Dermatology Practical & Conceptual

A prospective Real-Life Multicenter Study of Tildrakizumab 200 mg in Patients with Moderate-Severe Psoriasis: Who is the Ideal Patient?

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Key words: Tildrakizumab 200 mg, Psoriasis, Anti-IL23, Psoriasis treatment, Obesity, Dose escalation

Citation: Di Brizzi EV, Caccavale S, Di Caprio R, et al. A prospective Real-Life Multicenter Study of Tildrakizumab 200 mg in Patients with Moderate-Severe Psoriasis: Who is the Ideal Patient? *Dermatol Pract Concept*. 2024;14(4):e2024284. DOI: https://doi.org/10.5826/dpc.1404a284

Accepted: September 25, 2024; **Published:** October 2024

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT **Introduction:** Tildrakizumab, a humanized monoclonal antibody targeting the p19 subunit of interleukin 23 (IL-23), has shown promise in the management of moderate-to-severe plaque psoriasis, offering potential improvements in clinical outcomes and quality of life.
Objectives: The study aimed to identify patient characteristics that indicate the initiation of a 200 mg dosage of tildrakizumab in a real-world setting, focusing on factors that enhance treatment effectiveness and safety.
Methods: This prospective study included 54 adult patients with moderate-to-severe plaque psoriasis treated with tildrakizumab 200 mg from March 2023 to March 2024 across 13 Italian Dermatology Units. Data collected included demographics, disease duration, comorbidities, and previous treatments. PASI, BSA, and DLQI scores were recorded at baseline and at weeks 4, 16, and 28. Safety was assessed through adverse event reporting. Univariate analysis was performed to identify baseline characteristics significantly associated with achieving PASI ≤ 5 at week 16.
Results: Significant reductions in PASI scores were observed at week 4 (9 ± 6.9, $P < 0.001$), with further improvements at weeks 16 (3.9 ± 4.2, $P < 0.001$) and 28 (2.9 ± 4.4, $P < 0.001$). Univariate analysis showed that obese patients (BMI > 30) had higher odds (OR = 4.333, $P < 0.05$) of achieving PASI ≤ 5. Longer disease duration and starting with a 100 mg dosage also correlated with better outcomes. The safety profile was favorable, with minimal adverse events reported.
Conclusions: Tildrakizumab 200 mg is effective and safe for moderate-to-severe psoriasis, particularly in obese patients. These findings support its use as a long-term treatment option.

Introduction

Psoriasis is a chronic, recurring inflammatory condition of the skin, impacting around 2-4% of people worldwide [1,2]. It typically manifests as sharply defined erythematous topped with white scales. These are commonly located on the elbows, knees, scalp, and lower back, known as plaque psoriasis. Nonetheless, psoriasis can present in various forms, including erythrodermic, guttate, and pustular types [3]. It is also linked with several comorbidities, such as psoriatic arthritis (PsA), heart disease, diabetes, chronic inflammatory diseases of the bowel, and mental health disorders, highlighting its nature as a systemic condition [4,5]. Psoriasis impacts not only the physical health of patients but also profoundly affects their psychological well-being, social interactions, and overall quality of life [6,7].

The management of moderate-to-severe psoriasis, a chronic systemic inflammatory skin disease, represents a significant challenge in dermatological practice [8]. The advent of biologic therapies has revolutionized the treatment landscape, offering new hope for patients with moderate-to-severe forms of the disease. Among these therapies, tildrakizumab, a humanized monoclonal antibody designed to selectively target the p19 subunit of interleukin 23 (IL-23), has emerged as a transformative therapy in the treatment landscape of moderate-to-severe plaque psoriasis. By inhibiting IL-23, a cytokine critical to the pathogenesis of psoriasis, tildrakizumab effectively reduces the activation and proliferation of T_h17 cells, leading to a decrease in the production of pro-inflammatory cytokines and subsequent improvement in cutaneous lesions [9,10]. The advised dosage of tildrakizumab involves a 100-mg subcutaneous (SC) injection at baseline and at week 4, followed by administration every 12 weeks. Nonetheless, within the European context, a 200 mg dose is recommended for individuals with specific attributes, such as a higher body weight [11] and also in patients with high disease burden. Clinical trials and real-world evidence have underscored the efficacy of both dosages of tildrakizumab in achieving significant clinical improvements [12,13,14]. Metrics such as the Psoriasis Area and Severity Index (PASI) scores and the Dermatology Life Quality Index (DLQI) scores have consistently shown substantial improvements, indicating not only a reduction in the severity of skin lesions but also a marked enhancement in patients' quality of life. Importantly, both the 100 mg and 200 mg doses of tildrakizumab have demonstrated a favorable safety profile, with adverse events being infrequent and generally mild to moderate in nature [12-16].

Objective

The aim of the study was to define the patient characteristics that indicate the initiation of a 200 mg dosage of tildrakizumab in a real-life setting.

Methods

This prospective study collected data on adult patients affected by moderate-to-severe plaque psoriasis from March 2023 to March 2024 at 13 Italian Dermatology Units with specialized psoriasis units. Conducted in alignment with the Helsinki Declaration's guidelines, written informed consent was secured from all patients for the utilization of data gathered through regular clinical examinations Inclusion criteria were age ≥ 18 years with a diagnosis of moderate-to-severe

plaque psoriasis and treatment with tildrakizumab 200 mg. Exclusion criteria were malignancy or history of malignancy in the last five years. Each participating center was responsible for collecting data, including demographic information (e.g., age, sex, height, weight, and body mass index [BMI]), disease duration (defined as the time from diagnosis to the start of tildrakizumab treatment), comorbidities, and previous systemic, including biological, therapies. To ensure patient confidentiality and to comply with data protection regulations, all patient data were anonymized at the point of collection. Once anonymized, the data were securely transmitted to the coordinating center, where they were aggregated and analyzed. This centralized approach facilitated a comprehensive analysis of treatment outcomes across the diverse patient population involved in the study. The study duration was designed to cover several observation periods: baseline, week 4, week 16, and week 28. These intervals were chosen to effectively monitor the progression and response to tildrakizumab treatment over time. The PASI and Body Surface Area (BSA) scores at each visit (baseline, weeks 4, 16, and 28) were collected from the electronic medical records. The impact on patients' quality of life (QoL) was assessed through DLQI at each visit (baseline, weeks 4,16, and 28). Safety was assessed based on reported adverse events (AEs), encompassing serious AEs, AEs leading to the cessation of the study drug, and AEs necessitating changes in dosage, as well as on laboratory findings (hematology, clinical chemistry, and urinalysis) and outcomes from physical examinations. Serious adverse events were categorized as AEs that led to death, required hospital admission, or extended a hospital stay. The recording of AEs occurred at weeks 4, 16, and 28.

Statistical Analysis

Demographic information, clinical characteristics, and primary outcome metrics at the initial visit were compiled using descriptive statistical methods. This descriptive information utilized frequencies and percentages for categorical data and means plus standard deviations for continuous data. For continuous variables across various scheduled appointments, the Wilcoxon matched-pairs signed-rank test was applied. To explore the correlation among variables such as age, obesity, sex, PASI, prior biologic treatment use, the presence of comorbidities, and the effectiveness of tildrakizumab 200 mg as measured by PASI, BSA, and DLQI scores, univariate regression analysis was employed. A p-value of less than 0.05 was deemed to indicate significant statistical results. The statistical computations were performed with GraphPad Prism version 6.0 (GraphPad Software Inc., based in La Jolla, CA, USA) and SAS® software, version 9.3 (SAS Institute Inc., located in Cary, NC, USA).

Results

A total of 54 patients (36 male, 66.7%; mean age 52.9 ± 12.6 years, mean psoriasis duration 18.3 ± 10.9 years) were enrolled. Of the 54 patients included in this study, 52, 44, and 32 patients were treated for at least 4, 16, and 28 weeks, respectively (the declining number of patients at each timepoint does not represent treatment withdrawal). Dyslipidemia was the most common comorbidity assessed (n=30, 55.6%), followed by obesity (n=28, 51.8.2%), hypertension (n=27, 50%), diabetes mellitus (n=8, 14.8%), psychiatric disorders (n= 6;11.1%), atopy (n=5, 9.3%), immune-mediate disease (n=3,5.6%), and cardiopathy (n=1, 1.8%). Patients' clinical features are reported in Table 1. Baseline disease severity was moderate to severe, with a mean PASI score of 15.9 ± 8.9, mean BSA of 17.9 ± 14.9, and mean DLQI of 15.3 ± 6.2.

As regards difficult-to-treat area involvement, 14 (25.9%), 11 (20.3%), 10 (18.5%), 9 (16.7%), and 3 (5.5%) patients had the involvement of fingernails, folds, genitalia, head-neck, and palmoplantar area, respectively, underlying the complexity of the enrolled cohort of subjects. Moreover, PsA was collected in 13 (24.1%) patients.

The majority of the patients were previously treated with at least one conventional systemic treatment (cyclosporine 31 [57.4%], Nb-UVB phototherapy 19 [35.2%], methotrexate 16 [29.6%], acitretin 16 [29.6%]), and the most common biologic classes that patients had been exposed to previously were anti-TNF (adalimumab 19 [35.2%], etanercept 5 [9.3%], infliximab 2 [3.7%], and golimumab 2 [3.7%]), anti-IL-12/23 (ustekinumab 9 [16.7%], anti-IL-17 [secukinumab 7 [12.9%], ixekizumab 3 [5.6%], brodalumab 3 [5.6%]), and anti-IL-23 (risankizumab 3 [5.6%], guselkumab 2 [3.7%]). Prior to the start of the study, 19 patients (35.19%) had been treated with tildrakizumab 100 mg (before switching to 200 mg). Only 13 (24.1%) patients were bio-naïve (Table 1). Patients withdrawing from the study were defined as non-responders according to the non-responder imputation method. No treatment withdrawal was observed due to AEs. AEs that did not require tildrakizumab discontinuation were reported in 1.8%% (1/54) of patients and were represented by injection-site reactions, headache, and nausea/fatigue the day after injection.

A significant reduction in the mean baseline PASI score (9 ± 6.9, $P < 0.001$) was detected at week 4 of tildrakizumab 200 mg therapy, with a further improvement at weeks 16 (3.9 ± 4.2, $P < 0.001$) and 28 (2.9 ±4.4, $P < 0.001$) (Table 1). The PASI score reduction was associated with a significant decrease in both baseline BSA and DLQI scores. Data were analyzed according to the non-responder imputation analysis and are shown in Figure 1.

Our analysis focused on 24 patients who started tildrakizumab 200 mg and had completed up to 16 weeks of

Table 1. Patient Features at Baseline (Week 0) Nb-UVB (Narrow band – Ultraviolet B).

Number of Patients	54
Sex:	
Male	36 (66.7%)
Female	18 (33.3%)
Mean age *(years)*	52.9 ± 12.6
Mean duration of psoriasis *(years)*	18.3 ± 10.9
Psoriatic arthritis	13 (24%)
Difficult-to-treat area involvement	
Head-neck	9 (16.7%)
Palms or soles	3 (5.5%)
Genital	10 (18.5%)
Fingernails	14 (25.9%)
Folds	11 (20.3%)
Comorbidities:	
Hypertension	27 (50%)
Dyslipidemia	30 (55.6%)
Obesity	28 (51.8%)
Diabetes	8 (14.8%)
Cardiopathy	1 (1.8%)
Psychiatric disorders	6 (11.1%)
Immune-mediated diseases	3 (5.6%)
Atopy	5 (9.3%)
Previous systemic treatments (conventional):	
Methotrexate	16 (29.6%)
Cyclosporine	31 (57.4%)
Nb-UVB Phototherapy	19 (35.2%)
Acitretin	16 (29.6%)
Bionaïve	13 (24.1%)
Previous biologic treatments:	
Anti-TNFα	
Adalimumab	19 (35.2%)
Etanercept	5 (9.3%)
Infliximab	2 (3.7%)
Golimumab	2 (3.7%)
Certolizumab	0
Anti-IL-12/23	
Ustekinumab	9 (16.7%)
Anti-IL-17	
Secukinumab	7 (12.9%)
Ixekizumab	3 (5.6%)
Brodalumab	3 (5.6%)
Bimekizumab	0
Anti-IL-23	
Risankizumab	3 (5.6%)
Guselkumab	2 (3.7%)
Previous tildrakizumab 100 mg treatments:	19 (35.19%)

treatment at the time of analysis. At week 16, 44 patients had completed the treatment. However, only 24 of these 44 patients achieved a PASI score ≤ 5, which represents the subset of patients analyzed for effectiveness at week 16. Univariate analysis revealed several baseline patient characteristics significantly associated with achieving a PASI ≤ 5 at week 16.

Patients with a BMI over 30 had significantly higher odds of achieving a PASI ≤ 5 (OR = 4.333; 95% CI: 1.435–6.00, $P < 0.05$). Additionally, patients with a disease duration greater than two years at baseline were significantly associated with achieving a PASI ≤ 5 at week 16 (OR = 4.51; 95% CI: 2.891–5.923, $P < 0.001$). Patients without PsA at baseline had higher odds of achieving a PASI ≤ 5 compared to those with PsA (OR = 3.8; 95% CI: 1.193–5.530, $P < 0.05$). Lastly, patients starting with tildrakizumab 100 had significantly higher odds of achieving a PASI ≤ 5 at week 16 compared to naïve patients (OR = 3.00; 95% CI: 0.8482–5.305, $P < 0.05$).

Other variables showed associations with no statistical significance. Males had higher odds of achieving a PASI ≤ 5 compared to females. Patients aged 45-65 had higher odds of achieving a PASI ≤ 5 compared to those under 45, while patients over 65 had lower odds compared to those under 45. Patients with a BMI between 25 and 30 also had higher odds of achieving a PASI ≤ 5. Patients with more than two comorbidities had higher odds of achieving a PASI < 5 compared to those with fewer than two comorbidities.

Patients with nail psoriasis and genital psoriasis had lower odds of achieving a PASI ≤ 5 compared to those with trunk psoriasis. Those with a baseline PASI score greater than 10 had higher odds of achieving a PASI ≤ 5 compared to those with a PASI score less than 10. Regarding previous treatments, patients who had been treated with ciclosporin had higher odds of achieving a PASI ≤ 5 compared to those treated with methotrexate, and those treated with acitretin had similar odds. Patients who had received fewer than two previous systemic treatments had higher odds of achieving a PASI ≤ 5 compared to naïve patients, true also for those with more than two previous treatments (Figure 2).

Discussion

This study undertook a detailed evaluation of patient characteristics to determine the most suitable candidates for the 200 mg dosage of tildrakizumab, a drug used in the treatment of moderate-to-severe psoriasis. The objective was to identify specific factors that enhance treatment effectiveness and safety, thereby optimizing patient outcomes. Comprehensive data gathered from multiple clinical sites included patient demographics, disease severity, previous treatment histories, and specific comorbidities including obesity.

Our findings demonstrate a significant reduction in PASI scores as early as four weeks after initiation of tildrakizumab 200 mg treatment, with continued improvement observed up to 28 weeks. These results are in line with a previous randomized controlled trial [13]. This corroborates with the

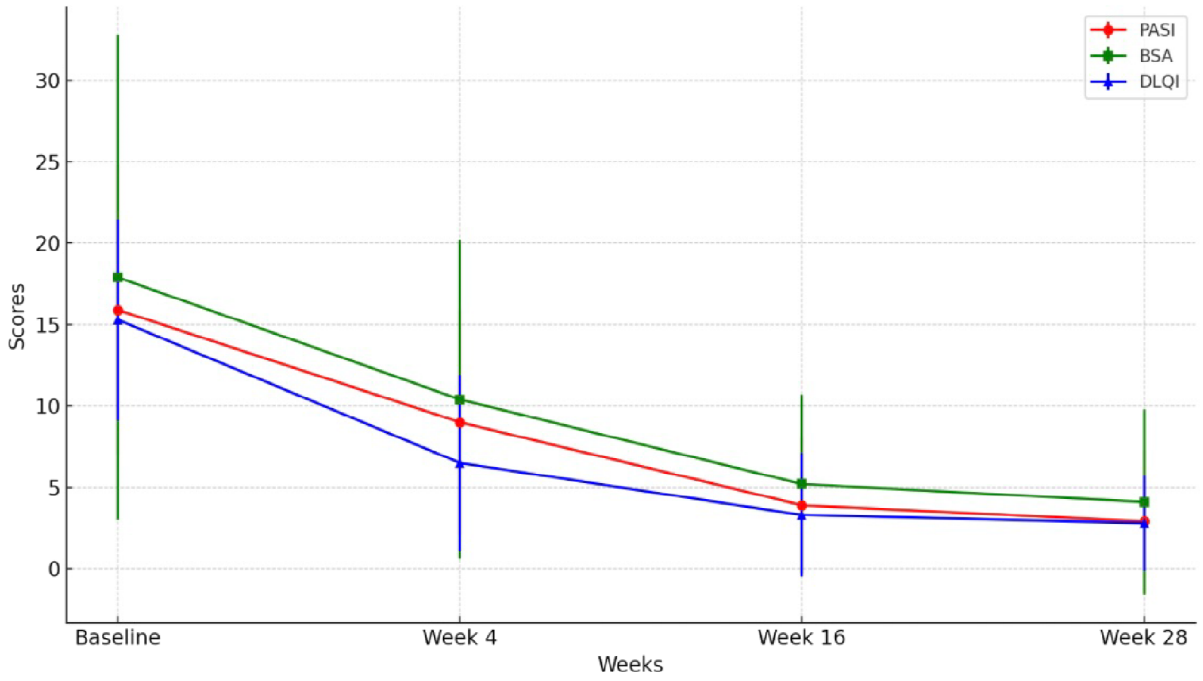

Figure 1. Mean Psoriasis Area Severity Index (PASI), body surface area (BSA), and Dermatology Life Quality Index (DLQI) score values.

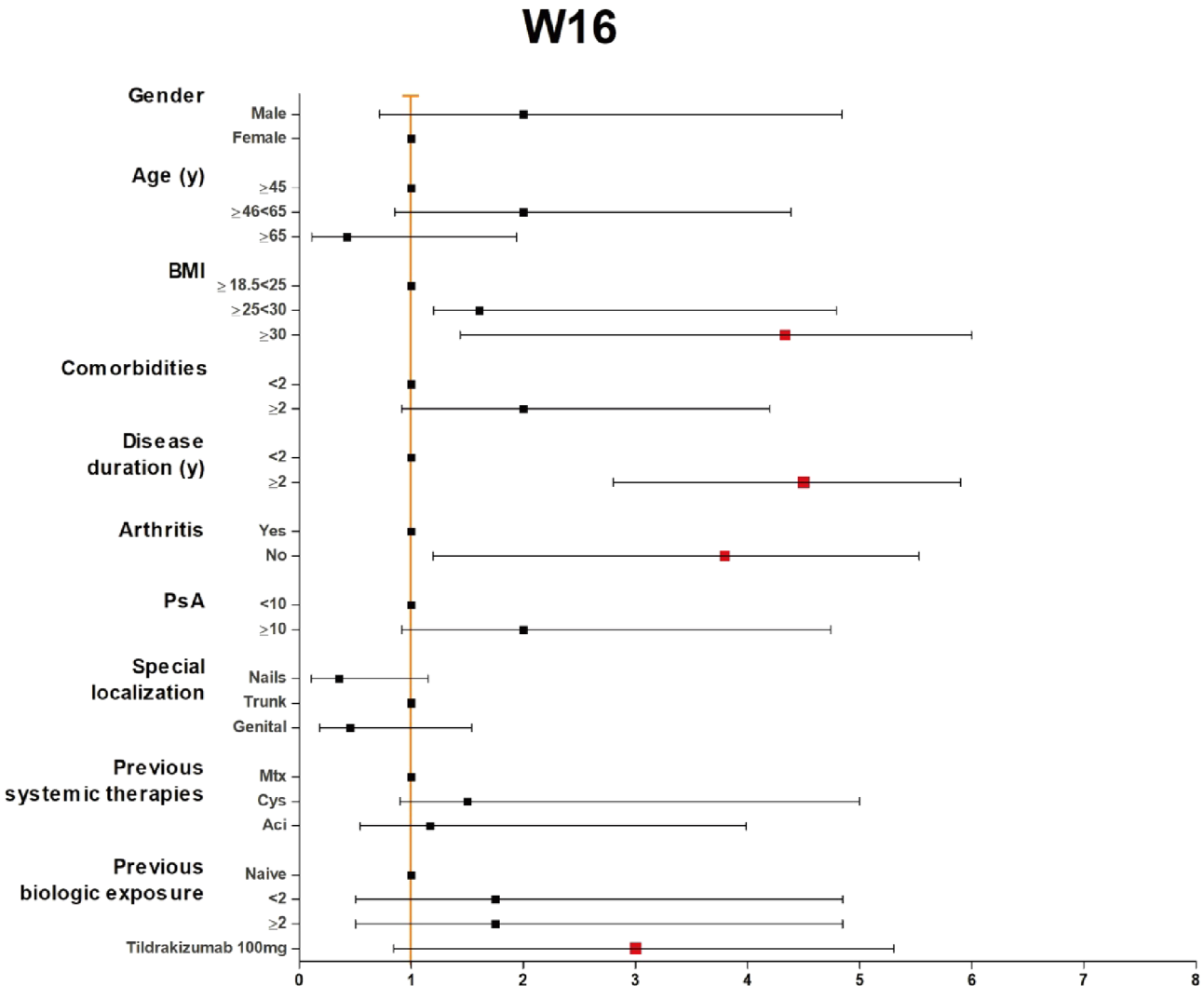

Figure 2. Forest plot of the fully adjusted logistic regression model to assess the association between patients' baseline characteristics and achieving a PASI ≤ 5 at week 16. Odds ratios (OR) and 95% confidence intervals (CI) are depicted. BMI, body mass index; PASI, psoriasis area severity index; PsA, psoriatic arthritis.

meta-analysis conducted by Bilal J et al. which highlighted the drug's robust efficacy profile [17]. The study cohort exhibited a variety of comorbid conditions, with dyslipidemia, hypertension, and obesity being the most common. Notably, a substantial proportion of patients (51.8%) were obese, presenting a unique opportunity to examine the efficacy of tildrakizumab in this subgroup. Obesity is recognized as a factor that can potentially influence the pharmacokinetics and pharmacodynamics of biologic therapies, possibly necessitating adjustments in dosing strategies to achieve optimal therapeutic outcomes [18-20].

The administration of increased dosages of biologic therapies in obese patients with psoriasis is a subject of considerable clinical interest, reflecting the broader shift towards personalized medicine in dermatology. Obesity, a common comorbidity in psoriasis, not only exacerbates the severity and progression of the disease but also influences the pharmacokinetic profiles of biologic treatments, necessitating a nuanced approach to dosage optimization [21,22].

Obesity alters the volume of distribution and clearance rates for biologics, which are primarily distributed in the vascular compartment and, to a lesser extent, in adipose tissue. This altered distribution can lead to lower drug concentrations at the site of action, potentially reducing efficacy. As such, increased dosages may be required to achieve therapeutic drug levels, a concept supported by pharmacokinetic modeling studies [23,24]. Evidence suggests that higher doses of biologics may significantly enhance treatment outcomes in obese patients with psoriasis. For example, studies have shown that obese patients receiving standard doses of TNF inhibitors or IL-17 and IL-23 blockers exhibit lower response rates compared to their non-obese counterparts. In contrast, dose escalation has been associated with improved clinical responses, as measured by PASI score reductions and quality of life improvements [25-26]. The safety profile of tildrakizumab 200 mg observed in our study was favorable, with only a minimal incidence of adverse events reported, none of which necessitated discontinuation of therapy. This is in alignment with the safety data from RCTs, further validating the tolerability of tildrakizumab in a real-world setting [9,13]. The absence of treatment withdrawal due to AEs in our study is particularly noteworthy, indicating that tildrakizumab 200 mg is well-tolerated among patients with moderate-to-severe psoriasis, including those with comorbid conditions.

The significant improvements in PASI, BSA, and DLQI scores observed in our study not only reflect the clinical effectiveness of tildrakizumab but also highlight its positive impact on patients' quality of life.

Our findings reinforce the importance of personalized medicine in the management of psoriasis. The effectivenessof tildrakizumab 200 mg in patients with moderate-to-severe psoriasis, particularly in obese patients, suggests that treatment strategies should consider patient-specific factors such as BMI to optimize therapeutic outcomes. Furthermore, the favorable safety profile of tildrakizumab 200 mg observed in this study supports its use as a long-term treatment option for psoriasis.

This study highlighted several baseline patient characteristics that influence the effectiveness of tildrakizumab 200 mg treatment in a real-world population with moderate-to-severe plaque psoriasis. The results emphasize the importance of considering specific demographic and clinical factors when predicting treatment response. Univariate analysis revealed several baseline patient characteristics significantly associated with achieving a PASI ≤ 5 at week 16. Firstly, patients with a BMI over 30 showed significantly higher odds of achieving a PASI ≤ 5 at week 16. This finding suggests that tildrakizumab is particularly effective in obese patients. The PASI reduction in these patients could be attributed to tildrakizumab's ability to effectively modulate inflammatory pathways that are upregulated in obesity [27].

A recent study evaluated the effectiveness and safety of tildrakizumab 200 mg in obese patients with moderate-to-severe psoriasis, suggesting that this higher dose may be more effective than the 100 mg dose in patients weighing ≥ 90 kg with high disease burden [14]. Second, a disease duration of greater than two years was associated with a significant improvement in PASI. Our findings suggest that tildrakizumab may be particularly effective in patients with a longer disease duration. However, it is worth noting that other studies on IL-23 inhibitors, such as risankizumab and guselkumab, have reported different outcomes regarding disease duration [28,29]. For instance, Schäkel et al. [29] observed that patients with a shorter disease duration (≤2 years) experienced higher rates of complete skin clearance and faster responses compared to those with longer disease duration. These contrasting results indicate that the impact of disease duration on treatment outcomes may vary depending on the specific IL-23 inhibitor used. Another important factor is the absence of PsA at baseline, which was associated with better treatment outcomes. This suggests that the presence of joint comorbidities might negatively influence the response to tildrakizumab, possibly due to the increased complexity of disease management in these patients. Finally, patients who started with a 100 mg dose of tildrakizumab before switching to 200 mg showed significantly higher odds of achieving a PASI ≤ 5 compared to naive patients. This might reflect an initial dosage adjustment that allows for optimizing treatment effectivenesswithout significantly increasing the risk of adverse events. Other variables that showed associations, though not statistically significant, still provide useful insights for clinical practice, as shown in Figure 2.

The safety profile of tildrakizumab was favorable, with few adverse events and no treatment withdrawal due to adverse events. This confirms previous clinical trial data and supports the use of tildrakizumab as a safe and effective therapy for moderate-to-severe plaque psoriasis.

Limitations

The study limitations were the small sample size, the lack of a control group, and the short study duration.

Future research should aim to further elucidate the pharmacokinetics of tildrakizumab in obese patients, exploring potential dose-response relationships and the impact of obesity on therapeutic efficacy and safety. Additionally, long-term studies focusing on the durability of response and the management of comorbid conditions in patients treated with tildrakizumab are needed to fully understand its role in the comprehensive care of psoriasis.

Conclusions

This study demonstrates that the 200 mg dose of tildrakizumab is effective and safe for treating moderate-to-severe psoriasis, particularly in obese patients. Significant improvements in PASI, BSA, and DLQI scores were observed as early as after the first few weeks of treatment, with a favorable tolerability profile and few adverse events. These results support the use of tildrakizumab as a long-term treatment option and highlight the importance of personalized medicine in managing psoriasis. Further studies are needed to confirm these findings and optimize dosing strategies.

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