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SHORT REPORT

Effectiveness and Safety of Tildrakizumab in Psoriasis Patients Who Failed Anti-IL17 Treatment: A 28-Week Real-Life Study

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Abstract: Tildrakizumab is a humanised IgG1/k-type monoclonal antibody that targets the p19 protein subunit of IL23. Despite its effectiveness and safety have been widely reported by clinical trials and real-life experiences, data regarding its use on patients who previously failed anti-IL17 (brodalumab, ixekizumab, bimekizumab and/or secukinumab) are scant. Therefore, further studies on this topic would be beneficial for clinicians in guiding the selection of biologic shifting, considering that anti-IL23, −12/23, and -IL17 partially share their therapeutic targets. In this context, we performed a 28-week, single-center, real-life, retrospective study, with the aim of assessing the efficacy and safety of tildrakizumab in patients who previously failed anti-IL17, also focusing the attention on psoriasis located in difficult-to-treat areas (scalp, palms or soles, fingernails, genitals). A total of 23 patients (12 male, 52.2%; mean age 52.8 ± 12.4 years) were enrolled. Of these, 11 (47.8%) failed secukinumab, 7 (30.4%) ixekizumab, 3 (13.0%) brodalumab, 1 (4.3%) both secukinumab and ixekizumab and 1 (4.3%) bimekizumab. At baseline, mean PASI and BSA were 12.8 ± 5.9 and 18.7 ± 9.6, respectively. At W16 PASI75 and PASI90 response were achieved by 15 (65.2%), and 9 (39.1%) patients, respectively, whereas 19 (82.6%) and 13 (56.6%) subjects reached these scores at W28. One (4.3%) case of primary inefficacy and 1 (4.3%) case of secondary inefficacy were assessed. Finally, no severe adverse events were collected. Tildrakizumab seems to be a valuable option in selected patients with psoriasis unresponsive to anti-IL17, suggesting that prior exposure to biological therapies seem not directly affect its effectiveness.

Keywords: Tildrakizumab, psoriasis, real-life, anti-IL23

Introduction

Psoriasis, a chronic inflammatory skin condition, affects approximately 3% of the global population.[1] Plaque psoriasis, the most prevalent form (up to 90% of cases), presents with distinct erythematous plaques primarily on areas like elbows, knees, lower back, scalp, and umbilicus, although it can affect any skin surface.[2] Psoriasis often coexists with various conditions such as psoriatic arthritis (PsA), inflammatory bowel diseases, metabolic syndrome, type 2 diabetes, cardiovascular disorders, and psychiatric illnesses.[3] Given these factors, an effective treatment strategy is essential, not only addressing the skin symptoms but also managing psoriatic disease comprehensively.[3]

Globally, mild forms of psoriasis are often well-controlled with the use of topical treatments, mainly calcipotriol/betamethasone.[4,5] However, the management of moderate-to-severe forms may be challenging as the use of conventional systemic drugs (acitretin, ciclosporin, methotrexate, and dimethyl fumarate) can be contraindicated for the presence of comorbidities or the development of adverse events (AEs).[4,5]

Recent knowledge on psoriasis pathogenesis, particularly on the role of interleukin (IL)23–Th17 axis, led to the development of new selective drugs.[6] Among these, tildrakizumab is a humanised IgG1/k-type monoclonal antibody that

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targets the p19 subunit of IL23, currently approved for the management of adult patients with moderate-to-severe plaque psoriasis.[7] Despite its efficacy and safety have been widely reported in literature, data regarding its use on patients who previously failed anti-IL17 are scant.[8–15] Therefore, further studies on this topic would be beneficial for clinicians in guiding the selection of biologic shifting, considering that anti-IL23, 12/23, and IL17 partially share their therapeutic targets.[16] In this context, we performed a 28-week, single-center, real-life, retrospective study, with the aim of assessing the efficacy and safety of tildrakizumab in patients who previously failed anti-IL17. Furthermore, the secondary outcome of our study was to investigate the effectiveness of tildrakizumab use following anti-IL17 failure in the so-called "difficult-to-treat areas" (scalp, genitals, palms and soles, fingernails), which are usually characterized by treatment resistance, as well as a strong impact on patients' quality of life.

Materials and Methods

A monocentric retrospective study enrolling patients affected by moderate-to-severe plaque psoriasis undergoing treatment with tildrakizumab and attending the Psoriasis Care Centre of Dermatology at the University Federico II of Naples was performed. In particular, patients with moderate-to-severe psoriasis undergoing treatment with tildrakizumab and who previously failed (primary or secondary failure) one or more anti-IL-17 (brodalumab, ixekizumab, bimekizumab and/or secukinumab) were screened.

Inclusion criteria were: presence of moderate-to-severe plaque psoriasis assessed by a dermatologist for at least 6 months; tildrakizumab treatment for psoriasis at labelled dosage for at least 16 weeks; previous failure of one or more anti-IL17 (brodalumab, ixekizumab, bimekizumab, and/or secukinumab). Exclusion criteria were: patients <18 years old; concomitant systemic treatment for psoriasis, erythrodermic psoriasis or generalized pustular psoriasis.

At baseline, demographic (age, sex) and clinical data [psoriasis duration, presence of PsA (if present), Body Surface Area (BSA), Psoriasis Activity Severity Index (PASI), difficult-to-treat areas involvement by using specific BSA (scalp, palms or soles, genital) and Nail Psoriasis Severity Index (NAPSI), comorbidities, previous and current psoriasis treatments] were registered. Psoriasis improvement and AEs were evaluated at each follow-up visit [week (W)16, W28].

The present study was conducted respecting the Declaration of Helsinki, and all patients signed an informed consent before starting the study. Statistical analysis was performed to assess the significance of clinical improvement using GraphPad Prism 8.0 (GraphPad Software Inc., La Jolla, CA, USA). P values <0.05 were considered statistically significant.

In particular, descriptive statistics was used to present clinical and demographic data showing mean ± standard deviation in case of continuous data and using number and proportion for categorical ones.

Moreover, Student's *t*-test was used to assess the significance of clinical improvement at the different timepoints of treatment, compared with baseline.

Results

Twenty-three patients (12 male, 52.2%; mean age 52.8 ± 12.4 years, mean psoriasis duration: 13.8 ± 9.7) were enrolled. Of these, 3 (13.0%) were also affected by PsA.

Clinical and demographic features are summarized in Table 1. All the patients were previously treated with at least one conventional and biological systemic treatment, with methotrexate as the commonest (n = 17, 73.9%) (Table 1). As regards previous anti-IL17, 11 (47.8%) patients failed secukinumab, 7 (30.4%) ixekizumab, 3 (13.0%) brodalumab, 1 (4.3%) both secukinumab and ixekizumab and 1 (4.3%) bimekizumab.

At baseline, mean PASI and BSA were 12.8 ± 5.9 and 18.7 ± 9.6, respectively. In particular, a statistically significant reduction of both scores was observed at W16 (PASI: 4.8 ± 4.2; BSA: 7.2 ± 4.6, p<0.0001 for both) and W28 (PASI: 2.1 ± 3.4; BSA: 3.7 ± 2.5, p<0.0001 for both).

At W16 PASI75 and PASI90 response were achieved by 15 (65.2%), and 9 (39.1%) patients, respectively, whereas 19 (82.6%) and 13 (56.6%) subjects reached these scores at W28.

A sub analysis of our patients showed that there were not differences in therapeutic outcomes comparing the previously failed anti-IL17 (secukinumab or ixekizumab or brodalumab or bimekizumab).

Table 1 Patients' Feature at Baseline (Week 0) and Psoriasis Assessment at Baseline, Week 16 and Week 28

Number of Patients	23		
Sex:			
Male	12 (52.2%)		
Female	11 (47.8%)		
Mean age *(years)*	52.8 ± 12.4		
Mean duration of psoriasis *(years)*	13.8 ± 9.7		
Psoriatic Arthritis	3 (13.0%)		
Difficult-to-treat areas involvement			
Scalp	12 (52.2%)		
Palms or soles	5 (21.7%)		
Genital	3 (13.0%)		
Fingernails	8 (34.8%)		
Comorbidities:			
Hypertension	7 (30.4%)		
Dyslipidemia	5 (21.7%)		
Obesity	5 (21.7%)		
Diabetes	3 (13.0%)		
Depression	1 (4.3%)		
Hypothyroidism	1 (4.3%)		
Cardiopathy	1 (4.3%)		
Previous systemic treatments (conventional and small molecules):			
Methotrexate	17 (73.9%)		
Cyclosporine	9 (39.1%)		
Nb-UVB Phototherapy	4 (17.4%)		
Acitretin	3 (13.0%)		
Apremilast	2 (8.7%)		
Previous biologic treatments:			
Anti-TNFα			
Adalimumab	13 (56.5%)		
Etanercept	5 (21.7%)		
Infliximab	2 (8.7%)		
Golimumab	2 (8.7%)		
Certolizumab	3 (13.0%)		
Anti-IL12/23	6 (26.1%)		
Anti-IL17			
Secukinumab	11 (47.8%)		
Ixekizumab	7 (30.4%)		
Brodalumab	3 (13.0%)		
Bimekizumab	1 (4.3%)		
Secukinumab + Ixekizumab	1 (4.3%)		
	BASELINE	**WEEK 16**	**WEEK 28**
Mean PASI	12.8 ± 5.9	4.8± 4.2 *P<0.0001*	2.1±3.4 *P<0.0001*
Mean BSA	18.7 ± 9.6	7.2±4.6 *P<0.0001*	3.7±2.5 *P<0.0001*
PASI75	NA	15 (65.2%)	19 (82.6%)
PASI90	NA	9 (39.1%)	13 (56.5%)

(*Continued*)

Table 1 (Continued).

Difficult-to-treat areas				Variation from T0		Variation from T0
Scalp BSA	30.6%	/	5.4%	−82.4%	1.8%	−94.1%
Palms or soles BSA	29.6%	/	17.8%	−39.9%	7.8%	−73.6%
Genital BSA	26.3%	/	8%	−69.6%	2.3%	−91.3%
NAPSI	13.4	/	7.1	−47.0%	2.9	−78.4%

Abbreviations: Nb-UVB, (Narrow band – Ultraviolet B); PASI, Psoriasis Activity Severity Index; BSA, Body Surface Area; PGA, Physician's Global Assessment; PASI, Psoriasis Activity Severity Index; BSA, Body Surface Area; NAPSI, Nail Psoriasis Severity Index.

As regards difficult-to-treat areas, scalp, palms or soles, genital, fingernails were involved in 12 (52.2%), 5 (21.7%), 3 (13.0%), and 8 (34.8%) subjects, respectively. Psoriasis located in these areas started to improve since W16, continuing to improve up to W28.

Clinical improvement was summarized in Table 1 and Figure 1. One (4.3%) case of primary inefficacy and 1 (4.3%) case of secondary inefficacy were assessed.

Discussion

Recent knowledge on psoriasis pathogenesis led to the development of new safe and effective drugs targeting IL23 and IL17 which showed excellent results in terms of effectiveness and safety (also during COVID-19 pandemic).[17]

Several biologics for psoriasis are available and the goal should be choosing the right drug at the right moment and for the right patient.[18] Tildrakizumab is a recently approved anti-IL23. Despite its efficacy and safety have been widely demonstrated, real-life data in patients who previously failed anti-IL17 are limited.[7,19–22] These data are important to understand if a previous failure of a drug acting on the IL23/17 axis may reduce the effectiveness of a second biologic active on the same pathway. In our study, we reported a statistically significant improvement of PASI and BSA, with PASI75 and PASI90 response reached by 65.2%, and 39.1% of patients at W16 and 82.6% and 56.6% at W28, respectively. Psoriasis located in difficult-to-treat areas improved as well, with a slower and less marked improvement in the palmoplantar area as compared with the others (Figure 1b). Moreover, no AEs were collected. Finally, only 2 (8.7%) treatment failures were reported.

Literature data on patients previously treated with IL17 switching to tildrakizumab are limited.

Giordano et al reported a single-center experience on interclass switch between IL17 and IL23 inhibitors in psoriasis.[13] Among the 48 patients described, 3 (6.3%) switched to tildrakizumab. However, despite a global PASI reduction from 11.6 (baseline) to 1.4 (W52, 21 patients analyzed) specific data on psoriasis improvement of subjects switching from IL-17 to tildrakizumab were not reported.[13]

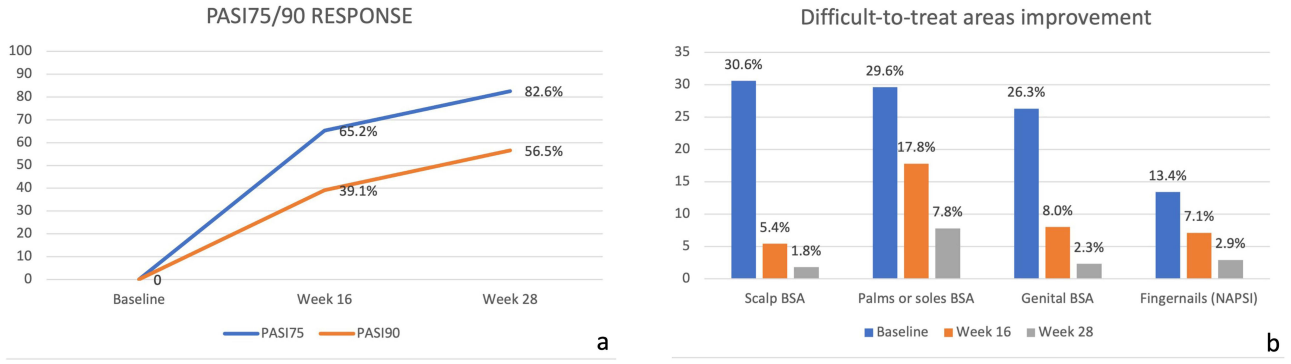

Figure 1 Percentage of patients achieving PASI75 and PASI90 response at week 16 and week 28 (**a**) and difficult-to-treat areas improvement from baseline to week 16 and week 28 (**b**).

Similarly, Di Brizzi et al reported a significant PASI reduction from baseline (19.2) to W12 (3.5, P<0.001), up to W48 (0.6, P<0.001), in their retrospective, multicenter study enrolling psoriasis patients who have switched to tildrakizumab.[15] Despite 18/51 (35.3%) tildrakizumab-treated patients previously received an anti-IL17, specific data on these subjects were not reported.[15]

Finally, other experiences reporting the use of tildrakizumab in real-life did not specifically investigate the use of this drug following the failure of at least an anti-IL17.

Strengths and Limitations

Main strengths of our study are data accuracy, the consideration of difficult-to-treat areas, and the homogeneity of clinical evaluation. Main limitations are the reduced cohort, the limited follow-up period and the retrospective design of the study.

Conclusions

Our study was the first to specifically investigate the effectiveness of tildrakizumab after anti-IL17 failure, also with a focus on difficult-to-treat areas. Tildrakizumab seems to be a valuable option in selected patients with psoriasis unresponsive to anti-IL17, suggesting that prior exposure to biological therapies seem not directly affect its effectiveness.

Data Sharing Statement

Data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical Approval

The present study was approved by the local ethics committee (University of Naples Federico II).

Patient Consent

The patient gave the consent for publication of their case details.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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