The Safety Profiles of Adalimumab, Infliximab, Etanercept, Secukinumab and Ustekinumab in Psoriasis – A 30-month Observational Cohort Prospective Study of Adverse Events in Biologic Therapy

Zoltán Paluch[1,2], Emanuel Marques[3,4,5], Petr Boháč[6], Kateřina Zemková[4], Jana Hercogová[7]

[1]Department of Clinical Pharmacology and Pharmacy, General University Hospital, Prague, Czech Republic; [2]St. Elizabeth University of Health and Social Work, St. J. N. Neumann Institute, Příbram, Czech Republic; [3]Department of Dermatology, and Venereology, Královské Vinohrady University Hospital, Prague, Czech Republic; [4]Department of Dermatology, and Venereology, Third Faculty of Medicine, Charles University, Prague, Czech Republic; [5]Department of Pharmacology, Second Faculty of Medicine, Charles University, Prague, Czech Republic; [6]Department of Dermatology, and Venereology, Bulovka University Hospital, Prague, Czech Republic; [7]Dermatologie Prof. Hercogové, Prague, Czech Republic

Corresponding author:
Kateřina Zemková, MD
Záběhlická 1721/41
100 60 Praha 10
Czech Republic
kackazemkova@gmail.com

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ABSTRACT

Background: Although biologic agents are very effective, long-term comparative studies demonstrating their safety relative to one another are still lacking.

Methods: A total of 124 patients with psoriasis 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, but increased liver enzymes, fatigue, and respiratory as well as dermatologic 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 dermatologic infections. The group receiving etanercept was more often diagnosed with musculoskeletal and reproductive disorders, 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.

KEY WORDS: 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 (1). Its pathogenesis is based on T-cell dysregulation. Biologic agents (BAs) ushered in a new era in terms of

pharmacotherapy: with an outstanding effect on symptom control and the disease prognosis, they have fundamentally changed the treatment of psoriasis (1,2).

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 (3-6), adverse events (AEs) such as infections and malignancies or immune-mediated complications may occur. These molecules and their properties are different, and can thus cause different AEs (7,8).

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

PATIENTS AND METHODS

This is a substudy of a 30-month observational cohort prospective study including a total of 289 patients with psoriasis vulgaris. We compared the incidence of AEs in a group of patients (n=124) treated with 5 different BAs (etanercept, adalimumab, infliximab, ustekinumab, secukinumab) (Table 1 and Table 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 of 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 the patient's health status, disease activity, and drug AEs, should there be any.

We grouped the AEs according to the system of organ classes of the Medical Dictionary for Regulatory Activities (version 16.0) (9) with one minor adaptation: except for dermatologic, respiratory, and urinary infections, infections and infestations were included into each affected system. We used Edwards' definition of AEs (10), and that of the European Medicines Agency's (EMA) for serious AEs (11).

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 same time interval. Results were statistically processed in STATISTICA SW, 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 and observed frequencies.

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 experiencing 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), towards the end of the study it was infliximab and secukinumab-treated patients who tended to report more of these AEs (infliximab: n=5, 50.0%; secukinumab: n=4, 36.4%; ANOVA and

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 (mean in years)	43.0±17.8	47.9±17.3	46.6±8.9	44.3±15.8	44.8±14.2	-
BMI (mean)	27.6±6.0	29.0±5.78	27.2±4.5	29.8±7.2	27.7±5.9	-

n: number of patients; BMI: Body Mass Index

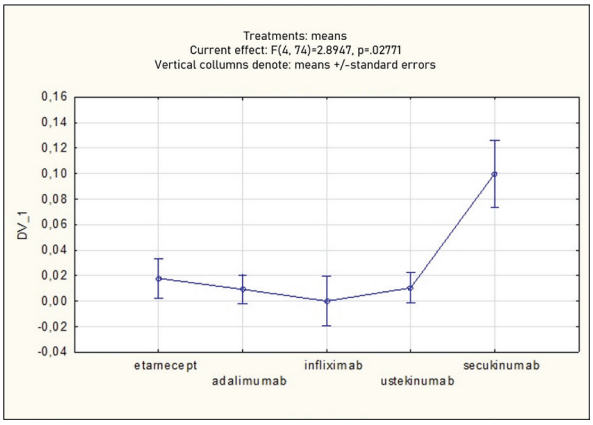

Figure 1. Incidence of cardiovascular disorders throughout the study. The graph represents the overall incidence of cardiovascular disorders among each of the 5 treated groups (etarnecept, adalimumab, infliximab, ustekinumab, secukinumab) (*P*=0.028). The graph was created in STATISTICA SW.

chi-square test *P*<0.001) (Table 3). Dermatologic 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 affected by urogenital infections more often 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 higher levels of cardiovascular disorders among the study groups. Cardiovascular disorders occurred more often in the group of patients treated with secukinumab (ANOVA *P*=0.028) (Figure 1).

A higher incidence of musculoskeletal disorders was observed throughout the study period among patients treated with etanercept and adalimumab (ANOVA *P*=0.031).

Within the category of general disorders and administration site reactions, higher incidences of fatigue were reported by patients treated with infliximab in the early follow-up period (chi-square test and ANOVA *P*=0.001) (Table 3). Such AEs did not, however, reveal statistically significant values during the rest of the study period (Table 3).

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) (12), (ANOVA *P*=0.031 and ANOVA *P*=0.035, respectively).

A total of 8 patients (6.4%) discontinued therapy: 5 patients (4.0%) temporarily interrupted their treatment, and 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

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%)
Dyslipidemia	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%)
Gastroenterologic diseases	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%)
Oncological disease	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

Table 3. Occurrence of AEs arranged by 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
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%)		

n: number of patients; ETN: etanercept; ADA: adalimumab; IFX: adalimumab; UST: ustekinumab; SEC: secukinumab

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%)

N: number of patients; discont: discontinuation; perman: permanent; QNF-TB: QuantiFERON-TB Gold; temp: temporary

due to possible AEs directly related to treatment with BAs (Table 4).

The most common reason for therapy discontinuation were malignancies (2 cases of breast cancer) in patients treated with adalimumab or ustekinumab; the 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 with the highest incidence of serious AEs (7.3%, chi-square test P=0.183).

We found no significant differences between individual treatment groups and their associated diseases (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, the investigated drugs 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).

Information about the potential AEs of these agents is crucial for a safe therapeutic approach (13-15). As it stands, 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 (16,17), there have been reports of significantly higher risks of infectious complications among patients treated with different BAs (18–21). 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) (22). 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). Another risk factor for these complications is older age (22,23); in fact, patients above 65 years of age are at a 4 times higher risk of developing infections (22). Rigorous screening before and during treatment is mandatory to avoid such complications.

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 (22,24). Addressing risk factors is essential for preventing respiratory infections, and smoking is a modifiable and very important risk factor (25). Our study population had a high number of smokers (34.7%) – smoking cessation should be encouraged among patients treated with BA.

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 (22,26-28). In our study, a higher incidence of these infections was observed 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 (29). 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 (30). Anti-TNF-alpha drugs practically double the risk of HPV and anogenital wart formation (31,32). Thus, it is important to advise patients treated with BA 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 (22). Women are at higher risk when treated with infliximab or anti-IL-17 agents (33). 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 (16,18,34). An increased incidence of serious infections including tuberculosis (TB) was reported with anti-TNF-alpha mAb treatment compared with soluble TNF receptor therapy (24,35,36). We did not register serious infections – the only reported case of QNF positivity did not present with a typical clinical picture, similarly to other studies (37), and it was therefore not classified as a TB case.

The effect of BAs on the development of oncological diseases 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 (38,39). 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 (40-42). The finding of two malignancies in our study highlights the need for careful age-appropriate cancer screening in patients treated with these agents (43).

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 are no data on the effect of anti-TNF-alpha inhibitors on women's menstrual cycles. The relevant literature only provides information on their safe use during pregnancy and possible effects on foetal development (44,45).

Our study also documented 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 have been subject to long-standing debate (46,47). Initial concerns about the impact of TNF-alpha inhibitors on the development of heart failure arose in the early post-marketing follow-up (48,49). However, anti-TNF-alpha therapy does not seem to increase the risk of cardiovascular events (50,51).

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, namely, patients receiving etanercept tended to experience musculoskeletal disorders including arthralgia and an increased number of muscle cramps, whereas individuals treated with adalimumab were found to be at an increased risk of fractures (26,52).

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 (53).

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, and one was diagnosed with severe liver steatosis. Reich (54) described results similar to ours, whereas Poulin (55) 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 (56,57). Our findings highlight the need for permanent surveillance of BA-treated patients, specifically those treated with infliximab.

An important issue with biological therapy is treatment discontinuation or nonadherence (58-61). In our study, a total of 8 patients (6.4%) temporarily or permanently discontinued their treatment, the highest number (5 patients) being in the group receiving adalimumab. Our numbers were significantly lower than those in a 5-year follow-up study of rheumatologic patients on BAs, where 32.8% discontinued their treatment. Similarly, another study with patients with psoriasis reported 46% of their patients discontinuing their treatment after one year (58,59).

It is well known that BA-treated patients are at increased risk of developing serious AEs (61,62), especially those on infliximab and adalimumab (63). In our study, only adalimumab-treated patients developed serious AEs (two malignancies and one case of systemic lupus erythematosus) – these 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 had already been treated for some time at the time of enrolment, which may have significantly compensated for this limitation; in fact, we cannot exclude that some of the above AEs were of the 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 enzymes, fatigue, and respiratory and dermatologic 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 and respiratory and dermatologic infections. The group treated with etanercept experienced more musculoskeletal and reproductive disorders, 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.

Conflict 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.

Data availability:

Data is available from the authors upon request.

Ethics approval:

This study was approved by the Ethics Committee of the Second Faculty of Medicine, Charles University, Prague.

List of abbreviations:

*	Statistically 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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