Dermatology Practical & Conceptual

Effectiveness and Safety After a Switch to Tildrakizumab: A Real World Multicenter Italian Study in Psoriasis

Eugenia Veronica Di Brizzi[1], Dario Buononato[1], Pierfrancesco Benvenuto[1], Giuseppe Argenziano[1], Rocco De Pasquale[2], Carmen Silvia Fiorella[3], Claudia Giofrè[4], Maria Letizia Musumeci[2], Giovanni Palazzo[5], Leonardo Zichichi[6], Anna Balato[1]

1 Dermatology Unit, University of Campania "Luigi Vanvitelli", Naples, Italy
2 U.O.C. Dermatology Unit, "G. Rodolico-S. Marco" Hospital, Catania, Italy
3 Dermatology Unit, "Monsignor Raffaele Dimiccoli" Hospital, Barletta, Italy
4 U.O.C. Dermatology Unit, "Papardo" Hospital, Messina, Italy
5 Dermatology Unit, Hospital of Tinchi Pisticci, Italy
6 U.O.C. Dermatology Unit, "S. Antonio Abate" Hospital, Trapani, Italy

Key words: Psoriasis, tildrakizumab, biologic drug, anti IL-23 monoclonal antibody

Citation: Di Brizzi EV, Buononato D, Benvenuto P, et al. Effectiveness and Safety After a Switch to Tildrakizumab: a Real World Multicenter Italian Study in Psoriasis. *Dermatol Pract Concept.* 2023;13(4):e2023215. DOI: https://doi.org/10.5826/dpc.1304a215

Accepted: April 21, 2023; **Published:** October 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Eugenia Veronica Di Brizzi, MD, ; Dermatology Unit, University of Campania Luigi Vanvitelli, Nuovo Policlinico (edificio 9C), Via Pansini 5, 80131 Naples Italy. E-mail: eugeniaveronica.dibrizzi@gmail.com

ABSTRACT

Introduction: Tildrakizumab is a humanized IgG1κ monoclonal antibody targeting the p19 subunit of interleukin (IL)-23, approved in 2018 for the treatment of patients with moderate-to-severe chronic plaque psoriasis.

Objectives: This study aimed to evaluate the effectiveness, safety and survival of tildrakizumab in the medium term (48 weeks) in psoriatic patients failure to previous biologic treatment in a real world setting.

Methods: This was a retrospective, multicenter observational study that included adult patients with moderate-to-severe plaque psoriasis, failure to previous biologic therapy, consecutively treated with tildrakizumab. Psoriasis Area Severity Index (PASI) and Body Surface Area (BSA) values were recorded at baseline, at 12 and 48 weeks of treatment. Safety and tolerability of tildrakizumab were investigated by examining the presence of any adverse events.

Results: Overall 51 patients were enrolled. Baseline disease severity was moderate to severe with a mean PASI score of 19.2 ± 8.5, mean BSA of 16 ± 10.4, and mean Dermatology Life Quality Index

(DLQI) of 18.2 ± 6.8. A significant reduction in the mean PASI score was detected at 12 weeks of tildrakizumab therapy (3.5 ± 2.7, P < 0.001), with a further improvement at week 48 (0.6 ± 1.5, P < 0.001). At week 12, there was a great improvement in BSA score for all groups (P <0.001) with further increase at week 48. The effectiveness was confirmed also by DLQI assessment, with a significant decrease at week 12 and even more at week 48 (P <0.001).

Conclusions: This study confirms the effectiveness of tildrakizumab in daily clinical practice in patients with moderate-to-severe plaque psoriasis.

Introduction

Psoriasis is a chronic immune-mediated disease with the IL-23/IL-17 axis playing the leading role [1].

Tildrakizumab is a humanized IgG1κ monoclonal antibody targeting the p19 subunit of interleukin (IL)-23, approved in 2018 for the treatment of patients with moderate-to-severe chronic plaque psoriasis [2]. The effectiveness and safety of tildrakizumab has been firstly evaluated in a phase 2b randomized placebo-controlled trial and in two randomized phase 3 clinical trials, compared with both placebo (reSURFACE 1 and 2) and etanercept (reSURFACE 2). Tildrakizumab has been also well-tolerated, showing no safety issues although the discrete higher risk of nasopharyngitis [3,4]. Recently, confirmatory data on efficacy and safety derived from real-world studies in patients affected by psoriasis, also involving difficult-to-treat areas as scalp, nail, palmoplantar and genital psoriasis are available [5-10].

Nevertheless, little evidence is currently available about the impact of previous biologic exposure on subsequent treatment with tildrakizumab, unlike other biologics [11,12] not allowing dermatologists to maximize patient therapeutic management after switching within and between classes. Hence, this multicenter retrospective study aimed to evaluate the effectiveness, safety and survival of tildrakizumab in the medium term (48 weeks) in psoriatic patients failure to previous biologic treatment in a real world setting.

Methods

Study Design, Patients Characteristics and Data Collection

This was a retrospective, multicenter observational study that included adult patients with moderate-to-severe plaque psoriasis consecutively treated with tildrakizumab at seven Italian Dermatology Units with psoriasis-specialized units. The study was performed in accordance with the principles of the Helsinki Declaration and informed written consent has been obtained from the patients for the use of retrospective data collected during routine clinical practice.

Inclusion criteria were age ≥ 18 years, concomitant presence of moderate-to-severe psoriasis (Psoriasis Area Severity Index [PASI] ≥ 10), failure to previous biologic therapy. Failure was defined as the loss of at least PASI 50. A washout period of at least 4 weeks from previous systemic treatments was required. Exclusion criteria were hepatitis B surface Ag positive, hepatitis C Ab positive, active tuberculosis (TB) or history of incompletely treated TB, malignancy or history of malignancy in the last 5 years. After appropriate screening tests, tildrakizumab was administered in monotherapy at the standard dose regimen (induction phase: 100 mg subcutaneously at weeks 0 and 4, and a maintenance dose every 12 weeks thereafter). Data collected included demographic data (eg, age, gender, height, weight and body mass index [BMI]), disease duration (defined as the time from diagnosis to start of tildrakizumab treatment), associated comorbidities and previous systemic, including biological therapies.

Outcome Measures

PASI and Body Surface Area (BSA) values were recorded at baseline (prior to treatment with tildrakizumab) at 12 and 48 weeks of treatment. The effectiveness of tildrakizumab was reported as the absolute PASI score as well as the relative percentage of patients achieving 75%, 90%, and 100% improvement from baseline PASI (PASI 75, PASI 90, and PASI 100, respectively) at 12 and 48 weeks. The impact on patients quality of life (QoL) was assessed through Dermatology Life Quality Index (DLQI) at each visit (baseline, weeks 12 and 48).

Safety

Safety and tolerability of tildrakizumab were investigated by examining the presence of any adverse events (AEs), including mild and serious AEs, laboratory values (hematology, clinical chemistry and urinalysis), physical examination and local tolerability. The occurrence of AEs was collected at weeks 12 and 48. Reasons for tildrakizumab withdrawal were also collected and classified as (i) lack or loss of efficacy; (ii) AEs; and (iii) other reasons (lost to follow-up, etc)

Statistical Analysis

Patient demographics, clinical characteristics, and primary outcome measures at the baseline visit were summarized using descriptive statistics. Descriptive data were reported using frequencies and percentage for categorical variables and mean values ± standard deviation for continuous ones.

The Wilcoxon matched pairs signed rank test was used for continuous variables at different scheduled visits. Univariate regression analysis was conducted to evaluate the relationship between the variables age, obesity, gender, previous use of biological treatment (anti-TNFα, anti-IL17, anti-IL12/23) and tildrakizumab clinical efficacy expressed in terms of PASI, BSA and DLQI values. A P value less than 0.05 was considered statistically significant. Statistical analyses were computed using GraphPad Prism 6.0 (GraphPad Software Inc.) and SAS® software version 9.3 (SAS Institute Inc.).

Results

Overall, 51 patients were enrolled; most were male (76.5%, 39/51) with a mean age at the time of starting tildrakizumab of 52.3 ± 14.7 years (Table 1). Baseline disease severity was moderate to severe with a mean PASI score of 19.2 ± 8.5, mean BSA of 16 ± 10.4, and mean DLQI of 18.2 ± 6.8. Mean body mass index (BMI) was 29.8 ± 11.9 kg/m^2, and 27.5% (14/51) of patients were obese (BMI ≥ 30). Comorbid conditions were reported in 66.7% (34/51) of patients. In particular, 17.6% (9/51) were affected by psoriatic arthritis (PsA) with the mean disease duration of 10.4 ± 9.7, the baseline disease severity was measured as DAS 28 of 4.9 ± 5.2; patients were not doing other arthritis therapies other than tildrakizumab. Hypertension and dyslipidemia were among the most frequent comorbidities. Regarding previous systemic therapy, and in particular conventional non-biologic one, the majority of patients were treated with cyclosporine. Obviously, all patients have been administered at least 1 biologic drug, since this represented an inclusion criterion. Furthermore, 54.9% (28/51) of patients had already received at least 2 biologic treatments. The most common biologic class that patients had been exposed previously was anti-TNF with 44/51 (86.3%) patients having received it (Table 1). The last biological therapy before starting tildrakizumab was distributed as follows: 47% of patients on anti-TNF (24/51), 31.4% on anti-IL-17 (16/51) and 21.6% on anti-IL-12/23 (11/51).

Treatment withdrawal was reported in 5.8% (3/51) of patients due to lack of efficacy (1/3 patients at week 12), loss of efficacy (1/6 patients at week 48) and lost to follow up (1/6 patient at week 48). Patients withdrawing from the study were defined as non-responders according to the non-responder imputation method. No treatment withdrawal was observed to AEs. AEs that did not require tildrakizumab discontinuation were reported in 3.9% (2/51) of patients and were represented by injection-site reactions,

Table 1. Demographic and baseline characteristics of the study population.

Characteristics	All patients (N = 51) [N (%) or mean ± SD]
Demographics	
Male	39 (76.5)
Age (years)	52.3± 14.7
Weight (kg)	82.6± 16.9
BMI (kg/m2)	29.8± 11.9
BMI >30	14 (27.5)
Difficult-to-treat locations	
Genital	12 (23.5)
Scalp	19 (37.3)
Nails	15 (29.4)
Palmar/plantar	8 (15.7)
Comorbidities	
Yes	34 (66.7)
Diabetes mellitus	8 (15.7)
Dyslipidemia	17 (33.3)
Hypertension	24 (47.1)
Cardiopathy	11 (21.6)
Other	
Psoriatic arthritis	
Yes	9 (17.6)
Age of onset (years)	53.2± 11.4
Duration of disease (years)	10.4± 9.7
Psoriasis	
Age of onset (years)	22.9± 10.3
Duration of disease (years)	21.7± 10.9
PASI	19.2± 8.5
BSA	16± 10.4
DLQI	18.2± 6.8
Previous therapies	
Phototherapy	28
Cyclosporine	43
Methotrexate	19
Acitretin	16
Anti-TNF	44
Anti-IL-17	18
Anti-IL-12/23	11
Anti-IL23	0
Number of prevoius biologic therapies	
1 biologic agent	23
≥ 2 biologic agents	28

BMI = body mass index; BSA = body surface area; DLQI = Dermatology Quality of Life Impairment; PASI = Psoriasis Area Severity Index; SD = standard deviation.

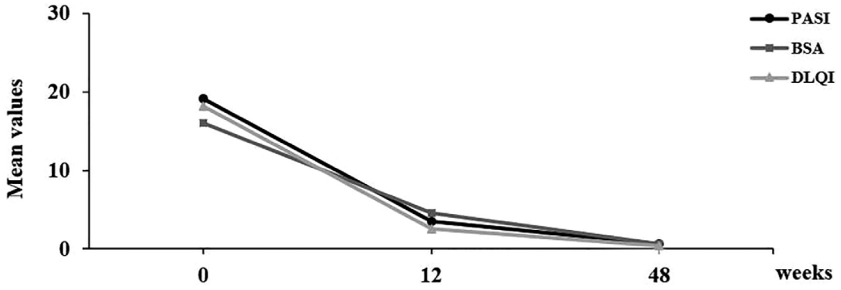

Figure 1. Mean Psoriasis Area Severity Index (PASI), Body Surface Area (BSA), and Dermatology Life Quality Index (DLQI) score values.

Table 2. Patients achieving residual absolute Psoriasis Area Severity Index scores of ≤ 2, ≤ 5 and > 5 after 12 and 48 weeks of tildrakizumab therapy. Non-responder imputation analysis.

Week	Total patients (N)	Ongoing patients (N)	Withdrawals (N)	PASI, N (%)		
				≤2	≤5	>5
12	51	50	1	22 (43)	46 (90)	5 (10)
48	51	48	2	46 (90)	48 (94)	3 (6)

PASI = Psoriasis Area Severity Index.

Table 3. Patients achieving PASI < 75, PASI ≥ 75, PASI ≥ 90 and PASI 100 response rates at 12 and 48 weeks of treatment with tildrakizumab. Non-responder imputation analysis.

Week	Total patients (N	Ongoing patients (N)	Withdrawals (N)	PASI, N (%)			
				<75	≥75	≥90	100
12	51	50	1	17 (33)	34 (67)	15 (30)	11 (22)
48	51	48	2	5 (10)	46 (90)	35 (68)	32 (63)

PASI = Psoriasis Area Severity Index.

headache and nausea/fatigue the day after injection. A significant reduction in the mean baseline PASI score (19.2 ± 8.5) was detected at 12 weeks of tildrakizumab therapy (3.5 ± 2.7, P < 0.001), with a further improvement at week 48 (0.6 ± 1.5, P < 0.001). The PASI score reduction was associated with significant decrease in both baseline BSA and DLQI scores (Figure 1). Absolute PASI scores of ≤ 2 and ≤ 5 were achieved by 43% and 90% of patients at week 12, respectively. A progressively higher proportion of patients achieved absolute PASI scores at weeks 48. Data were analyzed according to the non-responder imputation analysis and are shown in Table 2. Clinical amelioration was also confirmed by the high percentage of patients (67%, 30% and 22%) achieving PASI score improvement (PASI ≥ 75, PASI ≥ 90, and PASI 100) at week 12. An increase result over time up to week 48 was observed. Detailed data analyzed according to the non-responder imputation analysis are summarized in Table 3. The evolution of clinical parameters during treatment with tildrakizumab in patients whose last treatment was anti-TNFα, anti-IL-17 and/or anti-IL-12/23 are shown in Figure 2. A significant difference in PASI baseline values was detected in the anti-IL-12/23 group respect to anti-IL17 one. At week 12, the 3 groups (previous anti-TNFα, anti-IL17, anti-IL12/23) showed a dramatic improvement (P <0.001). No differences were found between groups also at week 48. Similarly, a difference in BSA score was also detected at baseline with the group on anti-IL-17 having a greater score than the anti-IL-12/23 group (P <0.001). At week 12, there was a great improvement in BSA score for all groups (P <0.001) with further increase at week 48. The effectiveness was confirmed also by DLQI assessment, with a significant decrease at week 12 and even more at week 48 (P <0.001). No differences were found among the 3 groups at all time points.

Conclusions

Tildrakizumab has been shown to be well-tolerated and effective in treating patients with plaque psoriasis in multiple clinical trials, but a limited number of real-world studies describing its safety and effectiveness have been published [5-10]. Our study confirmed the elevated effectiveness of tildrakizumab in treating moderate-to-severe plaque psoriasis, as demonstrated by the reduction of PASI, in terms

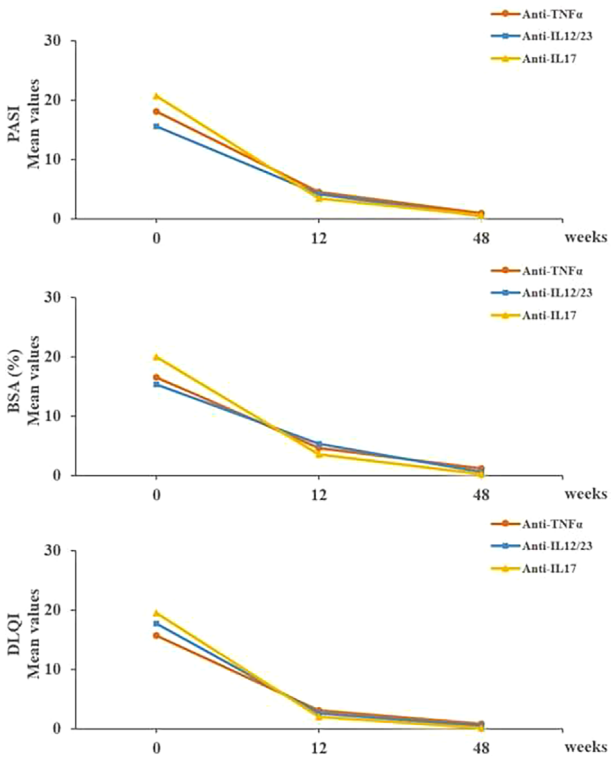

Figure 2. Mean Psoriasis Area Severity Index (PASI), Body Surface Area (BSA), and Dermatology Life Quality Index (DLQI) score values in the whole population stratified by last treatment before tildrakizumab (anti-TNFα, anti-IL17, anti-IL12/23).

of both mean PASI scores (mean baseline PASI: 19.2, mean PASI score at week 48: 0.6) and percentage of patients obtaining PASI 75, 90, and 100 responses. Our findings also showed a marked improvement in BSA and DLQI scores. Our findings are in line with other real-world studies. A retrospective chart review of 30 patients treated with tildrakizumab for moderate-to-severe plaque psoriasis from initial presentation to 12-month follow-up found that, similar to our study, the mean PASI reduced from 16 to 1.5 and that no serious adverse events were reported [13]. Another real-world data study involving 59 psoriatic patients also reported a favorable response to tildrakizumab, with a PASI ≤ 3 being achieved at 28 weeks in 80% of patients. In addition, the authors reported no statistically significant association between prior exposure to biological therapies and effectiveness, since PASI90 at 28 weeks was achieved by 68% of bio-naïve patients and by 60% of bio-experienced patients [8]. An Italian retrospective study included 237 adults with moderate-to-severe plaque psoriasis, enrolled in 10 different centers and treated with tildrakizumab up to week 52. At week 52, 90.91%, 73.55% and 58.68% of patients achieved a PASI 75, PASI 90 and PASI 100, respectively. An absolute PASI ≤ 2 was reached by 85.95% at Week 52 [14]. We observed similar rates of PASI 75/90/100 responses in the present study. Notably, it has to be taken into account that we assessed tildrakizumab effectiveness in psoriasis patients who all switched from anti-TNFα, anti-IL-17 and/or anti-IL-12/23.

A much larger retrospective sub-group analysis of a phase 2 study and two phase 3 studies of tildrakizumab featuring 2217 patients found no association between prior exposure to biological therapies and effectiveness; there was a numerically greater response to tildrakizumab in bio- naïve patients than bio-experienced patients, but it was not statistically significant [15]. Data from 197 patients (52.3% biologic non-naïve), who were treated with anti-IL-23p19 antibodies (127 guselkumab, 55 risankizumab and 15 tildrakizumab) for at least 3 months, were analyzed from the Psoriasis Registry Austria (PsoRA). Results from this study indicated that biologic-non-naïve patients displayed a less favorable response to anti IL-23 treatment as compared to biologic-naïve patients. However, after correction for previous biologic exposure, few differences in PASI improvement were detected among biologic-naïve and -non-naïve patients treated with different IL-23p19 inhibitors. The authors concluded that treatment effectiveness was not related to the class of the previously administered therapy in biologic-non-naïve patients [16]. In our study, patients who switched from anti-IL 17 drugs to tildrakizumab had a more severe disease. Anyhow, this difference did not affect the response to tildrakizumab respect to the other groups.

In general, the rate of adverse events (3.9%) observed in this study was lower than what reported in clinical trials, but similar or lower compared to real-world patients. [3-10,13-16] Thus, a good safety profile was observed for tildrakizumab in our cohort of patients.

This study has some limitations, firstly consisting of the retrospective design, which does not allow collection of missing data. Other significant limitations are the relatively small size of the sample, the lack of a randomized controlled setting, and the heterogeneity of clinical assessment among clinicians from different centers.

This study confirms the effectiveness of tildrakizumab in daily clinical practice in patients with moderate-to-severe plaque psoriasis. Moreover, our observation period up to week 48 confirms that the efficacy of tildrakizumab was maintained over time. All the enrolled patients were biologic-exposed, and the treatment effectiveness was not related to the class of the previously administered therapy. Therefore, this IL-23p19 inhibitor represents a promising treatment alternative for patients who have not responded to previous biologics.

Informed Consent: Informed consent was taken from all the patients for the application of treatment and for the use of data and photographs.

References

1. Ghoreschi K, Balato A, Enerbäck C, Sabat R. Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. *Lancet*. 2021; 397(10275):754-766. DOI: 10.1016/S0140-6736(21)00184-7. PMID: 33515492.
2. Markham A. Tildrakizumab: First Global Approval. *Drugs*. 2018;78(8):845–849. DOI: 10.1007/s40265-018-0917-3. PMID: 29752706.
3. Papp K, Thaçi D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol*. 2015;173(4):930–939. DOI: 10.1111/bjd.13932. PMID: 26042589.
4. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (ReSURFACE 1 and ReSURFACE 2): Results from two randomised controlled, phase 3 trials. *Lancet*. 2017;390(10091):276-288. DOI: 10.1016/S0140-6736(17)31279-5. PMID: 28596043.
5. Burlando M, Castelli R, Cozzani E, Parodi, A. Treatment of moderate-to-severe plaque psoriasis with tildrakizumab in the real-life setting. *Drugs Context*. 2021;10:2021-2-6. DOI: 10.7573/dic.2021-2-6. PMID: 34104197. PMCID: PMC8152773.
6. Galán-Gutierrez M, Rodriguez-Fernandez Freire L, Ruiz-Villaverde R. Tildrakizumab: Short-term efficacy and safety in real clinical practice. *Int J Dermatol*. 2022;61(9):e355-e357. DOI: 10.1111/ijd.15840. PMID: 34632570.
7. Drerup KA, Seemann C, Gerdes S, Mrowietz U. Effective and safe treatment of psoriatic disease with the anti-il-23p19 biologic tildrakizumab: Results of a real-world prospective cohort study in nonselected patients. *Dermatology*. 2022;238(4):615-619. DOI: 10.1159/000519924. PMID: 34775387. PMCID: PMC9393809.
8. Caldarola G, Galluzzo M, Bernardini N, et al. Tildrakizumab in moderate-to-severe plaque psoriasis: A multicenter, retrospective, real-life study. *Dermatol Ther*. 2022;35(6):e15488. DOI: 10.1111/dth.15488. PMID:35384168.PMCID: PMC9287013.
9. Simpson K, Low ZM, Howard A, Kern JS. Successful management of treatment resistant nail psoriasis with tildrakizumab. *Australas J Dermatol* 2021;62(3):390–393. DOI: 10.1111 /ajd.13642. PMID: 34114645.
10. Galluzzo M, Talamonti M, Cioni A, et al. Efficacy of Tildrakizumab for the Treatment of Difficult-to-Treat Areas: Scalp, Nail, Palmoplantar and Genital Psoriasis. *J Clin Med* 2022;11(9):2631. DOI: 10.3390/jcm11092631. PMID: 35566756. PMCID: PMC9100809.
11. Conti A, Peccerillo F, Amerio P, et al. Efficacy and safety of switching to ixekizumab in secukinumab nonresponder patients with psoriasis: results from a multicentre experience. *Br J Dermatol*. 2019;180(6):1547-1548. DOI: 10.1111/bjd.17580. PMID: 30578668.
12. Torres T, Puig L, Vender R, et al. Drug Survival of Interleukin (IL)-17 and IL-23 Inhibitors for the Treatment of Psoriasis: A Retrospective Multi-country, Multicentric Cohort Study. *Am J Clin Dermatol*. 2022;23(6):891-904. DOI: 10.1007/s40257 -022-00722-y. PMID: 35976568.
13. Wei NW, Chi S, Lebwohl MG. Retrospective analysis in patients with moderate to severe plaque psoriasis treated with tildrakizumab: real-life clinical data. *J Psoriasis Psoriatic Arthritis*. 2022;7(2):55–9. DOI: 5 10.1177/24755303221077211.
14. Narcisi A, Valenti M, Gargiulo L, et al. Real-life effectiveness of tildrakizumab in chronic plaque psoriasis: A 52-week multicentre retrospective study—IL PSO (Italian landscape psoriasis). *J Eur Acad Dermatol Venereol*. 2023;37(1):93-103. DOI: 10.1111/jdv.18594. PMID: 36156312. PMCID: PMC10092064.
15. Poulin Y, Ramon M, Rosoph L, et al. Efficacy of tildrakizumab by patient demographic and disease characteristics across a phase 2b and 2 phase 3 trials in patients with moderate-to-severe chronic plaque psoriasis. *J Eur Acad Dermatol Venereol*. 2020;34(7): 1500–1509. DOI: 10.1111/jdv.16187. PMID:31919889.
16. Graier1 T, Weger W, Jonak C, et al. Real world effectiveness of anti interleukin 23 antibodies in chronic plaque type psoriasis of patients from the Austrian Psoriasis Registry (PsoRA*). Sci Rep*. 2022;12(1):15078. DOI: 10.1038/s41598-022-18790-9. PMID: 36064563. PMCID: PMC9442573.