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ORIGINAL ARTICLE

Evaluation of the adverse effects of biological agents used in the treatment of psoriasis: A multicenter retrospective cohort study

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Abstract

The objective was to reveal and compare the adverse effects of infliximab, etanercept, adalimumab, ustekinumab and secukinumab, and determine possible risk factors. The follow-up files and computer-based records of patients with psoriasis were retrospectively screened between January 2007 and September 2019. The five biological agents were compared in terms of their adverse effects, and factors that might be related to these effects were explored. While there was no statistically significant difference between the agents in terms of the rate of serious adverse effects, when all the adverse effects were evaluated together, the highest rate was seen in the use of infliximab and the lowest in secukinumab (P = .001). The rates of adverse effects and related drug discontinuation were higher in the use of anti-TNF agents compared to interleukin inhibitors (P = .004 and P = .012, respectively). The agent with the highest drug discontinuation rate due to adverse effects was infliximab while the least discontinued agent was ustekinumab (P = .036). There were more side effects with anti-TNF than interleukin inhibitors, but the serious adverse effect rate was similar in both groups. The incidence of certain adverse effects increases depending on age, number of comorbidities, biological agent and its group, concomitant systemic therapy, and use of multiple agents.

KEYWORDS

adverse effects, biological agents, psoriasis, safety

1 | INTRODUCTION

Today, biological agents have an important place in the treatment of psoriasis and are frequently used in clinical practice. However, both physicians and patients may hesitate in using these agents due to their adverse effects. Most data on the reliable use of biological agents in psoriasis belong to phase studies,[1-6] but patient populations included in these studies do not reflect those encountered in real life.[7] In real life, the vast majority of patients undergoing psoriasis treatment have other comorbidities associated with or independent of psoriasis. Depending on the demographic data of the patients and these comorbidities, the adverse effect profile and their frequency vary. In this

study, our aim was to reveal the adverse effects of five agents used in the treatment of psoriasis in Turkey, namely infliximab, etanercept, adalimumab, ustekinumab and secukinumab, compare them in terms of adverse effect profiles, and determine possible risk factors.

2 | MATERIALS AND METHODS

The follow-up files and computer-based records of psoriasis patients who had been treated and/or were being treated and followed up in six dermatology clinics of reference health care centers for psoriasis treatment between January 2007 and September 2019, were retrospectively screened. The study included all psoriasis patients aged ≥18 years, who had used or were using at least one of the biological agents of infliximab, etanercept, adalimumab, ustekinumab, or secukinumab, and had available data on the adverse effects of the agent used. The patients were divided into groups depending on their use of tumor necrosis factor (TNF) or interleukin (IL) inhibitors, being biologically naïve, using single/multiple biological agents, and being < or ≥65 years, and the groups were compared in terms of their adverse effect profiles to determine factors that might be associated with the adverse effects. The ethical committees of the hospitals contributing to this research approved the study protocol.

SPSS v. 15.0 for Windows was used for statistical analysis. The descriptive statistics of the evaluation results were expressed as mean, SD, minimum and maximum values for numerical variables, and numbers and percentages for categorical variables. The comparisons of the rates between the groups were undertaken using the chi-square test. The statistical alpha significance level was accepted as $P < .05$.

3 | RESULTS

A total of 464 psoriasis patients, including 204 women and 260 men, were included in the study. The demographic and clinical data, comorbidities, and the treatments applied before the use of biological agents evaluated for their adverse effects are summarized in Table 1. Table 2 presents the distribution of 635 biological agents and concomitant systemic treatments. The mean duration of biological agent use was 41.7 ± 66.8 (min-max 0-560) months (Table 3). Of the patients, 73.1% used a single biological agent and 26.9% used multiple biological agents. At least one adverse effect was detected in 63.6% of the patients, and the biological agent that most led to the development of adverse effects was infliximab (78.8%) while the least number of adverse effects was seen in secukinumab (49.2%) ($P = .001$). Among TNF inhibitors (anti-TNF), the agent with the least number of adverse effects was adalimumab. The rate of serious adverse effects was 4.3%, most commonly seen in the use of infliximab (7.7%), and least frequently in secukinumab (1.6%) ($P > .05$) (Table 4). The mean duration of use of ustekinumab was statistically significantly higher in those with severe side effects than those without side effects ($P = .025$) (Table 5). In Adalimumab users, the mean duration of use was statistically significantly shorter in those with side effects compared with those without ($P = .005$) (Table 6). Since the use of sekukinumab was shorter than other agents, it is not possible to say anything clear about the relationship between adverse effects and duration of use (Table 3). The highest and lowest rates of drug discontinuation due to adverse effects were observed in infliximab (17.3%) and ustekinumab (3.8%), respectively ($P = .036$) (Table 4).

Figure 1 presents all the adverse effects detected in patients using biological agents. The incidence of adverse effects increased with the use of concomitant systemic treatments ($P = .012$) and isoniazid (INH) prophylaxis ($P = .002$), while the rate of serious adverse effects increased with the increasing number of comorbidities ($P = .014$). There was no difference between smokers and nonsmokers and alcohol users and nonusers in terms of side effects and serious side effects ($P > .05$). The most common adverse effects were infections (37.2%), these were followed by weight gain (12.8%), and hepatotoxicity (7.2%) respectively. It was also observed that hepatoxicity increased in those with INH prophylaxis ($P < .001$).

The presence of infection (44.2%) ($P = .014$), lower respiratory tract infections (21.2%) ($P < .001$), hypersensitivity reactions (17.3%) ($P < .001$), headache (15%, 4) ($P = .018$), and nausea (11.5%) ($P = .004$) were the common adverse effects associated with infliximab; injection site reactions were most observed in the use of etanercept (15.3%) ($P < .001$), and candida infections in secukinumab (12.7%) ($P < .001$). Weight gain was most frequently found in those who used ustekinumab (20.1%), followed by those using secukinumab (17.5%) ($P = .046$). There was no statistically significant difference between the biological agents evaluated in terms of the incidence of paradoxical psoriasis, latent tuberculosis and hepatitis B reactivation, MACE, IBD and malignancies ($P < .05$) (Table 4). The rate of weight gain ($P = .017$) was statistically significantly higher among patients under 65 years of age, and thrombocytopenia ($P = .002$) and skin cancer ($P = .047$) were seen at a significantly higher rate among those older than 65 years. The rate of adverse effects ($P = .004$) and drug discontinuation due to adverse effects ($P = .012$) were higher in those using anti-TNF (Table 7). The presence of infection ($P = .004$), upper respiratory tract infections ($P = .021$), injection site reactions ($P = .009$), and anemia ($P = .028$) were significantly higher in the group using anti-TNF while weight gain ($P = .003$) was more common among the patients using inhibitors of ILs, including IL-12/IL-23 and IL-17. However, no significant difference was observed between those who used anti-TNF and IL inhibitors in terms of serious side events ($P = .312$) (Table 7). The frequency of adverse effects ($P = .004$), hypersensitivity reactions ($P = .035$), presence of infection ($P = .033$), and urinary tract infections ($P = .031$) increased in patients with a history of multiple biological agent use compared to those having used a single agent.

4 | DISCUSSION

Newer biological agents, such as ustekinumab and secukinumab targeting IL-23/IL17 have been introduced having superior efficacy and safety claims compared to TNF-alpha inhibitors. These agents do

TABLE 1 Baseline demographic and disease characteristics of the patients

		n	%
Gender	Female	204	44.0
	Male	260	56.0
Age (years)	<65 years	416	89.7
	≥65 years	48	10.3
Age (years) Mean ± SD (Min-Max)		46.1 ± 14.1 (18-86)	
Smoking		203	44
Alcohol use		58	12.6
Psoriasis type	Plaque	433	93.3
	Other	31	6.7
Psoriatic arthritis		228	49.6
Nail involvement		294	63.9
Initial PASI Mean ± SD (Min-Max)		17.0 ± 8.6 (1-49)	
Duration of disease (month) Mean ± SD (Min-Max)		218.3 ± 138.6 (8-850)	
Family history		194	41.8
BMI (kg/m^2) Mean ± SD (Min-Max)		28.6 ± 5.5 (17.6-54)	
Obesity class	Normal weight	189	20.4
	Overweight	204	22.0
	Grade 1 obese	124	13.4
	Grade 2 obese	57	6.1
	Grade 3 obese	9	1.0
Comorbidities	None	90	22.2
	One	124	30.5
	Two	89	21.9
	Three or more	103	25.4
Previous systemic treatments	None	16	3.5
	Acitretin	270	58.2
	Methotrexate	393	84.7
	Ciclosporin	178	38.4
	Biological agent	8	1.6
Previous phototherapy	None	209	45.2
	NB-UVB	193	41.8
	PUVA	30	6.5
	NB-UVB + PUVA	30	6.5

Abbreviations: NB-UVB, narrowband ultraviolet B; PASI, Psoriasis Area and Severity Index; PUVA, psoralen and ultraviolet A.

not have black box warnings, which indicate an increased risk of serious infection and malignancy.[8] In clinical studies, they have been reported to have adverse effect profiles limited to mild upper respiratory infections, nasopharyngitis, back pain, and headache.[4,9] In the literature, it has been reported that the incidence of serious adverse effects is generally lower in patients with advanced psoriasis treated with IL12/23 and IL-17 inhibitors[10,11] whereas those using anti-TNF (infliximab, etanercept, and adalimumab) have been associated with a higher risk of serious infections, such as latent tuberculosis and hepatitis B reactivation, and lymphoma.[8,12]

In this study, the rate of drug discontinuation was higher in patients using anti-TNF, with infliximab being identified as the agent that was most discontinued due to its adverse effects, which is in agreement with the literature.[11,13,14] Furthermore, consistent with a previous study,[15] the most common adverse effects observed were infections. The infection rate was increased in patients using multiple biological agents (P = .033). Kalb et al found a higher risk of serious infections in patients with psoriasis who received adalimumab and infliximab compared to those treated with nonbiological agents, except for methotrexate.[16] In our study, the rates of infections and lower respiratory tract infections were higher in patients using infliximab (P < 0,05). There was no difference between the biological agents in terms of serious infections, other than those of the lower respiratory tract. An infusion reaction was detected in 17.3% of

TABLE 2 Distribution of biological agents and concomitant therapies

		n	%
Number of biological agents used	Single	339	73.1
	Multiple	125	26.9
First biological agent	Infliximab	35	7.5
	Etanercept	106	22.8
	Adalimumab	196	42.2
	Ustekinumab	91	19.6
	Secukinumab	36	7.8
Concomitant therapy	None	397	85.7
	Methotrexate	58	12.5
	Acitretin	4	0.9
	NB-UVB	1	0.2
	Ciclosporin	3	0.6
Second biological agent	Infliximab	9	7.8
	Etanercept	25	21.7
	Adalimumab	44	38.3
	Ustekinumab	23	20.0
	Secukinumab	14	12.2
Concomitant therapy	None	82	73.9
	Methotrexate	25	22.5
	Acitretin	3	2.7
	NB-UVB	1	0.9
Third biological agent	Infliximab	8	19.5
	Etanercept	4	9.8
	Adalimumab	9	22.0
	Ustekinumab	13	31.7
	Secukinumab	7	17.1
Concomitant therapy	None	27	65.9
	Methotrexate	7	17.1
	Acitretin	1	2.4
	Ciclosporin	5	12.2
Fourth biological agent	Etanercept	2	15.4
	Ustekinumab	7	53.8
	Secukinumab	4	30.8
Concomitant therapy	None	9	69.2
	Methotrexate	2	15.4
	Acitretin	1	7.7
	Ciclosporin	1	7.7
Fifth biological agent	Secukinumab	2	100
Concomitant therapy	None	2	100

patients, which is in accordance with the literature.[17] Hypersensitivity reactions were increased in patients using multiple biological agents (P = .035). In patients using anti-TNF, the rate of upper respiratory tract infections and the overall infection rate, injection site reactions, and anemia incidence were statistically significantly higher than those

TABLE 3 Duration of the biological agents used

		Total duration (month)		
		Mean ± SD	Median	P
Biological agent	Infliximab	41.8 ± 82.2	17	<.001
	Etanercept	23.6 ± 25.1	16	
	Adalimumab	45.2 ± 77.7	18	
	Ustekinumab	24.3 ± 39.2	16	
	Secukinumab	8.0 ± 8.5	5,5	

using IL inhibitors. The incidence of adverse effects was increased in those receiving concomitant systemic treatment and those using INH in addition to biological agents (P < 0,05). This was considered to be related to the rate of adverse effects seen in the two groups. In contrast to the literature, the agent with the least number of overall adverse effects (P = .001) and the least number of serious adverse effects (P = .605) was secukinumab, but ustekinumab was the least discontinued agent due to adverse effects (3.8%) (P < .05), which is consistent with the literature.[8,13,18] The second least discontinued drug due to adverse effects was secukinumab (6.9%). Similarly, in the literature, the rate of secukinumab discontinuation due to adverse effects is reported as 6.4%.[19]

Unlike the literature, there was no statistically significant difference between the groups in terms of the rates of serious adverse effects. The incidence of serious infections, latent tuberculosis and hepatitis B reactivation, and the incidence of malignancies was similar in group comparisons. In terms of serious adverse effects, IL inhibitors have no advantage over anti-TNF.[8,10] Wakkee et al reported that comorbidities can alter the safety profile of biological agents.[20] In our study, an increase was observed in the rate of serious adverse effects associated with the number of comorbidities.

In a systemic review and meta-analysis by Rungapiromnan et al covering 38 randomized controlled trials investigating the effect of biological agents on MACE in psoriatic patients, no statistically significant difference was observed between anti-TNF agents (adalimumab, etanercept, and infliximab), ustekinumab, and IL-17A inhibitors (secukinumab and ixekizumab) at least for the short term.[21] In agreement with the study of Rungapiromnan et al, we found no statistically significant difference between the agents evaluated in terms of the incidence of MACE. In a study by Ahlehoff et al, it was reported that the risk of cardiovascular events (myocardial infarction, stroke and cardiovascular death) was reduced in patients using anti-TNF and methotrexate while those using ustekinumab had a similar risk to the groups receiving phototherapy, topical therapy, and climatotherapy.[22] In our study, the difference between anti-TNF and IL inhibitors was not statistically significant in terms of MACE development. In another meta-analysis in which recently published randomized controlled trials were evaluated, no significant difference was found in the incidence of MACE between approved biological agents and placebos in the treatment of patients with psoriasis or psoriatic arthritis.[23]

TABLE 4 Characteristics of adverse effects associated with biological agents

Number of cycles Total (n = 635)		Biological agent										
		Infliximab		Etanercept		Adalimumab		Ustekinumab		Secukinumab		
		n = 52		n = 137		n = 249		n = 134		n = 63		
		n	%	n	%	n	%	n	%	n	%	*P*
Adverse effect		41	78.8	100	73.0	154	61.8	78	58.2	31	49.2	.001
Serious adverse effect		4	7.7	6	4.4	11	4.4	5	3.7	1	1.6	.605
Discontinuation of biological agent due to adverse effects		9	17.3	16	11.7	23	9.2	5	3.8	4	6.9	.036
Concomitant therapy	None	35	67.3	103	75.2	202	81.8	117	89.3	60	95.2	<.001
	Methotrexate	15	28.8	31	22.6	36	14.6	10	7.6	1	1.6	
	Acitretin	2	3.8	3	2.2	5	2.0	1	0.8	2	3.2	
	NB-UVB	0	0.0	0	0.0	2	0.8	0	0.0	0	0.0	
	Ciclosporin	0	0.0	0	0.0	2	0.8	3	2.3	0	0.0	
INH prophylaxis		35	70.0	80	59.7	111	49.8	49	38.3	21	34.4	<.001
Hepatitis B prophylaxis		4	7.7	13	9.5	16	6.5	6	4.5	8	12.7	.238
Urinary tract infection		4	7.7	8	5.8	9	3.6	7	5.2	0	0.0	.175
Infection		23	44.2	55	40.1	101	40.7	45	33.6	12	19.0	.014
Upper respiratory tract infection		19	36.5	50	36.5	92	36.9	42	31.3	12	19.0	.084
Lower respiratory tract infection		11	21.2	8	5.8	10	4.0	8	6.0	1	1.6	<.001
Sepsis		0	0.0	1	0.7	1	0.4	0	0.0	0	0.0	1.000
Injection site reactions		1	1.9	21	15.3	13	5.2	5	3.7	0	0.0	<.001
Hypersensitivity reactions		9	17.3	0	0.0	2	0.8	1	0.7	2	3.2	<.001
Alopecia		0	0.0	3	2.2	7	2.8	5	3.7	1	1.6	.769
Headache		8	15.4	5	3.6	11	4.4	6	4.5	4	6.3	.018
Nausea		6	11.5	1	0.7	4	1.6	5	3.7	1	1.6	.004
Vomiting		0	0.0	1	0.7	2	0.8	1	0.7	0	0.0	1.000
Diarrhea		0	0.0	3	2.2	2	0.8	3	2.2	0	0.0	.549
Candida infection		6	11.5	1	0.7	4	1.6	2	1.5	8	12.7	<.001
Herpes virus infections		1	1.9	2	1.5	5	2.0	4	3.0	2	3.2	.882
Herpes zoster infections		0	0.0	0	0.0	1	0.4	1	0.7	0	0.0	.830
Tuberculosis reactivation		1	1.9	0	0.0	1	0.4	0	0.0	0	0.0	.345
Hepatitis B reactivation		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–
Anemia		3	5.8	10	7.3	10	4.0	3	2.2	0	0.0	.098
Leukopenia		1	1.9	3	2.2	3	1.2	1	0.7	0	0.0	.682
Neutropenia		1	1.9	6	4.4	13	5.2	5	3.7	2	3.2	.819
Lymphopenia		3	5.8	8	5.8	8	3.2	3	2.2	1	1.6	.377
Thrombocytopenia		2	3.8	1	0.7	3	1.2	1	0.7	0	0.0	.408
Pancytopenia		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–
Aplastic anemia		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–
Hepatotoxicity		7	13.5	14	10.2	15	6.0	7	5.2	3	4.8	.150
Nephrotoxicity		2	3.8	1	0.7	3	1.2	1	0.7	0	0.0	.408
Drug eruption		0	0.0	3	2.2	2	0.8	0	0.0	1	1.6	.311
Skin cancer		1	1.9	0	0.0	2	0.8	0	0.0	1	1.6	.227
Lymphoma		0	0.0	0	0.0	1	0.4	0	0.0	0	0.0	1.000
Solid organ tumor		1	1.9	0	0.0	1	0.4	0	0.0	0	0.0	.345
Demyelinating disease (optic neuritis, Guillain-Barré syndrome, MS)		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	–
IBD		0	0.0	0	0.0	1	0.4	1	0.7	0	0.0	.831
Paradoxical psoriasis		3	5.8	3	2.2	4	1.6	2	1.5	1	1.6	.411
MACE		1	1.9	3	2.2	0	0.0	1	0.7	0	0.0	.066
Surgical procedure		0	0.0	2	1.5	5	2.0	7	5.2	0	0.0	.143
Weight gain		5	9.6	13	9.5	28	11.2	27	20.1	11	17.5	.046
Other adverse effects		4	7.7	5	3.6	17	6.8	11	8.2	5	8.1	.588

Abbreviations: IBD, inflammatory bowel disease; MACE, major adverse cardiac events; MS, multiple sclerosis; NB-UVB, narrowband ultraviolet B.

TABLE 5 Comparison of serious adverse effect and duration of biological usage

	Biological agent	Serious adverse effect	Total duration (month)		P
			Mean ± SD	Median	
Biological agent	Infliximab	No	42.9 ± 85.5	17	.843
		Yes	29.3 ± 28.5	18	
	Etanercept	No	23.6 ± 25.4	15.5	.744
		Yes	23.0 ± 17.3	18	
	Adalimumab	No	45.2 ± 78.4	17	.652
		Yes	44.0 ± 65.0	25.5	
	Ustekinumab	No	23.8 ± 39.8	15	.025
		Yes	35.8 ± 14.6	40	
	Secukinumab	No	8.1 ± 8.6	6	–
		Yes	3.0	3	

TABLE 6 Comparison of adverse effect and duration of biological usage

	Biological agent	Adverse effect	Total duration (month)		P
			Mean ± SD	Median	
Biological agent	Infliximab	No	93.1 ± 167.2	19	.647
		Yes	31.5 ± 49.7	17	
	Etanercept	No	26.3 ± 36.3	12	.434
		Yes	22.7 ± 19.9	17	
	Adalimumab	No	70.3 ± 110.0	24	.005
		Yes	30.2 ± 43.6	15	
	Ustekunimab	No	17.5 ± 18.5	12	.059
		Yes	29.0 ± 48.2	16	
	Secukinumab	No	6.3 ± 5.5	4	.206
		Yes	9.7 ± 10.6	6	

Kimball et al stated that all the rates of malignancies, except NMSC were similar between nonbiological treatments and etanercept, adalimumab, infliximab or phototherapy, but there might be variability in cases of lymphoma and NMSC.[24] Although there are studies reporting that malignancy rates are higher in psoriatic patients than the general adult population, it is not yet precisely known whether these treatments increase the risk of malignancy.[25] Some studies have shown an increased risk of NMSC development in patients receiving anti-TNF.[26] The use of some monoclonal antibody therapies, such as ustekinumab, IL-17 inhibitors, and IL-23 inhibitors does not appear to alter the risk of malignancy; however, larger and longer-term studies are required to confirm these findings. In our study, NMSC was seen at a rate of 0.6%, solid organ tumors at 0.3%, and lymphoma at 0.2%, and none of the patients using etanercept and ustekinumab had any malignancy. The differences between the agents was not statistically significant. The incidence of NMSC was higher in the ≥65 years group (P = .047). It has been reported that the risk of malignancy is higher in the elderly population, but there is no difference in terms of malignancies between elderly population using biological agents and those not using these agents. In the literature, it has been shown that the risk of infection increases three times in the elderly group taking biological agents.[27] In our study, we found the infection rate to be similar in both age groups.

Although weight gain is an adverse effect associated with anti-TNF,[28-30] in our study, it was more frequently seen in the group using IL inhibitors (P = .003). Ustekinumab was the most common biological agent causing weight gain, while anti-TNF agents fell behind secukinumab in terms of weight gain rate (P = .046). In addition, patients <65 years of age were more likely to gain weight than the ≥65 years group (P = .017). In the literature, it has been reported that ustekinumab and secukinumab, which are monoclonal antibodies of anti-IL-12/23 and anti-IL-17, respectively, have less effect on body weight and changes in BMI than anti-TNF agents. However, these cytokines, along with TNF, play a role in the pathogenesis of psoriasis by activating type 1 and type 17T-helper cells.[31] Therefore, suppression of these cytokines may cause weight gain with an effect similar to that of anti-TNF agents.[28]

Despite the increasing number of paradoxical reactions reported in psoriasis patients related to biological treatments, such as ustekinumab, secukinumab and ixekizumab in the literature, most

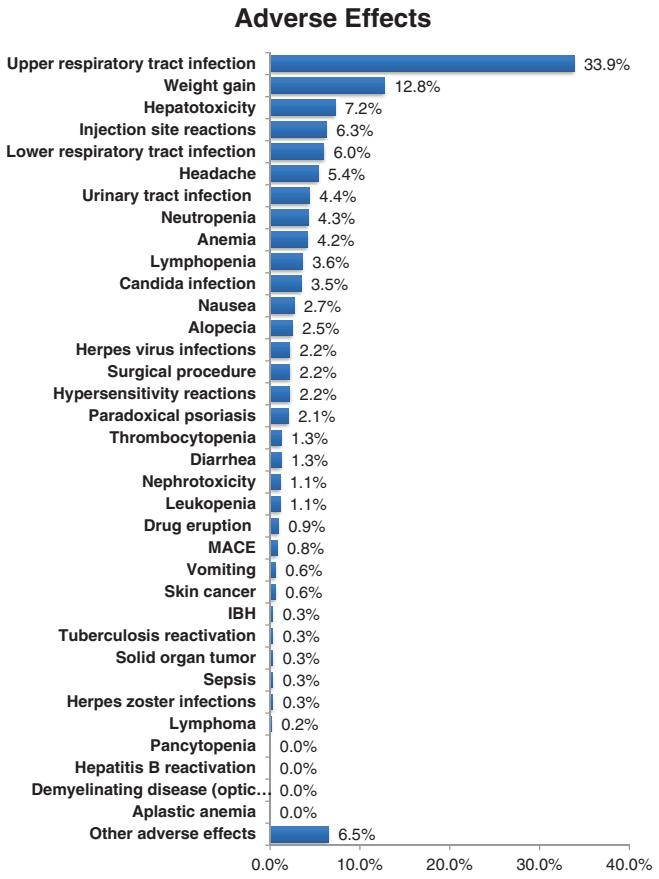

FIGURE 1 All adverse effects

paradoxical reactions have been associated with the use of anti-TNF.[32-36] Paradoxical psoriasis has been associated with so many anti-TNF agents that in some publications, even the definition of paradoxical psoriasis refers to the form of newly emerging or flaring psoriasis lesions during anti-TNF treatments.[34,35] In our study, paradoxical psoriasis was observed with the use of both ustekinumab and secukinumab in addition to anti-TNF. Although it was most frequently seen in patients using infliximab (5.8%), the difference between the agents was not statistically significant. In the literature, paradoxical psoriasis has been reported in 2%-5% of patients treated with anti-TNF.[35,36] In our study, we observed paradoxical psoriasis in patients using anti-TNF (2.3%) at a rate comparable to the literature. However, unlike the literature, we also detected a similar incidence in those using IL inhibitors (1.5%), with no statistically significant difference between the two groups ($P > .05$).

IL-17 inhibitors have been associated with an increased risk of infection, especially mucocutaneous candidiasis.[37] It has been reported that candida infection in secukinumab varies between 0.0% and 5.0%.[38] The IL-17 inhibitor that is most frequently associated with candida infections is brodalumab, which is observed to cause candida infection at a rate of 0.0% to 6.7%.[27] In our study, the rate of candida infections in patients using secukinumab was much higher (12.7%) than in the literature and even compared to candida infections that develop during brodalumab treatment. This may be due to the comorbidities of our patient population. However, in agreement with the literature,[12,38] candida infections did not prevent the continuation of secukinumab treatment in any of our patients. While dysgeusia due to oral candidiasis was observed in one patient, his complaint and oral candidiasis regressed with oral antimycotic treatment. Other adverse effects reported and discussed in relation to secukinumab include neutropenia and IBD.[12] In our study, neutropenia was most commonly detected in patients receiving adalimumab (5.2%), while there was no statistically significant difference between the agents in terms of the incidence of this adverse effect. IBD did not develop in any of our patients using secukinumab.

Regnault et al comparing the efficacy and safety data of patients who met the criteria of biological agent phase studies and those that were not eligible for these studies, reported the overall rate of adverse effects as 41.5% and 45.59%, respectively and the rate of serious adverse effects as 5.36% and 7.08%, respectively.[7] With that study, the authors showed that in real life, most patients had various comorbidities, and therefore would not meet the criteria of phase studies. They reported that the rate of adverse effects was higher in patients in the real life registry. In our study, 77.8% of the patients had at least one comorbidity accompanying psoriasis, while 25.4% had three or more comorbidities. The overall rate of adverse effects was 63.6%, and the rate of serious adverse effects was 4.3%. The rate of serious adverse effects increased associated with the number of comorbidities.

In conclusion, infliximab was the biological agent that resulted in the highest number of adverse effects and that was most discontinued due to these adverse effects. The least number of adverse effects was observed with secukinumab, while ustekinumab was the least discontinued agent due to adverse effects. Although anti-TNF agents had more adverse effects compared to IL inhibitors, the results were similar in both groups in terms of the rate of serious adverse effects. Age, comorbidities, other drugs used together with biological agents, and use of multiple biological agents increased the incidence of certain adverse effects while there was no relationship with smoking and alcohol usage. Prolonged use can be a risk factor for the occurrence of serious adverse effects for ustekinumab. Therefore, patients planned to receive biological agents should be evaluated in terms of these risk factors, and a treatment decision should be made accordingly.

The limitations of the study include its retrospective design, which may have caused some deficiencies in data access. In addition, the small number of patients in the sample may have prevented the analysis of minor differences and rare conditions between the groups. Furthermore, the inclusion of patients receiving combined therapy may have affected the results, but the differences between the groups were tried to be kept to a minimum by not excluding combined therapy cases from any of the groups.

The strengths of this study are that it is a multicenter study, it consists of real life data and contains the biological agents currently

TABLE 7 Comparison of anti-TNF agents with IL inhibitors in terms of adverse effects

		Biological agent						
		Anti-TNF agents		IL inhibitors			Anti-TNF agents	IL inhibitors
		n	%	n	%	*P*	OR (95% CI)	OR (95% CI)
Adverse effect		295	67.4	109	55.3	.004	1.67 (1.18-2.35)	0.60 (0.43-0.85)
Serious adverse effect		21	4.8	6	3.0	.312	1.60 (0.64-4.04)	0.62 (0.25-1.57)
Discontinuation of biological agent due to adverse effects		48	11.0	9	4.7	.012	2.78 (1.29-6.01)	0.36 (0.17-0.77)
Concomitant therapy	None	340	78.0	177	91.2	<.001		
	Methotrexate	82	18.8	11	5.7			
	Acitretin	10	2.3	3	1.5			
	NB-UVB	2	0.5	0	0.0			
	Ciclosporin	2	0.5	3	1.5			
INH prophylaxis		225	55.5	70	37.0	<.001	2.12 (1.49-3.02)	0.47 (0.33-0.67)
Hepatitis B prophylaxis		32	7.4	14	7.1	.906	1.06 (0.56-2.04)	0.94 (0.49-1.80)
Urinary tract infection		21	4.8	7	3.6	.464	1.37 (0.57-3.28)	0.73 (0.31-1.75)
Upper respiratory tract infection		161	36.8	54	27.4	.021	1.54 (1.06-2.22)	0.65 (0.45-0.94)
Lower respiratory tract infection		29	6.6	9	4.6	.313	1.48 (0.69-3.19)	0.68 (0.31-1.45)
Sepsis		2	0.5	0	0.0	1.000		
Injection site reactions		35	8.0	5	2.5	.009	3.33 (1.29-8.65)	0.30 (0.12-0.78)
Hypersensitivity reactions		11	2.5	3	1.5	.566	1.67 (0.46-6.04)	0.60 (0.17-2.18)
Alopecia		10	2.3	6	3.0	.589	0.74 (0.27-2.08)	1.34 (0.48-3.75)
Headache		24	5.5	10	5.1	.835	1.08 (0.51-2.31)	0.92 (0.43-1.97)
Nausea		11	2.5	6	3.0	.700	0.82 (0.30-2.25)	1.22 (0.44-3.35)
Vomiting		3	0.7	1	0.5	1.000	1.35 (0.14-13.08)	0.74 (0.08-7.16)
Diarrhea		5	1.1	3	1.5	.708	0.75 (0.18-3.16)	1.34 (0.32-5.66)
Candida infection		11	2.5	10	5.1	.096	0.53 (0.22-1.24)	1.90 (0.81-4.47)
Herpes virus infections		8	1.8	6	3.0	.383	0.59 (0.20-1.73)	1.69 (0.58-4.93)
Herpes zoster infections		1	0.2	1	0.5	.525	0.45 (0.03-7.21)	2.23 (0.14-35.83)
Tuberculosis reactivation		2	0.5	0	0.0	1.000		
Hepatitis B reactivation						–		
Anemia		23	5.3	3	1.5	.028	3.40 (1.01-11.46)	0.29 (0.09-0.99)
Leukopenia		7	1.6	1	0.5	.446	2.72 (0.33-22.76)	0.37 (0.04-3.07)
Neutropenia		20	4.6	7	3.6	.558	1.60 (0.64-4.04)	0.62 (0.25-1.57)
Lymphopenia		19	4.3	4	2.0	.150	1.65 (0.60-4.50)	0.61 (0.22-1.66)
Thrombocytopenia		6	1.4	1	0.5	.445	3.18 (0.39-26.05)	0.31 (0.04-2.57)
Pancytopenia						–		
Aplastic anemia						–		
Hepatotoxicity		36	8.2	10	5.1	.158	1.67 (0.81-3.45)	0.60 (0.29-1.23)
Nephrotoxicity		6	1.4	1	0.5	.445	2.72 (0.33-22.76)	0.37 (0.04-3.07)
Lupus-like syndrome						–		
Drug eruption		5	1.1	1	0.5	.672	2.26 (0.26-19.50)	0.44 (0.05-3.81)
Skin cancer		3	0.7	1	0.5	1.000	1.35 (0.14-13.08)	0.74 (0.08-7.16)
Lymphoma		1	0.2	0	0.0	1.000		
Solid organ tumor		2	0.5	0	0.0	1.000		
Demyelinating disease		0	0.0	0	0.0	–		
IBD		1	0.2	1	0.5	.525	0.45 (0.28-7.22)	2.22 (0.14-35.75)
Paradoxical psoriasis		10	2.3	3	1.5	.764	1.51 (0.41-5.56)	0.66 (0.18-2.43)
MACE		4	0.9	1	0.5	1.000	1.81 (0.20-16.27)	0.55 (0.06-4.98)
Surgical procedure		7	1.6	7	3.6	.145	0.44 (0.15-1.27)	2.27 (0.78-6.56)
Weight gain		46	10.5	38	19.3	.003	0.54 (0.34-0.87)	1.84 (1.14-2.96)
Other adverse effects		28	6.4	13	6.6	.922	0.97 (0.49-1.91)	1.03 (0.52-2.04)

Abbreviations: IBD, inflammatory bowel disease; IL, interleukin; MACE, major adverse cardiac events; NB-UVB, narrowband ultraviolet B; OR, odds ratio; TNF, tumor necrosis factor.

used in psoriasis. In order to minimize data loss, system records were examined retrospectively, except for patients' files.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conception: Filiz Topaloğlu Demir, İlknur Kıvanç Altunay, Ayşe Serap Karadağ. **Design**: Filiz Topaloğlu Demir, İlknur Kıvanç Altunay, Ayşe Serap Karadağ. **Supervision**: Filiz Topaloğlu Demir, İlknur Kıvanç Altunay, Ayşe Serap Karadağ, Ezgi Özkur. **Data collection and/or processing**: Filiz Topaloğlu Demir, Tuğba Özkok Akbulut, Sema Aytekin, İlteriş Oğuz Topal, Asude Kara Polat, Ezgi Özkür, İlknur Kıvanç Altunay, Ayşe Serap Karadağ. **Analysis and/or interpretation**: Filiz Topaloğlu Demir, Tuğba Özkok Akbulut, Ezgi Özkur, Ayse Serap Karadağ. **Literature review**: Filiz Topaloğlu Demir, Ezgi Özkur. **Writing**: Filiz Topaloğlu Demir. **Critical review**: Filiz Topaloğlu Demir, Ezgi Özkur, Ayse Serap Karadağ.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in xxxx at xxxx, reference number xxxx.

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