CHARLES UNIVERSITY
Second Faculty of Medicine

Summary of doctoral thesis

Nežádoucí účinky biologické léčby psoriázy

Adverse events of biologic therapy in psoriasis

Emanuel Carvalheiro Marques

Prague, 2022

Disertační práce byla vypracována v rámci prezenčního studia doktorského studijního programu Farmakologie a Toxikologie na Ústavu Farmakologie, 2. lékařské fakulty Univerzity Karlovy.

Školitel: doc. MUDr. Zoltán Paluch, Ph.D., MBA, 1. lékařská fakulta, Univerzita Karlova, Praha, Česká republika

Konzultantka: prof. MUDr. Jana Třešňák Hercogová, CSc., MHA, IFAAD

Oponenti:

Obhajoba se bude konat před komisí pro obhajoby oborové rady .....
dne ..... v ..... od .....
hod. Předsedou komise pro obhajobu disertační práce byl jmenován:

Předseda oborové rady a garant doktorského studijního programu: prof. MUDr. Ondřej Slanař, PhD., 1. lékařská fakulta, Ústav Farmakologie, Univerzita Karlova, Praha, Česká Republika

Děkan fakulty: prof. MUDr. Marek Babjuk, CSc

Table of contents

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

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

Introduction

Psoriasis vulgaris is a chronic inflammatory skin disease with a prevalence estimated to be 1.5–4.7%. Severe psoriasis is nowadays seen as a systemic inflammatory disease with an increased risk of complications such as metabolic syndrome, cardiovascular and gastrointestinal disease (Votrubova et al., 2014) (Juzlova et al., 2016) (Lotti et al., 2010). These patients live roughly 3-4 years less than psoriasis-free individuals (de Oliveira et al., 2015). Understanding how different comorbidities and epidemiological factors are related to psoriasis severity can help estimating patients' clinical outcome.

Biologic agents (BAs) are considered the most effective type of therapy (Zweegers et al., 2016). Apart from clinical trials, there are few real-world consistent and solid 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). Moreover, often, patient populations included in clinical trials not always reflect those encountered in our daily clinical practise (Topaloğlu Demir et al., 2020). Thus, it is not always easy to select a BA instead of another to treat a specific patient. In this fashion, comparing the safety profile of different BAs in real life is essential to improve clinicians' decision making.

Hypothesis and objectives

Hypothesis

1. Assumption that severe psoriatic patients have a different patient history than patients with less severe disease
2. Assumption that BAs have a different safety profile than topical therapy or NBSA
3. Assumption that different BAs have different safety profiles

Objectives

1. To establish possible trigger and prognostic factors of severe psoriasis.
2. To compare the occurrence of adverse events in three groups of psoriatic patients on different therapeutic regimens, aiming to determine the type of therapy with the lowest safety profile.
3. To investigate and compare possible differences in the occurrence of adverse events in individual groups of patients with psoriasis treated with different biologic agents.

Material and methods

This is a cross-sectional observational study incorporated in a prospective study, where a population of 289 psoriatic patients was followed for 30 months. A total of 118 patients were under topical therapy, a different group of 98 patients used non-biologic systemic agents (NBSA) (34 used acitretin, 13 were on cyclosporine and 51 were treated with methotrexate), the last group included 124 patients on BA (11 on infliximab, 17 on secukinumab, 22 on etanercept, 33 on ustekinumab and 41 on adalimumab).

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

Patient history was obtained by means of a questionnaire. A variety of comorbidities and epidemiological factors between the 3 groups of patients treated differently was studied, attempting to establish possible trigger and prognostic factors of severe psoriasis.

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 BSA (body surface area) plus PASI (Psoriasis Area Severity Index) scores recorded at each visit. Furthermore, urine, and blood collected for basic laboratory tests.

Adverse events were grouped according to the System Organ Class of the Medical Dictionary for Regulatory Activities (version 16.0) (SAS, 2013), that is according to each affected system. 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. Results were then statistically processed.

Detailed information on the methodology of each study is provided in the doctoral thesis.

Results

Table 1 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*

Table 2 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*

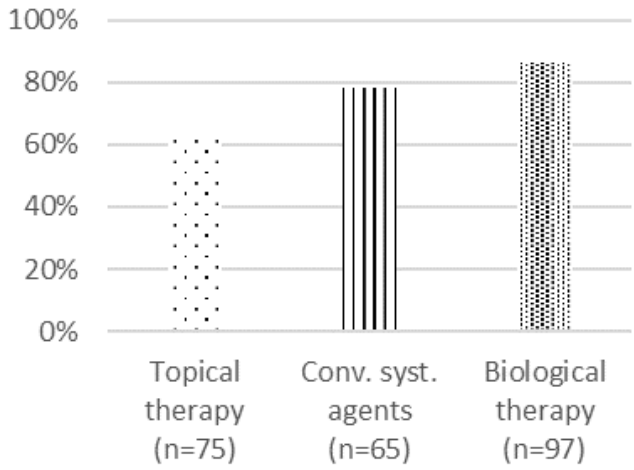

Fig. 1 Comparison of the overall incidence of AEs between patients treated with different types of therapy during the follow up (p=0.017).

Table 3 Occurrence of AEs arranged by system organ class between patients treated with different types of therapy during the follow up.

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%)		
	TT	2 (1.7%)		0 (0.0%)		0 (0.0%)		0 (0.0%)		1 (0.8%)		**<0.001***

Non-infectious renal and urinary disorders	NBSA	0 (0.0%)	0.667; 0.670	1 (2.4%)	0.170; 0.171	0 (0.0%)	**0.032*; 0.031***	0 (0.0%)	**0.013*; 0.013***	0 (0.0%)	0.278; 0.280	
	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%)		
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%)		
	BA	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***
	NBSA	6 (13.3%)		12 (28.6%)		8 (17.0%)		13 (27.7%)		8 (14.8%)		
	BA	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***
	NBSA	5 (11.9%)		3 (7.9%)		2 (4.4%)		4 (8.9%)		4 (7.7%)		
	BA	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***
	NBSA	22 (52.4%)		24 (63.2%)		23 (52.3%)		27 (60.0%)		25 (47.2%)		
	BA	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

Table 4 PASI and BSA scores between patients treated with different types of therapy during the follow up.

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

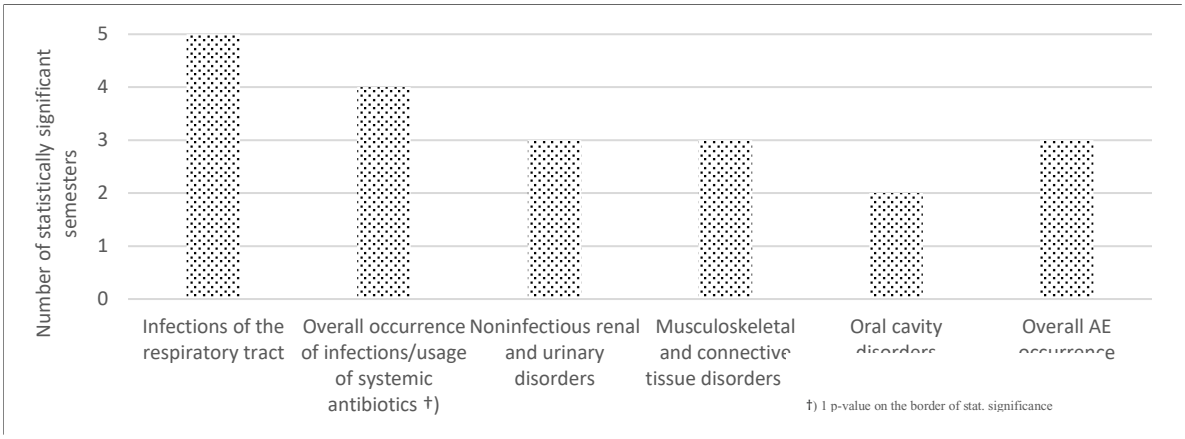

Fig. 2 Biologic agents' most frequent AEs during the follow up.

Table 3 Occurrence of AEs among BA-treated patients arranged by system organ class.

System organ class 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
Disorders of the reproductive system	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 conditions	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%)		

Note. n= absolute number of patients; ETN= etanercept; ADA= adalimumab; IFX= adalimumab; UST=ustekinumab; SEC= secukinumab

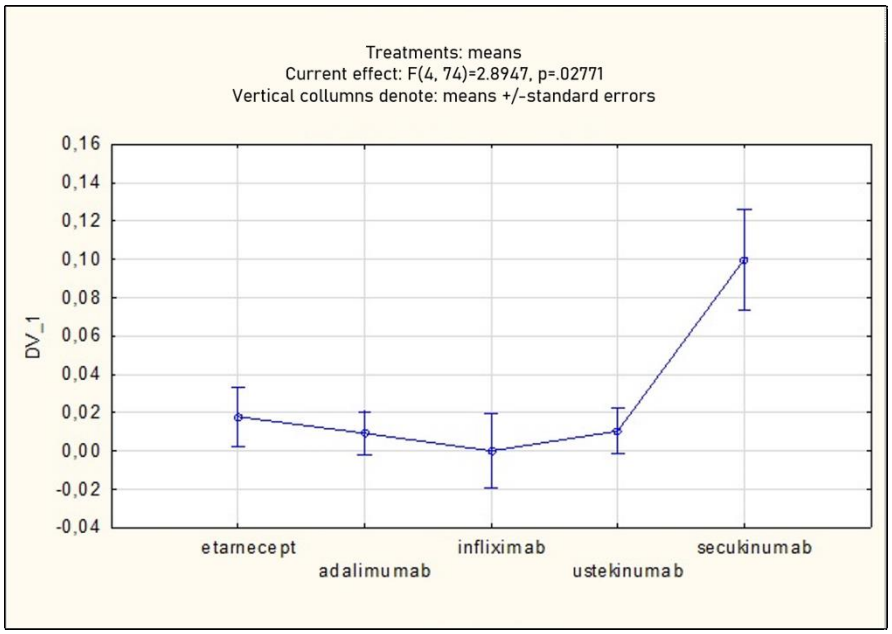

Fig. 3 Incidence of cardiovascular disorders among BA-treated patients throughout the study

Table 4 Discontinuation of BAs

		Adalimumab (n=41)	Etanercept (n=22)	Infliximab (n=11)	Secukinumab (n=17)	Ustekinumab (n=33)
Autoimmune diseases (SLE)		1 temp. discont.	0	0	0	0
Infections	Erysipelas	1 temp. discont.	0	0	0	0
	Urinary	0	1 temp. discont.	0	0	0
Malignancy (breast carcinoma)		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 (total knee replac.)		1 temp. discont.	0	0	0	0
Total		5 (12.2%)	2 (9.1%)	0	0	1 (3.0%)

Note. n= absolute number of patients; discont.= dicontinuation; replac.= replacement; temp.= temporary; perman= permanent; SLE= systemic lupus erythematodes

Detailed results of each study are provided in the doctoral thesis.

Discussion

BAs represent the latest step in the therapy of psoriasis (Nast et al., 2015), (Nast et al., 2017). Thus, one can assume that patients on topical therapy have a lower grade of disease severity than patients treated with systemic drugs, namely BAs. A variety of epidemiological parameters was studied aiming for any possible links with psoriasis severity. Results demonstrated how severe psoriasis 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, this research study pioneers increased height and puberty, menopause/andropause as independent prognostic factors of psoriasis severity. This 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.

BAs 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. This study also aimed 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. During the follow up, 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 this 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.

In a third analysis, possible differences in the occurrence of AEs in individual groups of patients with psoriasis treated with different BAs (adalimumab, etanercept, infliximab, secukinumab and ustekinumab) was studied. 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 disorders, specifically menstrual disorders. The rates of therapy discontinuation and serious adverse event 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. 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.

This 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 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 patients were already being treated for some time when the study started: in this fashion, one cannot exclude that some of the diseases assumed to be related to psoriasis severity were, in fact, adverse events of those same therapies (ex. liver disease due to methotrexate hepatoxicity).
3. 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 the study group may have biased the results;
4. Dose-dependent AEs were not considered; NBSAs are toxic when given at higher doses (Summary of Product Information - Sandimmun (Ciclosporin),

n.d.), (Summary of Product Information – Jylamvo (Methotrexate), n.d.), (Naldi & Griffiths, 2005), (Ho, 2004), (Pathirana et al., 2009), (Bissonnette et al., 2009).

5. 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.
6. Ideal conditions were if psoriasis severity scores were followed in untreated patients; however, such conditions are unrealistic because a patient with severe psoriasis eventually needs to be treated systemically.

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

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. This research pioneers the use of increased height and puberty, menopause/andropause as independent prognostic factors of psoriasis severity.

During the study, while BAs were the most effective therapies, they were associated with higher rates of treatment discontinuation and adverse events in comparison with other forms of therapy. A higher incidence of adverse events was observed among adalimumab- and infliximab-treated patients, with ustekinumab found to have the safest profile. 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.

Summary

Psoriasis vulgaris is a chronic inflammatory skin disease with a prevalence of 1.5–4.7%.

Today, 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; in other words, such factors may help us predict whether a certain patient will be at high risk of developing the condition.

Severe psoriasis is usually non-responsive to topical agents, phototherapy and, occasionally, to conventional systemic drugs. In such cases, a group of modern immunomodulatory drugs known as biologic agents are prescribed. Still, 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.

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.

Bibliography

Au SC, Madani A, Alhaddad M, Alkofide M, G. A. (2013). Comparison of the efficacy of biologics versus conventional systemic therapies in the treatment of psoriasis at a comprehensive psoriasis care center. *J Drugs Dermatol.*, *12*(8), 861–866.

Barker, J., Hoffmann, M., Wozel, G., Ortonne, J. P., Zheng, H., Van Hoogstraten, H., & Reich, K. (2011). Efficacy and safety of infliximab vs. Methotrexate in patients with moderate-to-severe plaque psoriasis: Results of an open-label, active-controlled, randomized trial (RESTORE1). *British Journal of Dermatology*, *165*(5), 1109–1117. https://doi.org/10.1111/j.1365-2133.2011.10615.x

Bissonnette, R., Ho, V., & Langley, R. G. (2009). Safety of conventional systemic agents and biologic agents in the treatment of psoriasis. *Journal of Cutaneous Medicine and Surgery*, *13*(SUPPL. 2). https://doi.org/10.2310/7750.2009.00023

de Oliveira, M. de F. S. P., Rocha, B. de O., & Duarte, G. V. (2015). Psoriasis: classical and emerging comorbidities. *Anais Brasileiros de Dermatologia*, *90*(1), 09–20. https://doi.org/10.1590/ABD1806-4841.20153038

Gisondi, P., Cotena, C., Tessari, G., & Girolomoni, G. (2008). Anti-tumour necrosis factor-α therapy increases body weight in patients with chronic plaque psoriasis: A retrospective cohort study. *Journal of the European Academy of Dermatology and Venereology*, *22*(3), 341–344. https://doi.org/10.1111/j.1468-3083.2007.02429.x

Ho, V. C. (2004). The use of ciclosporin in psoriasis: A clinical review. *British Journal of Dermatology, Supplement*, *150*(67), 1–10. https://doi.org/10.1111/j.0366-077x.2004.05950.x

Juzlova, K., Votrubova, J., Dzambova, M., Gopfertova, D., Hercogova, J., & Smerhovsky, Z. (2016). Gastrointestinal comorbidities in patients with psoriasis in the Czech Republic: The results of 189 patients with psoriasis and 378 controls. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia*, *160*(1), 100–105. https://doi.org/10.5507/BP.2015.048

Kothary, N., Diak, I. L., Brinker, A., Bezabeh, S., Avigan, M., & Dal Pan, G. (2011). Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. *Journal of the American Academy of Dermatology*, *65*(3), 546–551. https://doi.org/10.1016/J.JAAD.2010.05.033

Lotti, T., Hercogova, J., & Prignano, F. (2010). The concept of psoriatic disease: can cutaneous psoriasis any longer be separated by the systemic comorbidities? *Dermatologic Therapy*, *23*(2), 119–122. https://doi.org/10.1111/J.1529-8019.2010.01305.X

Naldi, L., & Griffiths, C. E. M. (2005). Traditional therapies in the management of moderate to severe chronic plaque psoriasis: An assessment of the benefits and risks. *British Journal of Dermatology*, *152*(4), 597–615. https://doi.org/10.1111/j.1365-2133.2005.06563.x

Nast, A., Gisondi, P., Ormerod, A. D., Saiag, P., Smith, C., Spuls, P. I., Arenberger, P., Bachelez, H., Barker, J., Dauden, E., de Jong, E. M., Feist, E., Jacobs, A., Jobling, R., Kemény, L., Maccarone, M., Mrowietz, U., Papp, K. A., Paul, C., … Yawalkar, N. (2015). European S3-Guidelines on the systemic treatment of psoriasis vulgaris--Update 2015--Short version--EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology : JEADV*, *29*(12), 2277–2294. https://doi.org/10.1111/JDV.13354

Nast, A., Spuls, P. I., van der Kraaij, G., Gisondi, P., Paul, C., Ormerod, A. D., Saiag, P., Smith, C. H., Dauden, E., de Jong, E. M., Feist, E., Jobling, R., Maccarone, M., Mrowietz, U., Papp, K. A., Reich, K., Rosumeck, S., Talme, T., Thio, H. B., … Dressler, C. (2017). European S3-Guideline on the systemic treatment of psoriasis vulgaris – Update Apremilast and Secukinumab – EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology*, *31*(12), 1951–1963. https://doi.org/10.1111/jdv.14454

Pathirana, D., Ormerod, A. D., Saiag, P., Smith, C., Spuls, P. I., Nast, A., Barker, J., Bos, J. D., Burmester, G. R., Chimenti, S., Dubertret, L., Eberlein, B., Erdmann, R., Ferguson, J., Girolomoni, G., Gisondi, P., Giunta, A., Griffiths, C.,

Hönigsmann, H., … Rzany, B. (2009). European S3-guidelines on the systemic treatment of psoriasis vulgaris. *Journal of the European Academy of Dermatology and Venereology*, *23*(SUPPL. 2), 1–70. https://doi.org/10.1111/j.1468-3083.2009.03389.x

Piaserico, S., Conti, A., Lo Console, F., De Simone, C., Prestinari, F., Mazzotta, A., Gualdi, G., Guarneri, C., Borsari, S., & Cassano, N. (2014). Efficacy and safety of systemic treatments for psoriasis in elderly patients. *Acta Dermato-Venereologica*, *94*(3), 293–297. https://doi.org/10.2340/00015555-1719

SAS. (2013). *Introductory Guide MedDRA Version 16.0* (Issue March).

Saurat, J. H., Stingl, G., Dubertret, L., Papp, K., Langley, R. G., Ortonne, J. P., Unnebrink, K., Kaul, M., & Camez, A. (2008). Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *British Journal of Dermatology*, *158*(3), 558–566. https://doi.org/10.1111/j.1365-2133.2007.08315.x

Schmitt, J., Zhang, Z., Wozel, G., Meurer, M., & Kirch, W. (2008). Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: Meta-analysis of randomized controlled trials. *British Journal of Dermatology*, *159*(3), 513–526. https://doi.org/10.1111/j.1365-2133.2008.08732.x

Summary of Product Information – Jylamvo (methotrexate). (n.d.). https://www.ema.europa.eu/en/documents/product-information/jylamvo-epar-product-information_en.pdf

Summary of Product Information - Sandimmun (ciclosporin). (n.d.). http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Sandimmun_30/WC500158912.pdf

Topaloğlu Demir, F., Özkök Akbulut, T., Kıvanç Altunay, İ., Aytekin, S., Oğuz Topal, İ., Kara Polat, A., Özkur, E., & Karadağ, A. S. (2020). Evaluation of the adverse effects of biological agents used in the treatment of psoriasis: A multicenter retrospective cohort study. *Dermatologic Therapy*, *33*(6), e14216. https://doi.org/10.1111/DTH.14216

Votrubova, J., Juzlova, K., Smerhovsky, Z., Fialova, J., Gopfertova, D., Vojackova, N., & Hercogova, J. (2014). Risk factors for comorbidities in Czech psoriatic patients: results of a hospital-based case-control study. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia*, *158*(2), 288–294. https://doi.org/10.5507/BP.2013.062

Zweegers, J., Otero, M. E., van den Reek, J. M. P. A., van Lümig, P. P., Driessen, R. J., Kievit, W., Seyger, M. M. B., van de kerkhof, P. C. M., & de Jong, E. M. G. J. (2016). Effectiveness of biologic and conventional systemic therapies in adults with chronic plaque psoriasis in daily practice: A systematic review. *Acta Dermato-Venereologica*, *96*(4), 453–458. https://doi.org/10.2340/00015555-2276

Publications of the author

1. Publications related to the doctoral research

a. With impact factor

Marques E, Paluch Z, Boháč P, Slanař O, Běláček J, Hercogová J. 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 study. *International J of Clinical Practice.* 2021; **75(12):** e14915.

IF = 2.503

Marques E, Paluch Z, Boháč P, Slanař O, Běláček J, Hercogová J. Epidemiology of moderate-to-severe psoriasis: a comparison between psoriasis patients treated with biological agents, conventional systemic drugs and topical agents. *J Dermatolog Treat.* 2020; **20**:1-14.

IF = 3.359

Paluch Z, **Marques E**, Boháč P, Zemková K, Hercogová J. Adverse events of adalimumab, infliximab, etanercept, secukinumab and ustekinumab in psoriasis. *Journal of Cutaneous Medicine and Surgery*. [Manuscript submitted for publication].

IF = 2.854

b. Without impact factor

Běláček J, **Marques E**, Paluch Z. Statistical analysis of data of patients with psoriasis. *MEDSOFT 2020; **32**:81-84.*

Marques E, Paluch Z, Hercogová J. The use of biologics in the therapy of psoriasis – an overview. *Česká dermatovenerologie 2019; **9(3)**:172-179.*

Boháč P, **Marques E**, Hercogová J, *et al*. Incidence of infectious complications of biological drugs in the treatment of psoriatic patients. *Česká dermatovenerologie 2016; **6(4)**:232-237.*

2. Publications unrelated to the doctoral research

a. With impact factor

Paluch Z, Trojánek M, Velíšková Z, Mlíchová J, Chrbolka P, Gregorová J, **Marques E**, et al. Neurotoxic side effects of acyclovir: two case reports. *Neuro Endocrinol Lett.* 2021; **42(6):** 375-382.

IF = 0.765

Arenbergerová M, Gkalpakiotis S, **Marques E**, et al. Corticosteroid rescue therapy in relapsing hidradenitis suppurativa treated with adalimumab. *J of the European Academy of Dermatology and Venereology* 2021; **35(6)**: e381-e383

IF = 6.166

Marques E, Arenberger P, Smetanová A, et al. Successful treatment of recalcitrant hidradenitis suppurativa with risankizumab after anti-TNF failure. *British Journal of Dermatology* 2021; **184(5)**: 966-967**.**

IF = 9.302

Paluch Z, Biriczová L, Pallag G, **Marques E**, et al. The therapeutic effects of Agrimonia eupatoria L. *Physiological Research 2020 [online];* **69(4)**: 555-571.

IF = 1.881

Arenbergerová M, Arenberger P, **Marques E**, et al. Successful treatment of recalcitrant gluteal hidradenitis suppurativa with brodalumab after anti-TNF failure. *International Journal of Dermatology* 2020; **59(6)**:735-735**.**

IF = 2.736

Palanová P, **Marques E**, Dobšák P, et al. Home-based training using neuromuscular electrical stimulation in patients on continuous ambulatory peritoneal dialysis: A pilot study. *Artificial Organs [online]* 2019; **43(8)**:796-805.

IF = 3.094

b. Without impact factor

Smetanová A, **Marques E**. Hidradenitis suppurativa. *Farmakoterapie Revue* 2022; **7(3)**:278-283**.**

Marques E., Arenbergerová M., Smetanová A., Zimová D., Gkalpakiotis S. Úspěšná léčba risankizumabem u pacientky s hidradenitis suppurativa a s roztroušenou sklerózou. In Kazuistiky z dermatologie. Praha: Maxdorf, 2021, s. 46-50. ISBN 978-80-7345-700-6.

Smetanová A., **Marques E.**, Arenbergerová M. Kombinovaná biologická a chirurgická léčba hidradenitis suppurativa u adolescenta. In Kazuistiky z dermatologie. Praha: Maxdorf, 2021, s. 46-50. ISBN 978-80-7345-700-6.

Marques E, Tanczosová M, Arenbergerová M. Alopecia - overview, causes and current treatment options. *Dermatologie pro praxi 2020; **14(3)**:124-132.*

3. Poster/oral presentations

Marques E. (2022, September 9). *Surgery in advanced squamous cell carcinoma*. [Oral presentation]. 31st EADV Congress 2022, Milan, Italy. https://eadvcongress2022.org/scientific/programme/

Marques E. (2022, September 9). *Update on botulinum toxin indications*. [Oral presentation]. 31st EADV Congress 2022, Milan, Italy. https://eadvcongress2022.org/scientific/programme/

Marques E, Arenbergerová M, Smetanová A, et al. (2022, February 9-11) *Anti-IL-23 in Hidradenitis Suppurativa: unveiling a new pathway.* [Poster, online presentation]. 11th conference of the European Hidradenitis Suppurativa Foundation. www.ehsf2022.com

Smetanová A, **Marques E**, Horáčková Z, et al. (2022, May 24) *Risk of squamous cell carcinoma in patients with Hidradenitis suppurativa treated with TNF-alpha inhibitors.* [Poster]. 2022 Students' scientific conference of the 3rd Faculty of Medicine, Charles University, Prague, Czech Republic. https://www.lf3.cuni.cz/3LF-2146.html

Note: awarded by the dean, prof. MUDr. Petr Widimský, DrSc., as the 3rd best poster of the conference

Smetanová A, Olivová L, **Marques E**, et al. (2020, November 6) *Comparison of epidemiological data in hidradenitis suppurativa vs psoriasis in Czech patient population.* [Poster]. 2020 Students' scientific conference of the 3rd Faculty of Medicine, Charles University, Prague, Czech Republic. https://www.lf3.cuni.cz/3LF-1776.html

Note: awarded by the dean, prof. MUDr. Petr Widimský, DrSc., as the 2nd best poster of the conference

Marques E, Paluch Z, Biricz L, et al. (2020, September 3-5). *The therapeutic effects of Agrimonia Eupatoria*. [Oral presentation]. TOXCON conference - 25th Interdisciplinary Toxicology Conference, Prague, Czech Republic. http://web.natur.cuni.cz/toxcon2020/

Quarenta J, Barranha R, **Marques E**, et al. (2020, July 4-7). *Alopecia areata, from the brain to the skin – a case report.* [Poster]. EPA 2020, 28th European Congress of Psychiatry, Madrid, Spain. www.2020.epa-congress.org/

Marques E, Paluch Z, Hercogová J. (2019, October 9-13). *Biological (Super Safe ?) Agents.* [Poster]. 28th European Academy of Dermatovenereology Congress, Madrid, Spain. www.eadvmadrid2019.org

Marques E, Boháč P, Paluch Z, et al. (2019, September 19-21). *Biologics have won for their effectiveness, but are they safer than older therapies?* [Oral presentation]. 8th Czech-Slovak conference of clinical pharmacology, Rožnov pod Radhoštěm, Czech Republic. https://www.health.gov.sk/Zdroje?/Sources/veda_vyskum_vyvoj/program-cskkf-2019.pdf

Marques E, Boháč P, Jůzlová K, et al. (2019, April 10-11). *Adverse reactions to biologic agents: infectious complications in the treatment of psoriasis.* [Poster].

2019 Students' scientific conference of the 2nd Faculty of Medicine, Charles University, Prague, Czech Republic. https://vedecka-konference.lf2.cuni.cz/en/archive

Marques E. (2018, May 31). *Adverse reactions to biologic agents.* [Oral presentation]. Multidisciplinary seminar of young pharmacologists and toxicologists, "Květinův den". Brno, Czech Republic. https://www.cazv.cz/pozvanka-na-kvetinuv-den-2018/

Marques E. (2015, January 15). *Living in a country? Learn the language!* [Oral presentation]. International conference of Language Centres in Higher Education, Brno, Czech Republic. https://slideslive.com/cjv/language-centres-in-higher-education-2015