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ORIGINAL RESEARCH

Tildrakizumab for the treatment of moderate-to-severe psoriasis: a 52-week, real-world Portuguese multicentric study

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Abstract

Background: Real-world evidence plays a pivotal role in validating the efficacy of biologic drugs beyond the controlled environment of randomized trials. This study aimed to evaluate the effectiveness of tildrakizumab in treating moderate-to-severe psoriasis within a real-world setting over a 52-week period in Portugal.

Methods: This multicentric, prospective, observational study included adult patients with moderate-to-severe psoriasis. All participants received tildrakizumab 100 mg at weeks 0 and 4, followed by a maintenance dose every 12 weeks, and were monitored for 52 weeks. Primary endpoints were determined based on Psoriasis Area and Severity Index (PASI) assessments at baseline, 16 (±2) weeks, 28 (±2) weeks and 52 (±2) weeks.

Results: A total of 54 patients were enrolled in the study (56% men, mean age of 50.3 ± 14.4 years). Half of the sample (n=27) had no prior experience with biologic treatments. About 74% of patients (n=40) presented at least one comorbidity during the study, with psoriatic arthritis being the most prevalent (29.6%). By week 52, there was a significant decrease in the mean PASI from 17.8±10.3 at baseline to 1.3±1.9 (p<0.001), indicating an overall improvement of 93%. By week 52, more than 85% of patients attained PASI ≤5, more than 80% reached PASI ≤3, and nearly 60% achieved PASI ≤1. Infections were observed in 9.3% of patients, and one patient required hospitalization (1.9%). The cumulative proportion of patients continuing treatment at 52 weeks was 88.9%.

Conclusions: This study demonstrates that tildrakizumab is an effective and safe agent for the treatment of moderate-to-severe psoriasis in a diverse, real-world setting.

Keywords: biologic, effectiveness, IL-23, psoriasis, real-world, safety, tildrakizumab.

Citation

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Introduction

Psoriasis is an immune-mediated skin disease that is estimated to affect 4.4% of the Portuguese population.[1] It can manifest at any age and imposes a significant burden on the patients due to its chronic nature, disfigurement, disability and associated comorbidities.[2,3]

Major advances in immunological and genetic studies have identified IL-17 and IL-23 as key drivers in psoriatic inflammation.[4] IL-23, in particular, is a heterodimeric regulatory cytokine mainly produced by dendritic cells, playing a major role in late-stage differentiation and maturation of pathogenic T helper 17 lymphocytes, which subsequently fuels the inflammatory cascade.[5] Biological therapies targeting these cytokines have revolutionized the management of psoriasis by markedly reducing disease activity and enhancing the quality of life of patients, especially in moderate-to-severe disease forms.[6,7]

Tildrakizumab is a humanized monoclonal antibody that selectively binds to the p19 subunit of IL-23.[8] Its efficacy in treating moderate-to-severe psoriasis, compared with a placebo or etanercept, was evaluated in two double-blind randomized controlled trials: reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754).[9] These studies also demonstrated the effectiveness of tildrakizumab in maintaining a long-term response, with a favourable safety profile.[10]

Recent extensive studies have shown that a significant proportion of patients (up to 78%) receiving systemic drugs for psoriasis in clinical practice is not adequately represented in randomized controlled trials due to ineligibility.[11] Consequently, the patient population evaluated in psoriasis clinical trials may not always mirror patients with psoriasis in clinical settings, highlighting the importance of reports from real-world scenarios following the approval of a new drug to validate and challenge clinical trial results. Real-world evidence demonstrating the effectiveness and safety of tildrakizumab in diverse clinical practices and settings is therefore desirable to assist clinicians in making informed decisions.

This multicentric prospective study aims to assess the effectiveness and safety of tildrakizumab for the treatment of moderate-to-severe psoriasis in a real-world clinical setting over 52 weeks in Portugal.

Methods

This is a multicentric, observational, prospective cohort study involving patients with psoriasis from five Portuguese centres. The present study was conducted in accordance with the Declaration of Helsinki initially published in 1964 on Ethical Principles for Medical Research Involving Human Subjects and after approval by the local ethical committee. Patient consent was exempted due to the retrospective nature of the study: the study protocol did not deviate from standard clinical practice, and data collection and handling complied with applicable laws, regulations, and guidance regarding patient protection, including patient privacy.

Sampling and study design

In this prospective multicentric study, we included consecutive adult (>18 years old) patients diagnosed with moderate-to-severe psoriasis who began treatment with tildrakizumab between September 2021 and September 2022. This encompassed both naïve patients and those who experienced failure with previous therapies, including biologic agents. Patients discontinued from other treatments due to adverse effects were also included. Study visits were scheduled at baseline and at 16 (±2) weeks, 28 (±2) weeks and 52 (±2) weeks. Treatment with tildrakizumab adhered to current clinical care practice recommendations. No strict exclusion criteria were applied to ensure the study's objectives, namely to represent a heterogeneous clinical setting by including a diverse, representative sample of patients encountered in daily clinical practice.

Main outcome measures

Disease severity and treatment response was assessed using the absolute Psoriasis Area and Severity Index (PASI). Additionally, the Body Surface Area (BSA) index and the Dermatology Life Quality Index (DLQI) were estimated whenever feasible.

Primary endpoints included (1) absolute PASI variation; (2) the proportion of patients achieving PASI ≤1, PASI ≤3 and PASI ≤5; and (3) the percentage of patients achieving PASI100, PASI90 and PASI75 (representing a 100%, 90% and 75% or greater reduction in PASI scores from baseline). These primary endpoints were evaluated at 16 (±2) weeks, at 28 (±2) weeks and at 52 (±2) weeks.

Secondary endpoints encompassed tildrakizumab's safety, discontinuation rate and causes, drug survival, and effectiveness based on previous biologic agent use (if applicable). A subgroup analysis was conducted for effectiveness concerning previous treatments (biologic treatment naïve vs non-naïve) and obesity (BMI <30 vs ≥30 kg/m^2). Relevant clinical data on comorbidities, family history and previous treatments were also collected and incorporated for analysis.

Statistical analysis

Descriptive analysis is presented for all variables. Continuous variables are presented as mean ± standard deviation, whilst categorical variables are expressed as proportions. The paired *t*-test and Wilcoxon test were used to compare paired variables with normal and skewed distributions, respectively, and the independent *t*-test and Mann–Whitney test were used similarly for non-paired variables. Pearson (normal distributions) and Spearman (skewed distributions) correlations were also used to study continuous variables, whereas χ^2 and Fisher tests were used to compare categorical variables. Non-responder imputation was adopted in the case of drug discontinuation due to adverse effects during follow-up. Drug survival was estimated using the Kaplan–Meier method.

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences software, version 24 (IBM Corporation), with a p value of <0.05 considered to be statistically significant.

Results

A total of 54 patients were included in the study, comprising 56% males (*n*=30), with a mean age of 50.3±14.4 years old, and all received treatment with tildrakizumab. Table 1 displays the baseline characteristics of the sample, whereas Tables 2 and 3 present the previous treatments and comorbidities of participants, respectively.

Primary endpoints

At 52 weeks, the mean PASI decreased significantly from 17.8±10.3 at baseline to 1.3±1.9 at week 52 (p<0.001), reflecting an overall improvement of 93%. Amongst a subset of 47 patients, the mean BSA decreased from 20.3±13.5 at baseline to 1.3±1.8 at week 52 (p<0.001), indicating an overall improvement of 94%. Additionally, in a subset of 42 patients, the mean DLQI decreased from 18.5±6.7 at baseline to 0.6±1.2 at week 52 (p<0.001), demonstrating an overall improvement of 97%. Figure 1 illustrates the notable decrease in PASI, BSA and DLQI throughout the follow-up visits.

More than 85% of patients reached PASI75 by week 52, whilst 80% achieved PASI90 and 40% attained PASI100. The detailed progression of PASI75, PASI90 and PASI100 throughout the study's follow-up period is depicted in Figure 2.

In addition, more than 85% of patients achieved PASI ≤5 at week 52 and more than 80% achieved PASI ≤3, with nearly 60% achieving PASI ≤1. The detailed proportion of patients achieving PASI ≤5, ≤3 and ≤1 during the follow-up is illustrated in Figure 3.

Secondary endpoints

Overall, biologic-naive patients achieved a more favourable clinical response compared to those who had previously received a biologic agent, a difference that

Table 1. Baseline characteristics of patients treated with tildrakizumab (*n*=54).

Characteristic	*n*=54
Age (years), mean ± SD	50.3±14.4
Male, *n* (%)	30 (55.6)
Weight (kg), mean ± SD	76.4±15.6
BMI (kg/m²), mean ± SD	26.7±4.4
Family history of PsO, *n* (%)	15 (27.8)
Disease duration (years), mean ± SD	20.5±13.6
PASI score, mean ± SD	17.8±10.3
DLQI score, mean ± SD	18.3±6.6

DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; PsO, psoriasis; SD, standard deviation.

Table 2. Previous treatment of patients treated with tildrakizumab (*n*=54).

Previous treatment	*n* (%)
Biologic naive	27 (50)
Biologic experienced	27 (50)
1 agent	21 (77.8)
2 agents	3 (11.1)
>2 agents	3 (11.1)
Last biologic before tildrakizumab	
Adalimumab	8 (29.6)
Ustekinumab	6 (22.2)
Secukinumab	6 (22.2)
Etanercept	4 (14.8)
Guselkumab	1 (3.7)
Ixekizumab	1 (3.7)

Table 3. Comorbidities of patients treated with tildrakizumab (*n*=54).

Comorbidities	*n* (%)
None	40 (74.1)
Psoriatic arthritis	16 (26.9)
Dyslipidaemia	15 (27.8)
Hypertension	15 (27.8)
Obesity	9 (16.7)
Diabetes	7 (13.0)
Cardiovascular disease	6 (11.1)
Depression	5 (9.3)
Hepatitis C	2 (3.7)
Cirrhosis	1 (1.9)
Inflammatory bowel disease	1 (1.9)
Monoclonal gammopathy	1 (1.9)
Latent tuberculosis	17 (31.5)
Smoking	
Never	40 (74.1)
Current	12 (22.2)
Former	2 (3.7)

Figure 1. Evolution of disease severity up to week 52 at different follow-up intervals. Disease severity and treatment response were assessed using the absolute Psoriasis Area and Severity Index (PASI) for the entire sample (*n*=54). The mean PASI values are depicted at different follow-up visits. Additionally, the Body Surface Area (BSA) index and Dermatology Life Quality Index (DLQI) were estimated for 47 and 42 participants, respectively, with mean values presented at various follow-up intervals. Non-responder imputation was adopted in the case of drug discontinuation.

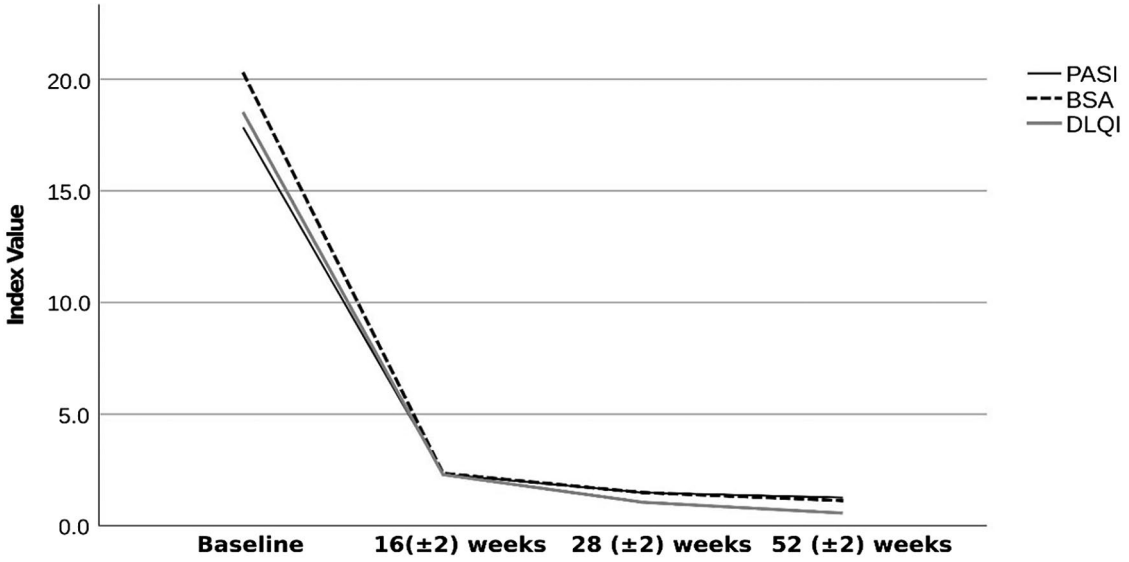
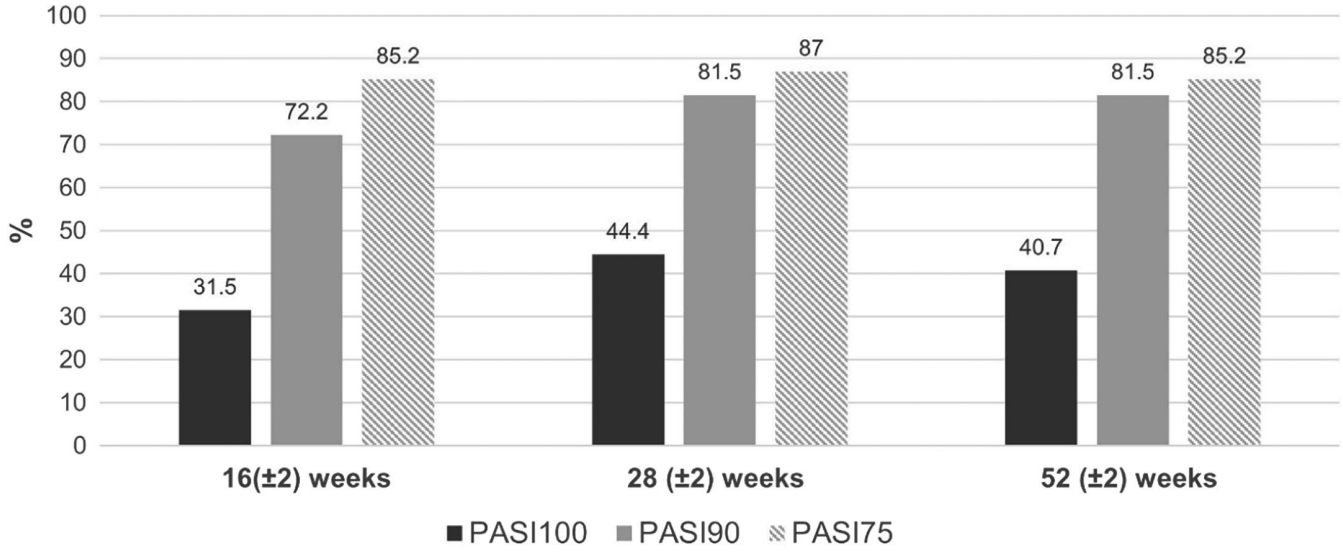


Figure 2. Proportion of patients (*n*=54) achieving Psoriasis Area and Severity Index (PASI) 100, PASI90 and PASI75 at week 52 and intermediate follow-up visits. Non-responder imputation was adopted in the case of drug discontinuation.



was statistically significant only for the PASI90 response (Figure 4). By week 52, 92.6% of biologic-naive patients achieved PASI75, 92.6% attained PASI90 and 51.9% reached PASI100 whereas, 77.8% (p=0.11), 70.4% (p=0.02) and 29.6% (p=0.11) of biologic-experienced patients attained the same targets, respectively. At the same time point, biologic-naive patients achieved a numerically higher clinical response (measured by absolute PASI) compared with biologic-experienced patients: 92.6% of biologic-naive patients achieved PASI <5, 85.1% reached PASI <3 and 63.0% attained PASI <1, whilst in the biologic-experienced group, 77.8% (p=0.11), 77.8% (p=0.67) and 55.6% (p=0.69) achieved the same thresholds, respectively. Supplementary Table 1 (available at: https://www.drugsincontext.com/wp-content/uploads/2024/02/dic.2023-12-5-Suppl.pdf) shows baseline characteristics

Figure 3. The proportion of patients (*n*=54) achieving Psoriasis Area and Severity Index (PASI) ≤1, PASI ≤3 and PASI ≤5 at week 52 and intermediate follow-up visits. Non-responder imputation was adopted in the case of drug discontinuation.

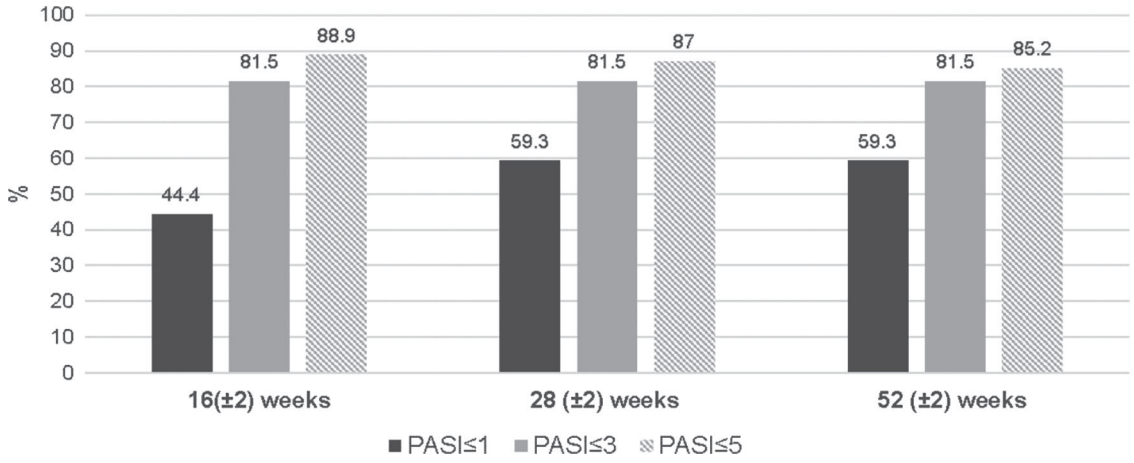
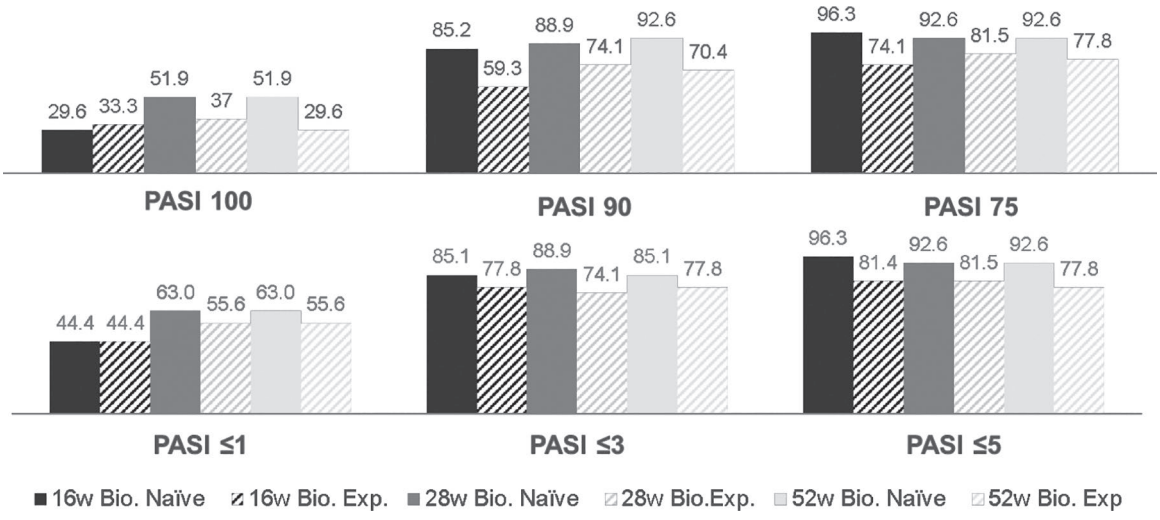


Figure 4. Effectiveness of tildrakizumab in biologic-naive patients *versus* patients previously treated with at least one biologic agent. The top graph displays the percentage (%, *y*) of patients (*n*=54) achieving Psoriasis Area and Severity Index (PASI) scores of 100, 90 and 75 at week 52 and intermediate follow-up visits based on prior experience with a biologic agent. The bottom graph illustrates the percentage (%, *y*) of patients (*n*=54) achieving PASI scores ≤5, PASI ≤3 and PASI ≤1 at week 52 and intermediate follow-up visits, categorized according to previous experience with a biologic agent. Non-responder imputation was adopted in the case of drug discontinuation. Bio. Naive: group of patients that had never received a biologic agent before tildrakizumab. Bio. Exp: group of patients that had a previous experience with a biologic agent. W: weeks.



of biologic-naive or biologic-experienced patients treated with tildrakizumab.

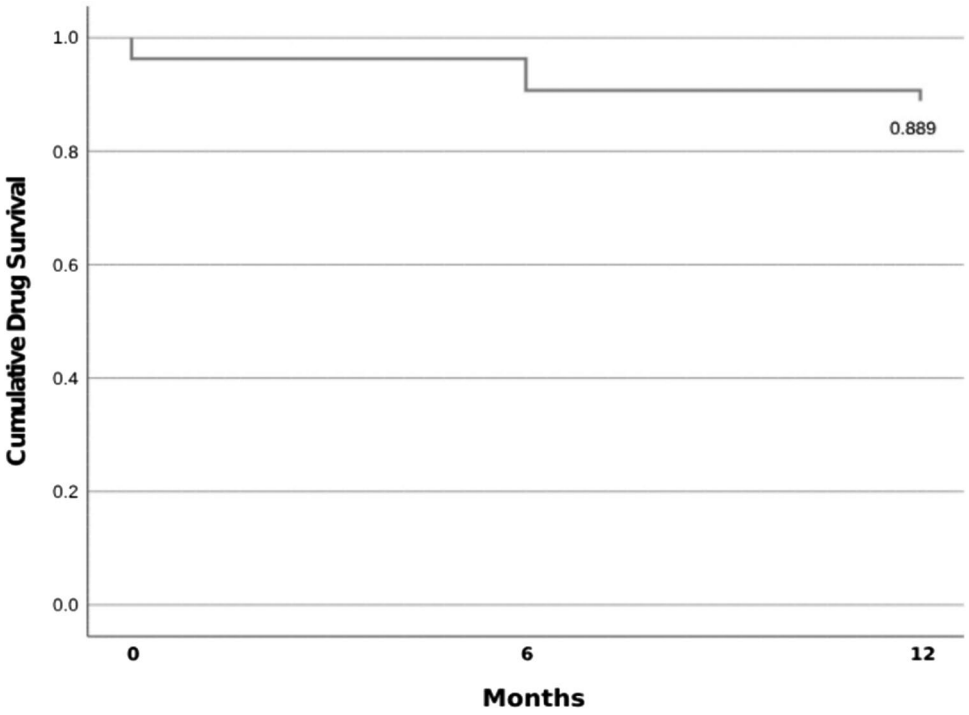
The mean PASI variation from baseline up to 52 weeks did not display a significant difference between patients with and without obesity (−18.1±11.1 *vs* −11.4±7.6; *p*=0.112).

Drug survival and safety

During the study period, six patients discontinued treatment, accounting for 11.1% of the total sample. Amongst these, 5.6% (*n*=3) discontinued because of secondary treatment failure, 3.7% (*n*=2) because of adverse events (pustular paradoxical reaction), and 1.9% (*n*=1) was lost in follow-up. The drug survival curve indicates that the cumulative proportion of patients remaining under treatment at 52 weeks was 88.9% (Figure 5). In addition, methotrexate was administered concomitantly in three patients (5.6%).

Infections were noted in 9.3% (*n*=5) of patients, which included cases of urinary tract infection, upper respiratory

Figure 5. Drug survival curve at 12 months (52 weeks).



infection and tonsillitis. Notably, only one patient (1.9%) required hospitalization due to septic arthritis, which was resolved without any complications. There were no reported instances of malignancies or deaths associated with treatment.

Discussion

This observational, real-world study aimed to assess the effectiveness and safety of tildrakizumab in treating moderate-to-severe psoriasis in a Portuguese population. Over the 52-week period, a significant improvement in mean PASI scores was observed, decreasing from 17.8±10.3 at baseline to 1.3±1.9 ($p<0.001$), signifying an overall improvement of 93%. This improvement was associated with enhancements in patient quality of life. Our sample was heterogeneous and encompassed a broad spectrum of clinical scenarios, markedly different from the population evaluated in clinical trials: 74% of patients had at least one comorbid condition, 30% had psoriatic arthritis, 17% had obesity and nearly 30% had cardiovascular risk factors. Additionally, half of the sample had prior treatment with a biologic agent. Our results validate the effectiveness of tildrakizumab in such challenging, real-world, clinical settings.

Remarkable progress has been made in understanding psoriasis pathogenesis and in developing innovative therapies in recent decades. IL-23 inhibitors (guselkumab, risankizumab and tildrakizumab) are the latest group of biologic drugs approved for the treatment of psoriasis and represent an important mark in managing the disease due to their demonstrated efficacy and safety in clinical trials.[12] However, the post-approval phase of clinical implementation is pivotal in determining the actual role of these agents in managing the disease.[11] Real-world studies involve the use of drugs in more challenging conditions than those represented by clinical trials, encompassing multiple comorbidities, treatment failures, difficult-to-treat areas and challenging compliance. Current real-world evidence is predominantly available for guselkumab and risankizumab.[12]

Tildrakizumab, one of the latest IL-23 inhibitors approved for psoriasis, blocks the IL-23-mediated signalling pathway by selectively binding to the p19 subunit of this cytokine, thus preventing its interaction with the receptor.[13] As mentioned, the efficacy of subcutaneous tildrakizumab in the treatment of moderate-to-severe chronic plaque psoriasis has been evaluated in two large, randomized, double-blind, placebo-controlled, multinational studies: reSURFACE 1 and 2. Compared with reSURFACE 1 and 2, patients in our sample had more comorbidities, a higher rate of previous use of biologic treatment and a lower baseline PASI. Despite these differences, we demonstrated that tildrakizumab had a clinical effect similar to that achieved in trials (PASI75 85.2% *vs* 87.8%, PASI90 81.5% *vs* 70.5% and PASI100 40.7% *vs* 33.1% at 52 weeks, with tildrakizumab 100 mg in our study *vs* reSURFACE).[10]

Previous studies have reported real-world evidence on tildrakizumab for psoriasis treatment, mainly retrospectively or with shorter follow-ups.[14–23] Campione et al. prospectively reported the results of tildrakizumab in 53 patients.[24] At week 52, 93%, 90.2% and 77% of patients achieved PASI75, PASI90 and PASI100, respectively, *versus* 85.2%, 81.5% and 40.7% in our study. Similarly, ~50% of the sample was biologic naïve but the percentage of patients with psoriatic arthritis was inferior (18% *vs* 27% in our study) and no data regarding obesity are available. Three additional prospective studies (Drerup et al.,[25] Costanzo et al.[26] and Tsianakas et al.[27]) reported data on the effectiveness of tildrakizumab in real-world settings. However, a fewer proportion of the sample was biologic naïve (31%, 37% and 25%, respectively) when compared with our study and the influence of obesity was not evaluated. Importantly, we found no significant differences in tildrakizumab effectiveness regarding obesity or previous biologic experience. Pooled data from the reSURFACE trials previously supported that metabolic syndrome does not affect drug efficacy.[28,29]

In our study, the cumulative proportion of patients persisting on treatment at 52 weeks was 88.9%. This was in line with the drug survival found in a previous multicentric observational study including IL-17 (drug survival of secukinumab at 12 months, 85.5%; drug survival of ixekizumab 12 months, 86.7%; drug survival of brodalumab at 12 months, 89.0%) and IL-23 agents (drug survival of guselkumab at 12 months, 92.0%; drug survival of risankizumab at 12 months, 96.5%).[7]

In our study, six patients discontinued treatment during the study period: 5.6% due to secondary cutaneous failure (no patients discontinued treatment due to worsening of psoriatic arthritis), 3.7% due to adverse events (pustular paradoxical reaction) and 1.9% lost follow-up, which corroborates the safety profile reported in literature. The choice of treatment in clinical settings considers not only drug efficacy but also patient-related factors, such as comorbid conditions and administration preferences, to maximize compliance. Tildrakizumab's favourable dosing profile, with a maintenance dose every 12 weeks, contributes positively to treatment adherence.[30]

The specific evaluation of psoriatic arthritis progression after tildrakizumab treatment was not within the scope of this study and no systematic, objective assessments regarding arthritis, enthesitis and dactylitis were performed. Consequently, any conclusions drawn should be approached with caution. Nonetheless, it is noteworthy that no patient discontinued treatment due to an exacerbation of psoriatic arthritis. This fact allows us to infer that psoriatic arthritis remained effectively managed, thereby supporting the potential role of tildrakizumab in the context of concomitant presentations of psoriasis and psoriatic arthritis.[6,31]

In terms of safety, our data are in line with pooled data from reSURFACE trials, from tildrakizumab real-world studies and safety data from other IL-23 studies with a low incidence of infections, with minimal severe outcomes and the absence of other adverse effects such as major cardiovascular events, cancer, inflammatory bowel disease or candida infection.[13,32–34]

Limitations of our study include its observational nature, lack of a control group and sample heterogeneity. Nevertheless, these limitations reflect real-world clinical practice, providing crucial insights for future clinical decisions. Future larger-scale international studies may further strengthen these conclusions.

Conclusion

Our data demonstrate that tildrakizumab's effectiveness in a real-world setting is comparable to that seen in phase III clinical trials at 52 weeks. Despite a sample comprising patients with challenging conditions, treatment response remained unaffected. Adverse events were mild and consistent with previous study observations. Hence, tildrakizumab appears to be an effective and well-tolerated agent for the treatment of moderate-to-severe psoriasis, even in diverse real-world clinical settings.

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