kontraindikováno očkování ži- vými vakcínami.

Kromě výše uvedených infekcí byly popsány při terapii TNF-α inhibitory případy reaktivace tuberkulózy a hepatitidy B. Vzhledem k možnosti roz- voje tuberkulózy je u pacientů nutné vyloučit aktivní či latentní formu tu- berkulózy a vyšetření na tyto infekce pravidelně v průběhu léčby opakovat. V klinickém hodnocení přípravku usteki- numab nedošlo u pacientů s latentní tu- berkulózou, kteří byli souběžně léčeni izoniazidem, k rozvoji tuberkulózy.[12] Při pozitivitě výsledku testu na HBV je do- poručeno konzultovat odborné pracoviště zabývající se terapií této infekce a pacien- ty v průběhu léčby důsledně monitorovat k vyloučení reaktivace infekce.[9, 10, 11]

V rámci klinických studií s jednotlivými léčivy byly zkoumány i infekční komplikace (Tab. 1).

METODIKA

Studie se věnuje výskytu infekčních komplikací během jednoho roku biologické léčby u našich pacientů. Analýza získaných dat je založena na srovnání souboru zahrnujícího pacienty rozdělené do dvou skupin podle typu biologických léčiv (TNFα inhibitory a inhibitor IL-12/-23) a kontrolní skupiny pacientů bez imunosupresivní léčby. Zjištění jsou rovněž konfrontována s daty uvedenými v jednotlivých SPC biologických přípravků. Jedná se o zpracování souboru pacientů z jednoho centra biologické léčby v České republice.

Za sledované období duben 2015 až březen 2016 byly studovány dekurzy nemocných provedené během pravidelných kontrol pacientů. Byly vyhodnoceny zaznamenané zdravotní komplikace pacientů. Do kontrolní skupiny byli zařazeni ambulantní pacienti, kteří navštívili naši všeobecnou ambulanci v průběhu září 2016, a to bez ohledu na kožní onemocnění. Tito pacienti vyplnili dotazník cílený na výskyt infekcí v uplynulém roce. Následně byly vyřazeny dotazníky pacientů, kteří v době vyplnění dotazníku užívali imunosupresivní terapii. Data byla rovněž porovnána s údaji uvedenými v SPC jednotlivých biologických léčiv. K testování statistických hypotéz byly použity chi-kvadrát test a Fischerův exaktní test. Síla asociace mezi sledovanými parametry byla vyjádřena jako odds ratio a k tomuto ukazateli byly vypočteny příslušné 95% intervaly statistické spolehlivosti.

SOUBOR PACIENTŮ

Vesledovaném období 12 měsíců (duben 2015 až březen 2016) bylo studováno celkem 98 pacientů, z toho 32 žen a 66 mužů. K 1. 4. 2015 byl průměrný věk celého souboru 46,3 roku, nejmladší pacientce bylo 15 let, nejstarší pacientce bylo 80 let. Průměrná doba biologické léčby (nezahrnuje pacienty, kterým byla biologická léčba nasazena v průbě- hu sledovaného období) činila 62,4 mě- síce (min. 3 a max. 119 měsíců).

Z celkového počtu 98 pacientů bylo léčeno 22 pacientů etanerceptem, 35 pacientů adalimumabem, 29 ustekinumabem, de- set infliximabem a dva secukinumabem – léčba těchto dvou pacientů byla zahájena v prosinci 2015, jejich výsledky nebyly pro- to dále statisticky zpracovávány. Z 29 pacientů léčených ustekinumabem bylo 17 mužů a 12 žen, průměrný věk pa- cientů byl 43,6 roku (min 21,7, max. 66,4 roku), průměrná délka biologické léčby těchto pacientů byla 4,11 roku (min. 0,3, max. 8 let), z 67 pacientů léčených TNF-α inhibitory bylo 47 mužů a 20 žen,

Tab. Infekční komplikace biologické léčby

adalimumab	velmi časté (≥ 1/10)	infekce dýchacích cest
	časté (≥ 1/100 až < 1/10)	systémové infekce, střevní infekce, infekce kůže a měkkých tkání (včetně paronychia, celulitidy, impetiga, ušní infekce, orální infekce, infekce močových cest, plísňové infekce)
	málo časté (≥ 1/1000 až <1/100)	neurologické infekce, oportunní infekce a tuberkulóza, oční infekce
etanercept	velmi časté (≥ 1/10)	infekce cest dýchacích, cystitidy, infekce kůže
	málo časté (≥ 1/1000 až < 1/100)	závažné infekce (včetně pneumonie, celulitidy, sepse a parazitárních infekcí)
	vzácné (≥ 1/10 000 až < 1/1 000)	tuberkulóza, oportunní infekce
infliximab	velmi časté (≥ 1/10)	virové infekce (např. chřipková onemocnění, infekce virem herpes simplex)
	časté (≥ 1/100 až < 1/10)	bakteriální infekce (např. sepse, celulitida, abscesy)
	méněčasté(≥ 1/1000až<1/100)	tuberkulóza, plísňové infekce, (např. kandidóza)
ustekinumab	časté (≥ 1/100 až < 1/10)	zubní infekce, infekce horních cest dýchacích, nazofaryngitida
	méněčasté(≥ 1/1000až<1/100)	celulitida, herpes zoster, virová infekce horních cest dýchacích
secukinumab	velmi časté (≥ 1/10)	infekce horních cest dýchacích
	časté (≥ 1/100 až < 1/10)	orální herpes
	méněčasté(≥ 1/1,000až<1/100)	orální kandidóza, tinea pedis, otitis externa

průměrný věk 47 let (min. 14,7, max. 80 let), průměrná délka biologické léčby 5,64 roku (min 0,25, max. 10 let). Průměrná délka léčby je počítána od zahájení samotné biologické terapie včetně případných změn biologických léčiv.

KONTROLNÍ SKUPINA

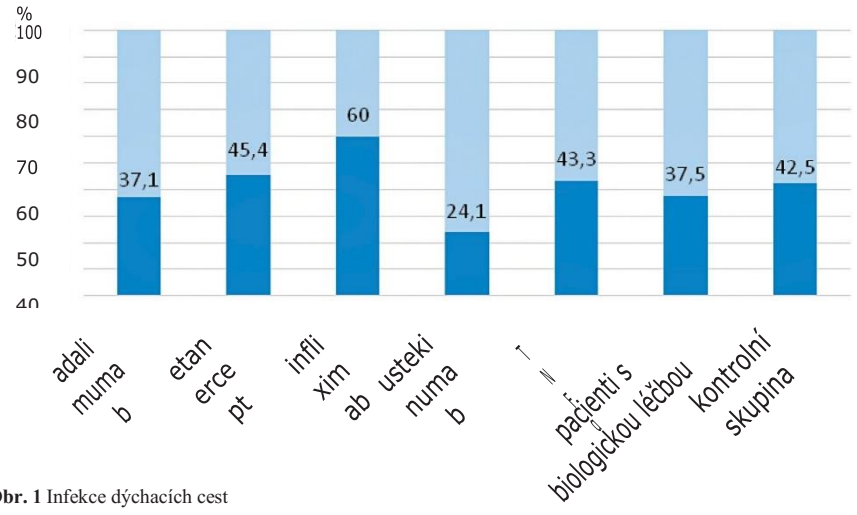
V anonymním dotazníkovém šetření byli osloveni pacienti Dermatovenerologické kliniky Nemocnice Na Bulovce. Celkem jsme obdrželi 100 vyplněných dotazníků, z tohoto množství bylo vyřazeno pět pacientů léčených imunosupresivy a jeden dotazník byl vyřazen pro zjevné nesrovnalosti udané pacientem. Zařazeno bylo 44 mužů (průměrný věk 47,2 roku, 9–78 let) a 51 žen (průměrný věk 42,7 roku, 8–97 let). Průměrný věk celého souboru byl 45,3 roku.

VÝSLEDKY

Nádory ani nově diagnostikovaná tuberkulóza se nevyskytly ani jednou.

INFEKCE DÝCHACÍCHCEST

Během 12 měsíců byla nejčastější zdravotní komplikací infekce dýchacích cest. Byly sem zahrnuty infekce horních i dolních cest dýchacích, nejčastěji se jednalo o rinofaryngitidu, tonzilitidu, tonzilofaryngitidu, laryngitidu, bronchitidu. Onemocnělo celkem 37 pacientů (37,5 % všech pacientů). Z toho bylo deset pacientů léčených etanerceptem (45 % pacientů léčených etanerceptem), adalimumabem 13 pacientů (37 % pacientů s adalimumabem), infliximabem šest pacientů (60 % pacientů s infliximabem), sedm pacientů ustekinumabem (24 % pacientů s ustekinumabem) a jeden pacient léčený secukinumabem. Jedenáct pacientů (11 %) mělo infekt dýchacích cest více než jednou. Onemocnělo celkem 29 pacientů léčených TNF-α inhibitory (tzn. 43,3 % pacientů léčených TNF-α). Četnost infekčních komplikací dýchacích cest byla vyšší u skupiny pacientů léčených TNF-α inhibitory než u skupiny léčených ustekinumabem, data se pohybovala na hranici statistické významnosti (OR = 2,4, 95% CI pro OR 0,4–6,38, p = 0,077). Infekci dýchacích cest v kontrolní skupině prodělalo celkem 40 pacientů (42,5 %). Nebyl prokázán statisticky významně rozdílný výskyt infekcí dýchacích cest u skupiny pacientů na biologické léčběoproti kontrolní skupině (OR = 0,83, 95% CI pro OR 0,46–1,47, p = 0,517). Srovnání procentuálního zastoupení pacientů s infektem dýchacích cest na jednotlivých biologických preparátech uvádí Obr. 1.



Obr. 1 Infekce dýchacích cest

INFEKCE MOČOVÝCH CEST

Z celkového počtu 98 pacientů, kteří měli za sledované období nasazenou biologickou léčbu, se vyskytla uroinfekce u tří pacientů (3 %), z toho dva pacienti byli léčeni adalimumabem a jeden ustekinumabem. Infekci močových cest v kontrolní skupině prodělalo deset pacientů (10,6 % pacientů), rozdíl výskytu infekcí močových cest u skupiny pacientů na biologické léčbě a u kontrolní skupiny je na hranici statistické významnosti (OR = 0,27, 95% CI pro OR 0,07–1,02 , p = 0,07).

LATENTNÍ TUBERKULÓZA

Za sledované období byla léčba pro výskyt pozitivního Quantiferonu přerušena u čtyř pacientů. U dvou došlo v uvedeném období k nové pozitivitě a dva pacienti měli nově pozitivní výsledek krátce před sledovaným obdobím a k 1. 4. 2015 měli přerušenou biologickou léčbu (za současné terapie isoniazidem). Všichni pacienti byli léčeni TNF-α inhibitory. Ve třech případech se jednalo o pacienty léčené adalimumabem (8,6 % pacientů), v jednom případě byl pacient léčený etanerceptem (4,5 % pacientů). Průměrná doba biologické léčby do výskytu pozitivního Quantiferonu byla 82,2 měsíce (min. 3 měsíce, max. 119 měsíců), u všech pacientů byla podle pneumologické indikace biologická léčba přerušena a byla zahájena terapie isoniazidem.

NÁDOROVÁ ONEMOCNĚNÍ

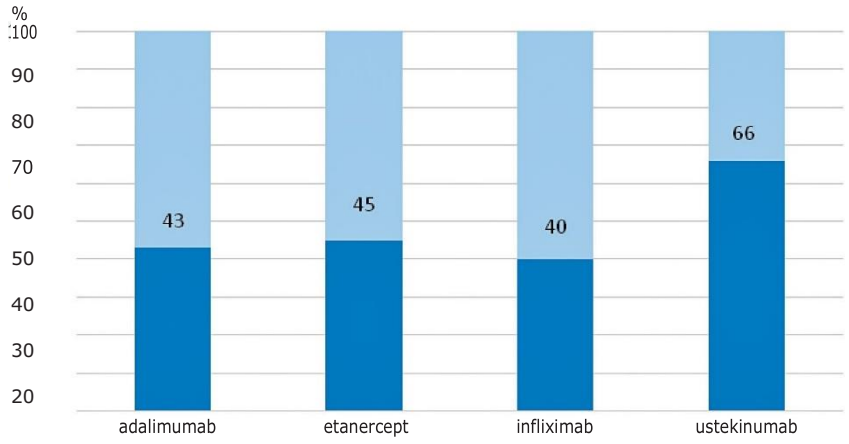
Dva pacienti ukončili biologickou léčbu z důvodu výskytu maligního onemocnění. U pacienta ve věku 66 let léčeného etanerceptem byl diagnostikován adenokarcinom prostaty za 98 měsíců od zahájení terapie. Pacientka na terapii ustekinumabem onemocněla invazivním karcinomem prsu ve věku 45 let, šest let po zahájení biologické léčby. Jiné zhoubné či nezhoubné nádory jsme u našeho vzorku pacientů nezaznamenali.

KOŽNÍ INFEKCE

Z kožních infekcí se u dvou pacientů vyskytly virové infekce – herpes simplex labialis s nekomplikovaným průběhem a u druhého pacienta terapeuticky špatně ovlivnitelné virové bradavice. Z kvasinkových infekcí bylo u jednoho pacienta diagnostikováno kandidové paronychium s nutností systémové antimykotické terapie. Jeden pacient byl léčen antibiotiky pro flegmónu palce dolní končetiny.
Z ostatních, méně častých infekčních komplikací, se u dvou pacientů vyskytl zánět dásní, u jednoho nemocného absces dutiny ústní, u jednoho lamblióza a u dalšího otitis media acuta, komplikovaná perforací bubínku s nutností následné myringoplastiky a hospitalizace.

LÉČBA ANTIBIOTIKY

Dalším sledovaným faktorem byla antibiotická terapie, která byla za sledované období užita u celkem 21 pacientů. Nejčastějším důvodem nasazení antibiotické terapie byla infekce dýchacích cest – celkem u 13 pacientů (62 % pacientů léčených antibiotiky). Dalšími důvody byla uroinfekce (2 pacienti), gingivitida (2 pacienti), absces dutiny ústní, otitis media acuta, lamblióza a v jednom případě byla antibiotika nasazena při stomatologickém zákroku. U jedné pacientky byla nasazena systémová antimykotická terapie pro kandidové paronychium. Antibiotika byla nasazena u tří pacientů léčených etanerceptem, u devíti pacientů léčených adalimuma-



Obr. 2 Pacienti bez infekčních komplikací

bem, u čtyř pacientů léčených infliximabem, u čtyř pacientů léčených ustekinumabem (tzn. u 23,9 % pacientů léčených TNF-α a u 13,8 % pacientů léčených ustekinumabem). Nebyl prokázán statisticky významný rozdíl četnosti antibiotické léčby u skupiny pacientů na TNF-α inhibitorech a ustekinumabu (OR = 1,92, 95% CI pro OR 0,58–6,35, p = 0,28). Za období 12 měsíců byla nasazena antibiotická léčba celkem u 31 pacientů kontrolní skupiny (32,9 %), rozdíl se pohyboval na hranici statistické významnosti (OR = 0,54, 95% CI pro OR 0,28–1,04, p= 0,066).

Z celkového počtu 98 pacientů bylo bez jakýchkoliv infekčních komplikací 49 pacientů (50 %), léčených etanerceptem bylo 10 (45 %), adalimumabem 15 (43%), infliximabem 4 (40 % pacientů), ustekinumabem 19 (66 % pacientů) ajeden pacient léčený secukinumabem (50%). Z celkového počtu 67 pacientů na TNF-α inhibitorech bylo bez infekčních komplikací 29 pacientů (43,3 %). Statisticky významně byl vyšší podíl pacientů bez infekčních kompli- kací u skupiny léčené ustekinumabem než u skupiny léčené TNFα inhibito- ry (OR = 0,4, 95% CI pro OR 0,16–0,99,
p = 0,041) (Obr. 2).

DISKUSE

Podle Souhrnu údajů o léčivých přípravcích (SPC) jednotlivých biologik jsou nejčastější infekční komplikace infekty dýchacích cest. Při terapii TNF-α inhibitory a secukinumabem se vyskytují velmi často (≥ 1/10), u ustekinumabu je udáván výskyt (≥ 1/100 až < 1/10). V naší studii byly nejčastějšími infekčními komplikacemi rovněž infekty dýchacích cest. U TNF-α inhibitorů byly infekce popsány u 43,3 % pacientů, u pacientů léčených ustekinumabem tomu bylo u 24 % pacientů, což u obou skupin odpovídalo četnosti výskytu ≥ 1/10.[9, 10, 11, 12]

Uroinfekce je podle SPC adalimumabu infekční komplikací častou (≥ 1/100 až < 1/10), SPC nezmiňuje data o hodnocení uroinfekcí u ustekinumabu. Náš záchyt dvou pacientů s uroinfektem (5,7 % pacientů léčených adalimumabem) odpovídá frekvenci časté (≥ 1/100 až < 1/10).[11]

V SPC adalimumabu je hodnocen výskyt latentní tuberkulózy jako málo častý (≥ 1/1000 až < 1/100), u etanerceptu jako vzácný (≥ 1/10 000 až < 1/1000). Za sledovaného období se latentní tuberkulóza objevila u 8,6 % pacientů léčených adalimumabem a u 4,5 % pacientů léčených etanerceptem. V obou dvou případech četnost odpovídala výskytu komplikace časté (≥ 1/100 až < 1/10).[11, 12]

Na základě naší zkušenosti nebyl prokázán statisticky významný rozdílný výskyt infekcí dýchacích cest u pacientů léčených biologickou léčbou v porovnání s kontrolní skupinou. Byl zaznamenán nižší výskyt infekcí dýchacích cestu u skupiny pacientů léčených ustekinumabem než u skupiny pacientů léčených TNF-α inhibitory, výsledky se pohybovaly na hranici statistické významnosti. Nebyl statisticky významně rozdílný výskyt infekcí močových cest při porovnání skupin biologik (TNF-α vs. ustekinumab) ani při srovnání skupin pacientů léčených biologickou léčbou a bez této terapie. Některá námi zjištěná data byla na hranici statistické významnosti. Při hodnocení pacientů bez infekčních komplikací byl prokázán statisticky významně nižší výskyt infekčních komplikací u skupiny pacientů léčených ustekinumabem ve srovnání s TNF-α inhibitory. Při interpretaci výsledků je nutno upozornit na delší dobu trvání biologické léčby a na vyšší průměrný věk pacientů na TNF-α inhibitorech.

Pacienti, kteří vyplnili dotazníky, byli pacienti naší všeobecné ambulance, kromě vyřazených pacientů s imunosupresivní terapií nebylo dále rozlišováno, pro jaké základní onemocnění vyhledali lékařskou péči. Z tohoto důvodu vzorek neodpovídá zcela běžné populaci.

ZÁVĚR

Výsledky této roční retrospektivní analý- zy dat včetně incidence výše uvedených infekčních komplikací je nutno hodnotit s přihlédnutím k nízkému počtu pacientoroků za sledované období. Uvedená data ukazují na celkově vyšší podíl pacientů bez infekčních komplikací u pacientů léčených ustekinumabem než u pacientů léčených TNF-α inhibitory. Nebyly zjištěny rozdíly výskytu infekčních komplikací u skupiny pacientů na biologické léčbě v porovnání s kontrolní skupinou.

Článek nemá ambice oponovat rozsáhlým, mnohaletým, často placebem kontrolovaným klinickým studiím, přesto by některá naše data mohla být podnětem k další práci zkoumající reálnou incidenci infekčních komplikací u pacientů s biologickou léčbou.

Na našem pracovišti probíhá sběr dalších dat, jejichž vyhodnocení, včetně zhodnocení dalších komplikací biologické terapie, budou obsahem příštích sdělení.

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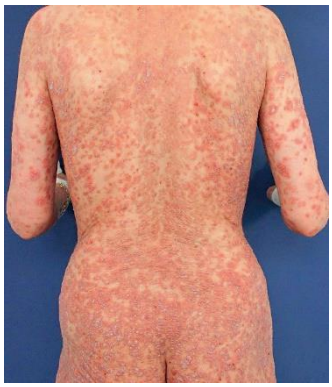
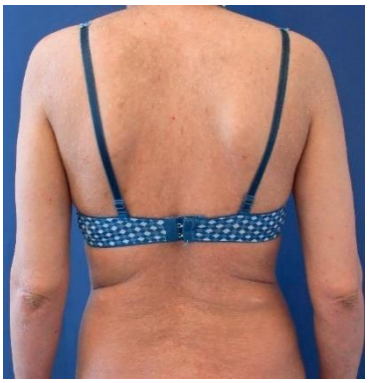
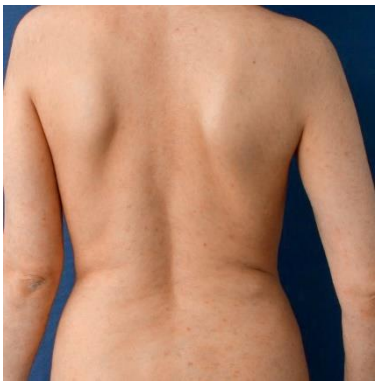


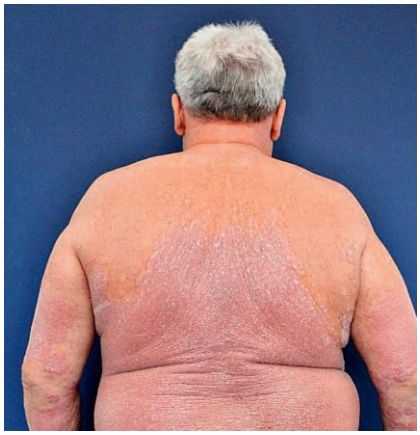
Pacientka č.1: před zahájením ustekinumabem



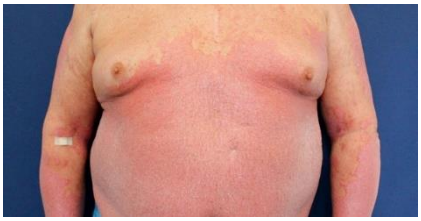
Pacientka č.1: dva měsíce po zahájení terapie



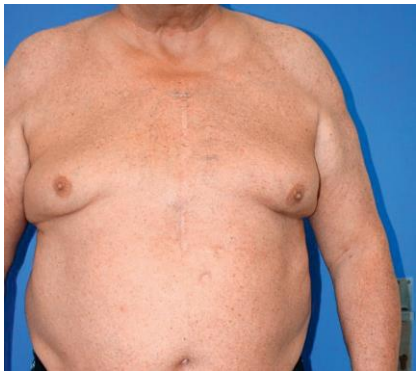
Pacientka č.1: 8 měsíců po zahájení ustekinumabem



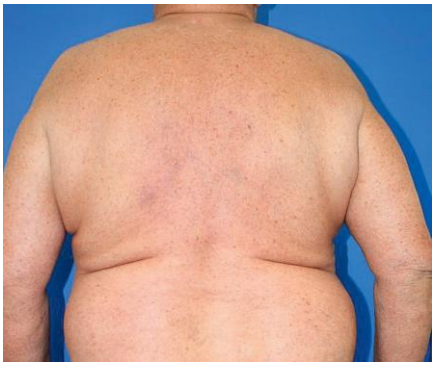
Pacient č.2: před zahájenímbiologické léčby (záda).



Pacient č.2: před zahájenímbiologické léčby (břicho).



Pacient č.2: 11 měsíců po zahájení infliximabu (břicho).



Pacient č.2: 11 měsíců po zahájení terapie infliximabem (záda)

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