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ORIGINAL ARTICLE

Real-life effectiveness of tildrakizumab in chronic plaque psoriasis: A 52-week multicentre retrospective study—IL PSO (Italian landscape psoriasis)

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Abstract

Background: Tildrakizumab is a humanized monoclonal antibody that binds selectively the p19 subunit of interleukin-23. It is approved for treatment of moderate–severe chronic plaque psoriasis.

Objectives: We conducted a 52-week retrospective study to assess the effectiveness and safety of tildrakizumab in a real-life setting.

Methods: Our retrospective study included 237 consecutive adults with moderate-to-severe plaque psoriasis, enrolled in 10 different Italian centres, treated with tildrakizumab up to Week 52. Patient characteristics, comorbidities, previous treatments

and the PASI (Psoriasis Area and Severity Index) score at each visit (baseline, Week 16, Week 28 and Week 52) were retrieved from the electronic medical records. The percentages of patients achieving 75%, 90% and 100% (PASI 75, PASI 90 and PASI 100) improvement in PASI with respect to baseline PASI were registered.

Results: At Week 52, 90.91%, 73.55% and 58.68% of patients achieved a PASI reduction ≥75% (PASI 75), PASI 90 and PASI 100, respectively. An absolute PASI ≤ 2 was reached by 85.95% at Week 52. Compared with Phase 3 clinical trials, we observed similar rates of PASI 75/90 responses and higher percentages of patients achieving PASI 100. Patients who had not responded to previous biologic treatments and patients with cardio-metabolic comorbidities were significantly more likely to achieve PASI 100 at Week 28 and PASI 90 at Week 52. The higher body mass index did not interfere with the odds of reaching PASI 75/90/100 at each time point. No significant safety findings were recorded throughout the study, and none of the patients had to interrupt the treatment because of adverse events.

Conclusion: Our data suggest that the efficacy of tildrakizumab for plaque psoriasis in 'real-life' clinical practice is comparable with Phase 3 clinical trials with higher percentages of patients achieving complete skin clearance (PASI 100) at Weeks 16, 28 and 52.

KEYWORDS
Biologics, psoriasis, psoriasis treatment

INTRODUCTION

Psoriasis is a common, chronic, skin disease that affects approximately 125 million people worldwide.[1–3] The estimated prevalence rates of psoriasis range from 2% to 4%.[4,5] The most common form of psoriasis is plaque psoriasis, which affects 80% to 90% of patients.[6] Plaque psoriasis can present as a mild-to-moderate condition in about 80% of patients, whereas it is moderate-to-severe in 20% of patients, affecting more than 10% of body surface area (BSA) or body areas like palms/soles, face/scalp, nails or genitals.[6,7]

Psoriasis most commonly manifests itself as a skin disease, consisting of well demarcated, erythematous scaly plaques that can occur anywhere on the body, but particularly the elbows, knees, scalp and lumbosacral area. However, psoriasis is well established as a multisystemic inflammatory disease that can affect the joints, the immune system, the cardiovascular system and metabolism.[4,8] It can substantially impair the quality of life and the mental well-being of the patients.[8]

Topical corticosteroids, vitamin D3 derivates or phototherapy are first-line options to manage mild-to-moderate psoriasis. However, moderate-to-severe psoriasis usually requires the use of systemic disease-modifying antirheumatic drugs (DMARDs), such as cyclosporin, methotrexate, acitretin. Among the systemic agents, biologics are engineered monoclonal antibodies and fusion proteins that block-specific cytokines or receptors critical to psoriatic inflammation and have a high benefit-to-risk ratio.[6]

The pathogenesis of psoriasis involves the activation of T-cells, which induce keratinocyte proliferation. The discovery of the contribution of cytokines IL-17 and IL-23 to the development of psoriasis has led to a paradigm shift in the treatment of this condition.[9–11] Psoriatic plaques have been found to contain an increased number of IL-17 producing lymphocytes, as well as p40 and p19 subunits, the components of the heterodimeric cytokine IL-23. Eventually, IL-23 was identified as the primary regulator of IL-17 producing lymphocytes in psoriatic lesions.[12] Once this signalling axis was clarified, antagonists of the p19 subunit of IL-23 were developed for the treatment of psoriasis. Several inhibitors of the IL-23/IL-17 signalling axis have elicited dramatic improvement in 80% to 90% of patients with psoriasis. Tildrakizumab, a humanized immunoglobulin monoclonal antibody that selectively binds the p19 subunit of IL-23, was recently approved for moderate–severe chronic plaque psoriasis.[13,14]

The efficacy and safety of tildrakizumab has been documented in a phase 2b randomized placebo-controlled trial[15] and in two randomized phase 3 clinical trials, compared with both placebo and etanercept.[13,16] Tildrakizumab was approved for use by the U.S. Food and Drugs Administration in March 2018 and by the European Medicines agency in September 2018.[17]

Real-life studies with tildrakizumab have confirmed the effectiveness of this biologic agent in the treatment of plaque psoriasis.[18,19] The study reported here is a retrospective real-life multicentre study of 237 patients followed up for 16 weeks and 28 weeks, as well as a smaller group followed up for 52 weeks.

MATERIALS AND METHODS

This non-interventional retrospective multicenter study was carried out by analysing the psoriasis database records of ten Italian hospitals between January 2020 and July 2021. Two hundred and thirty-seven patients were included in this study. Patient eligibility for tildrakizumab treatment was assessed in accordance with the Italian adaptation of EuroGuiDerm guideline on the systemic treatment of chronic plaque psoriasis.[20]

All selected patients received 1 subcutaneous injection of 100 mg tildrakizumab at Weeks 0 and 4 and every 12 weeks after that, according to the summary of product characteristics.[21]

Patient characteristics, comorbidities, previous treatments and the PASI (Psoriasis Area and Severity Index) score at each visit (baseline, Week 16, Week 28 and Week 52) were retrieved from the electronic medical records. The percentages of patients achieving 75%, 90% and 100% (PASI 75, PASI 90 and PASI 100) improvement in PASI with respect to baseline PASI were registered, accounting for the PASI response percentage. PASI ≤2 was also selected as an efficacy endpoint, according to an Italian adaptation of EuroGuiDerm guidelines.[20] Previous use, or not, of biologic agents before starting tildrakizumab was recorded. BMI (Body Mass Index) class and cardio-metabolic comorbidities were also recorded. The involvement of difficult-to-treat areas was also recorded, including palms/soles, nails, face/scalp and genitals.[7,22,23]

Safety was evaluated according to reported adverse events (AEs), including serious AEs, laboratory values (haematology, clinical chemistry and urinalysis), physical examination and local tolerability. The occurrence of AEs was collected at Weeks 16, 28 and 52.

As patient recruitment took place over an 18-month period from January 2020 to July 2021, not all the patients were seen for a full 18 months. Data for any follow-up visits, they had not yet attended were deemed missing.

Institutional review board approval was exempted as the study protocol did not deviate from standard clinical practice. All included patients had provided written consent for retrospective study of data collected during routine clinical practice.

Statistical analysis was guided by the intention-to-treat principle with the full analysis set being 237 patients treated with tildrakizumab. Stata/SE 17.0 software was used for analysis, and Microsoft Excel was used to generate tables.

Continuous parameters were reported using frequency, mean and standard deviation (SD) values. Discrete parameters were reported as count and percentage. The percentage of patients achieving an absolute PASI ≤2 and PASI75, PASI 90, PASI100 responses with tildrakizumab treatment was examined in relation to various parameters: biologic-naive versus biologic-experienced patients, BMI class, involvement of difficult areas, presence of PsA (psoriatic arthritis) and cardio-metabolic comorbidities. The categorical variables were analysed using the Chi-square test, while the continuous variables were tested with Student's t-test and Exact Fisher's Test where needed. Non-normal distributions were tested using the Kruskal–Wallis test.

Statistical significance was defined as a probability value of less than 0.05.

RESULTS

A total of 237 patients were recruited to this study. All of them, reached at least 16 weeks of treatment. At Week 28, the study population included 201 patients, while at Week 52 data were available for 121 of them. Regarding the patients' gender, 142 (59.9%) were males and 95 (40.1%) were females, with a mean age of 48.6 (SD 14.6). A total of 192 patients (81%) were naive to biologic therapies, and 45 (19%) had failed at least one biologic therapy (bio-experienced). All of these 45 patients were switched to tildrakizumab following primary or secondary inefficacy of previous biologic drugs or because of treatment-related adverse events. Thirty-eight (16%) patients had previously received anti-TNF-α drugs, 3 (1.3%) ustekinumab, and 14 (5.9%) inhibitors of IL-17. Seven patients (3%) had previously received apremilast. Mean body mass index (BMI) at baseline was 26.2 kg/m^2 (SD 4.5). A total of 106 patients (44.7%) had at least 1 comorbidity, with 89 (37.6%) having at least one cardio-metabolic comorbidity. The most common comorbidities were arterial hypertension (57 patients, 24.1%), obesity (30, 12.7%) and diabetes mellitus (13, 5.5%). Thirty-six patients (15.2%) were affected by psoriatic arthritis. Fifteen patients had infectious comorbidities, including chronic viral hepatitis (9) and latent tuberculosis (6). Demographic characteristics of our population at baseline are summarized in Table 1.

The mean absolute PASI scores at baseline and Weeks 16, 28 and 52 are summarized in Figure 1. Over the course of the study, our patients saw their absolute PASI scores decrease from a mean (SD) of 14.45 (4.66) at baseline to 3.23 (2.48) at Week 16, 1.5 (1.74) at Week 28 and 0.97 (1.63) at Week 52.

At Week 16, 52.74%, 25.74% and 18.14% of the 237 patients achieved PASI 75, PASI 90 and PASI 100, respectively. Those percentages were higher at Week 28, when PASI 75 was reached by 81.59% of the 201 patients, PASI 90 by 55.72% and PASI 100 by 38.31%. At Week 52, out of 121 patients, the percentages of PASI 75, PASI 90 and PASI 100 responses were 90.91%, 73.55% and 58.68%, respectively. Regarding absolute PASI, at Week 16 34.60% of the patients reached an absolute PASI ≤2. At Weeks 28 and 52, PASI ≤2 was achieved by 78.11% and 85.95%, respectively. Data regarding PASI 75, PASI 90, PASI 100 and PASI ≤2 of our cohort of patients are summarized in Figure 1.

In our study, no BMI-related differences were observed in response to tildrakizumab therapy (Table 2; Figure 2). Data on BMI were available for 153 patients at baseline and Week 16 (30 obese, 61 overweight and 62 normal weight), 126 (24 obese, 54 overweight and 48 normal weight) at Week 28 and 96 (19 obese, 39 overweight and 38 normal

TABLE 1 Demographic characteristics of the 237 patients receiving tildrakizumab

Number of patients	237
Male	142/237 (59.9%)
Age	48.6 SD 14.6
BMI	26.2 SD 4.5
Obese	30/153 (19.6%)
PsA	36/237 (15.2%)
Difficult-site involvement	108/237 (45.6%)
Comorbidity	106/237 (44.7%)
Cardio-metabolic comorbidities	89/237 (37.6%)
Infectious disease	15/237 (6.3%)
Bio-Naive	192/237 (81%)
Previous biologic treatments	
Adalimumab	23/237 (9.7%)
Etanercept	15/237 (6.3%)
Secukinumab	12/237 (5.1%)
Apremilast	7/237 (3%)
Ustekinumab	3/237 (1.3%)
Brodalumab	1/237 (0.4%)
Ixekizumab	1/237 (0.4%)

Abbreviations: BMI, Body mass index; PsA, Psoriatic arthritis; SD, Standard deviation.

weight) at Week 52. In obese patients (BMI ≥ 30), mean PASI at baseline was 16.51, compared with 15.55 in overweight patients (25 ≤ BMI < 30) and with 16.24 in subjects with BMI < 25 (p = 0.558). PASI 75 responses were comparable at Week 16 (70%, 65.6% and 71%, respectively, p = 0.73), at Week 28 (87.5%, 90.7% and 91.7%, p = 0.848) and at Week 52 (94.7%, 97.4% and 100%, p = 0.408). Similar data were obtained regarding PASI 90 (Week 16: 30%, 34.4% and 35.5%, p = 0.848; Week 28: 66.7%, 72.2% and 81.3%, p = 0.354) and PASI 100 (Week 16: 20%, 24.6% and 24.2%, p = 0.869; Week 28: 41.7%, 62.9% and 50%, p = 0.172). PASI ≤ 2 was achieved at Week 16 by 43.3% of obese patients, 49.2% of overweight subjects and 45.2% of normal weight patients (p = 0.859). At Week 28, PASI ≤ 2 was achieved by 87.5%, 83.3% and 91.7% of patients, respectively (p = 0.451). Comparable data were also observed at Week 52 (94.7%, 92.3% and 94.7%, respectively, p = 0.89). Mean PASI at Week 16 decreased to 3.48 in obese patients, compared with 3.09 in overweight patients and with 3.04 in subjects with BMI < 25 (p = 0.698). At Week 28, mean PASI scores in the three subsets were 1.16, 1.04 and 1.13 (p = 0.1), while at Week 52 they were even lower (0.89, 0.9 and 0.47; p = 0.704).

Regarding previous exposure to biologics (Table 2; Figure 3). Mean PASI at baseline was higher in bio-experienced patients (16.74 versus 16.74 in bio-naive, p = 0.0002). PASI 75 at Week 16 was achieved by a significantly higher proportion of bio-experienced patients (66.7% compared with 49.5% p = 0.038). PASI 90, on the contrary, was reached by comparable percentages of patients (26.6% and 22.2%, p = 0.549). At Week 16, 17.7% of bio-naive patients achieved PASI 100 (versus 20.0%, p = 0.72), while a PASI ≤ 2 was observed in 34.4% (compared with 35.6%, p = 0.881). At Week 28, no significant differences were observed regarding PASI 75 and PASI 90 between bio-naive and bio-experienced patients (80.1% vs 88.6%, p = 0.241; 53.6% vs 65.7%, p = 0.190, respectively). Higher PASI 100 responses were observed in the bio-experienced cohort (54.3% compared with 34.9%, p = 0.032). At Week 52, we observed better percentages of PASI 90 again in bio-experienced patients (89.3% vs 68.8%, p = 0.031). All the other efficacy endpoints at Week 52 were comparable. Mean PASI scores decreased in both groups, as at Week 52 mean PASI was 1.04 in bio-naive patients and 0.77 in bio-experienced (p = 0.77).

In our study, psoriatic arthritis did not interfere with the clinical response to tildrakizumab, as comparable responses were observed at all visits regarding all efficacy endpoints (Table 2). The only exception was represented from PASI ≤2 at Week 16, which achieved by more patients without PsA (37.8% versus 16.7%, p = 0.014). At the following visits, no differences were detected. Mean PASI scores were comparable between the two groups at baseline and at the subsequent visits, without any significant difference.

Concerning the involvement of difficult-to-treat areas, at least one of them was affected in 108 patients (45.6%) at baseline. These patients had also a higher mean PASI before starting tildrakizumab (15.44 compared with 13.62, p = 0.003). At Week 16, they experienced a better PASI75 response (64.8% versus 42.6%, p = 0.001). However, at Week 28, the proportion of patients achieving complete skin clearance (PASI100) was significantly higher in patients without the involvement of difficult-to-treat areas (44.7% versus 29.9%, p = 0.032). At Week 52, no differences were observed (Table 2; Figure 4).

The improvement in PASI scores was also examined in relation to the presence or absence of cardio-metabolic comorbidities (including cardiovascular diseases, arterial hypertension, type 2 diabetes mellitus and hyperlipidaemia) (Table 2; Figure 5). At baseline, mean PASI was higher in patients with these comorbidities (16.11 compared with 13.46, p = 0.0001). Surprisingly, we observed significantly better responses in this cohort of patients, compared with the other patients. At Week 28, PASI 75/90/100 were all reached by more patients with cardio-metabolic comorbidities (89.9% vs 77.3%, p = 0.029; 71.00% vs 47.7%, p = 0.002; 52.2% vs 31.1%, p = 0.003). At Week 52 those results were once again confirmed, with the addiction of better rates of PASI ≤ 2 in patients with cardio-metabolic comorbidities (94.1% vs 80%, p = 0.027), despite a higher absolute PASI at baseline.

Regarding the safety of tildrakizumab, none of our 237 patients discontinued the treatment because of adverse events (Table 3). Although most of the patients received tildrakizumab treatment during the apex of COVID-19 pandemic, no COVID-19-related hospitalizations, or deaths were reported during the whole study period. Although 9 patients had a history of viral hepatitis, follow-up laboratory tests and periodic hepatological visits showed no signs of viral reactivation during tildrakizumab therapy.

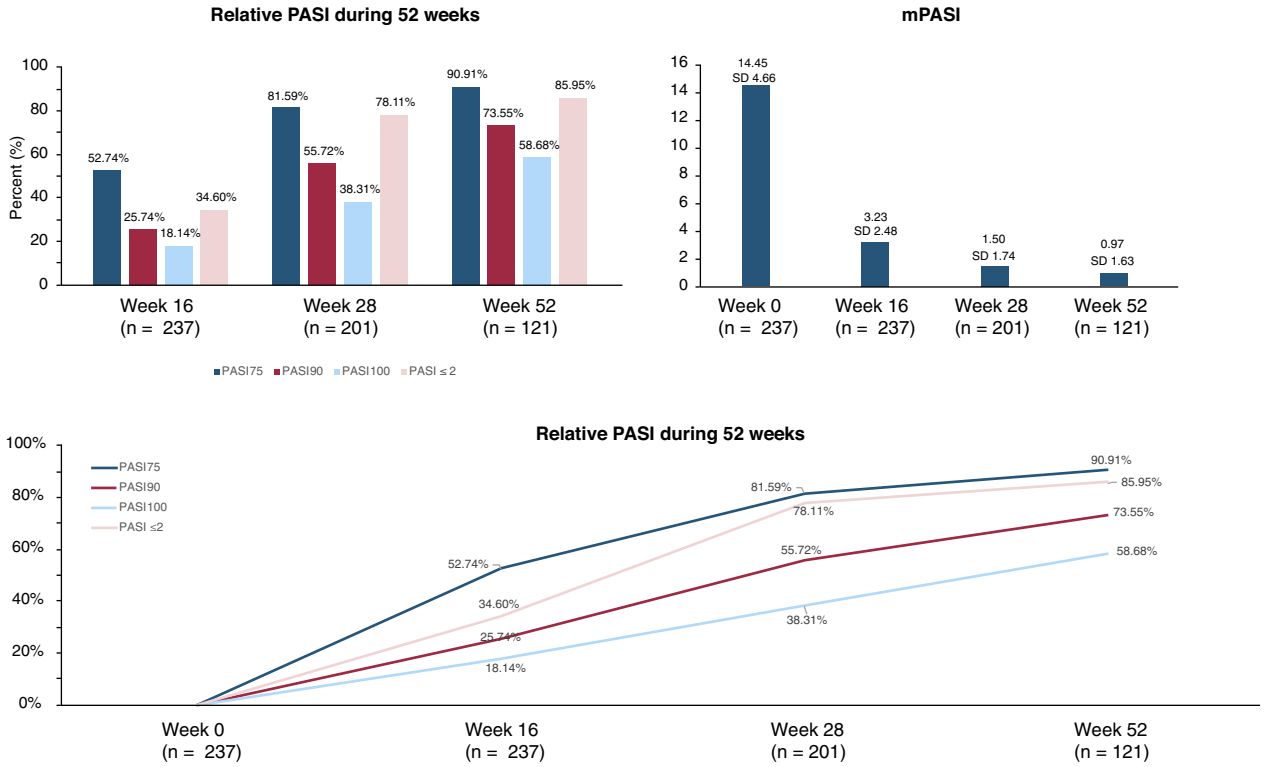

FIGURE 1 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤ 2 at Weeks 16, 28 and 52, compared with baseline.

DISCUSSION

This study confirms the effectiveness of tildrakizumab in daily clinical practice in patients with moderate-to-severe plaque psoriasis, with the longest real-life follow-up and the widest cohort of patients, to date.

Tildrakizumab is a monoclonal antibody that selectively binds to the p19 subunit of interleukin-23 cytokine, inhibiting its interaction with the IL-23 receptor.[21] Several studies have been conducted with tildrakizumab to obtain real-life evidence of its effectiveness since the product was authorized in 2018 in Europe and the U.S. after phase 3 clinical trials provided sufficient evidence of efficacy and safety under strictly controlled conditions.[17,21]

The retrospective study reported here is the largest real-life study conducted to date, with a study population of 237 patients with moderate-to-severe chronic plaque psoriasis cared for at ten different Italian hospitals. Compared with the reSURFACE 1 and 2 clinical trials, the characteristics of our patients were similar, aside from having a lower baseline PASI score, which is due to the stricter inclusion criteria of the phase 3 clinical trials.[16,24]

The findings regarding the effectiveness of tildrakizumab generally confirmed those of the reSURFACE 1 and 2 trials, with better PASI 100 responses. In the reSURFACE 1 and 2 trials, tildrakizumab was found to be superior to placebo in achieving PASI75 at Week 12 (reSURFACE 1 64% vs. 6%; reSURFACE 2 61% vs. 6%).[15,16,21] In our study, 52.74% of patients treated with tildrakizumab achieved PASI75 by Week 16. At Week 16, we observed a PASI 90 response in 25.74% of the patients, compared with 35% and 39% of reSURFACE 1 and 2. Regarding PASI 100, our study demonstrated a superior efficacy of tildrakizumab at Week 16, with 18.14% of patients achieving complete skin clearance (compared with 14% and 12% in phase 3 RCTs).

At Week 28, our data were comparable to those observed in the reSURFACE 1 and 2 studies, with 81.59 patients achieving PASI 75 (compared with 80% and 73%), 55.72% reaching PASI 90 (compared with 52% and 56%). Regarding PASI 100, once again, our patients experienced better responses (38.31% versus 24% and 23%).[15,16,21] At Week 52, PASI 75 and PASI 90 responses were again comparable with pooled analyses of reSURFACE 1 and reSURFACE 2 (PASI 75: 90.91% versus 91.2%; PASI 90: 73.55% versus 73.2%). Once again, we observed better percentages of patients achieving complete skin clearance (58.68% of our patients reached PASI 100 compared with 34.4% from phase 3 studies).[25]

In our study, we did not observe any significant difference in response to tildrakizumab therapy regarding the BMI of the patients, with comparable PASI 75/90/100 responses throughout the study among the three subsets of patients (obese, overweight and normal weight patients). On this topic, our data support the efficacy of tildrakizumab in a large population of patients, as already observed by *Drerup* et al.[26] Similarly, no significant

TABLE 2 Reduction in mean PASI score (mPASI) and percentages of patients achieving PASI 75/90/100 and ≤2 at Weeks 16/28/52 in the analysed subpopulations (according to BMI, presence of PsA, previous exposure to biologics, involvement of difficult-to-treat areas and presence of cardio-metabolic comorbidities)

	BMI ≥30	25 ≤ BMI <30	BMI < 25	*p*-value	PsA	Non PsA	*p*-value
mPASI w0	16.51	15.55	16.24	0.558	14.59	14.43	0.854
mPASI w16	3.48	3.09	3.04	0.698	3.26	3.23	0.9483
PASI75 w16	21/30 (70%)	40/61 (65.6%)	44/62 (71%)	0.730	18/36 (50%)	107/201 (53.2%)	0.720
PASI90 w16	9/30 (30%)	21/61 (34.4%)	22/62 (35.5%)	0.848	6/36 (16.7%)	55/201 (27.4%)	0.176
PASI100 w16	6/30 (20%)	15/61 (24.6%)	15/62 (24.2%)	0.869	5/36 (13.9%)	38/201 (18.9%)	0.472
PASI ≤2 w16	13/30 (43.3%)	30/61 (49.2%)	28/62 (45.2%)	0.859	6/36 (16.7%)	76/201 (37.8%)	**0.014**
mPASI w28	1.16	1.04	1.13	0.100	1.75	1.46	0.382
PASI75 w28	21/24 (87.5%)	49/54 (90.7%)	44/48 (91.7%)	0.848	26/32 (81.3%)	138/169 (81.7%)	0.957
PASI90 w28	16/24 (66.7%)	39/54 (72.2%)	39/48 (81.3%)	0.354	14/32 (43.8%)	98/169 (58%)	0.137
PASI100 w28	10/24 (41.7%)	34/54 (62.9%)	24/48 (50%)	0.172	9/32 (28.1%)	68/169 (40.2%)	0.196
PASI ≤2 w28	21/24 (87.5%)	45/54 (83.3%)	44/48 (91.7%)	0.451	24/32 (75%)	133/169 (78.7%)	0.643
mPASI w52	0.89	0.90	0.47	0.704	1.07	0.96	0.814
PASI75 w52	18/19 (94.7%)	38/39 (97.4%)	38/38 (100%)	0.408	13/14 (92.9%)	97/107 (90.7%)	0.787
PASI90 w52	15/19 (78.9%)	30/39 (76.9%)	36/38 (94.7%)	0.076	9/14 (64.3%)	80/107 (74.8%)	0.403
PASI100 w52	14/19 (73.7%)	25/39 (64.1%)	25/38 (65.8%)	0.760	8/14 (57.1%)	63/107 (58.9%)	0.901
PASI ≤2 w52	18/19 (94.7%)	36/39 (92.3%)	36/38 (94.7%)	0.890	11/14 (78.6%)	93/107 (86.9%)	0.398

	Bio-naive	Bio-experienced	*p*-value	Non difficult areas	Difficult areas	*p*-value	CMD	Non-CMD	*p*-value
mPASI w0	13.92	16.74	**0.0002**	13.62	15.44	**0.003**	16.11	13.46	**0.0001**
mPASI w16	3.15	3.58	0.2919	3.37	3.06	0.347	3.66	2.97	**0.0377**
PASI75 w16	95/192 (49.5%)	30/45 (66.7%)	**0.038**	55/129 (42.6%)	70/108 (64.8%)	**0.001**	53/89 (59.6%)	72/148 (48.6%)	0.104
PASI90 w16	51/192 (26.6%)	10/45 (22.2%)	0.549	32/129 (24.8%)	29/108 (26.9%)	0.720	24/89 (27%)	37/148 (25%)	0.737
PASI100 w16	34/192 (17.7%)	9/45 (20%)	0.720	28/129 (21.7%)	15/108 (13.9%)	0.120	18/89 (20.2%)	25/148 (16.9%)	0.519
PASI ≤2 w16	66/192 (34.4%)	16/45 (35.6%)	0.881	41/129 (31.8%)	41/108 (38%)	0.319	33/89 (37.1%)	49/148 (33.1%)	0.104
mPASI w28	1.57	1.20	0.257	1.53	1.47	0.815	1.10	1.71	0.017
PASI75 w28	133/166 (80.1%)	31/35 (88.6%)	0.241	88/114 (77.2%)	76/87 (87.4%)	0.065	62/69 (89.9%)	102/132 (77.3%)	**0.029**
PASI90 w28	89/166 (53.6%)	23/35 (65.7%)	0.190	64/114 (56.1%)	48/87 (55.2%)	0.891	49/69 (71.0%)	63/132 (47.7%)	**0.002**
PASI100 w28	58/166 (34.9%)	19/35 (54.3%)	**0.032**	51/114 (44.7%)	26/87 (29.9%)	**0.032**	36/69 (52.2%)	41/132 (31.1%)	**0.003**
PASI ≤2 w28	127/166 (76.5%)	30/35 (85.7%)	0.231	83/114 (72.8%)	74/87 (85.1%)	**0.037**	59/69 (85.5%)	98/132 (74.2%)	0.067
mPASI w52	1.04	0.77	0.447	0.83	1.12	0.343	0.82	1.08	0.387
PASI75 w52	83/93 (89.2%)	27/28 (96.4%)	0.247	55/61 (90.2%)	55/60 (91.7%)	0.774	49/51 (96.1%)	61/70 (87.1%)	0.091
PASI90 w52	64/93 (68.8%)	25/28 (89.3%)	**0.031**	46/61 (75.4%)	43/60 (71.7%)	0.641	43/51 (84.3%)	46/70 (65.7%)	**0.022**
PASI100 w52	52/93 (55.9%)	19/28 (67.9%)	0.261	40/61 (65.6%)	31/60 (51.7%)	0.120	36/51 (70.6%)	35/70 (50%)	**0.023**
PASI ≤2 w52	78/93 (83.9%)	26/28 (92.9%)	0.230	53/61 (86.9%)	51/60 (85%)	0.765	48/51 (94.1%)	56/70 (80%)	**0.027**

Significant *p* value < 0.05 are indicated in bold.

Abbreviations: BMI, Body mass index; PASI, Psoriasis area and severity index; PsA, Psoriatic arthritis; CMD, Cardio-metabolic diseases.

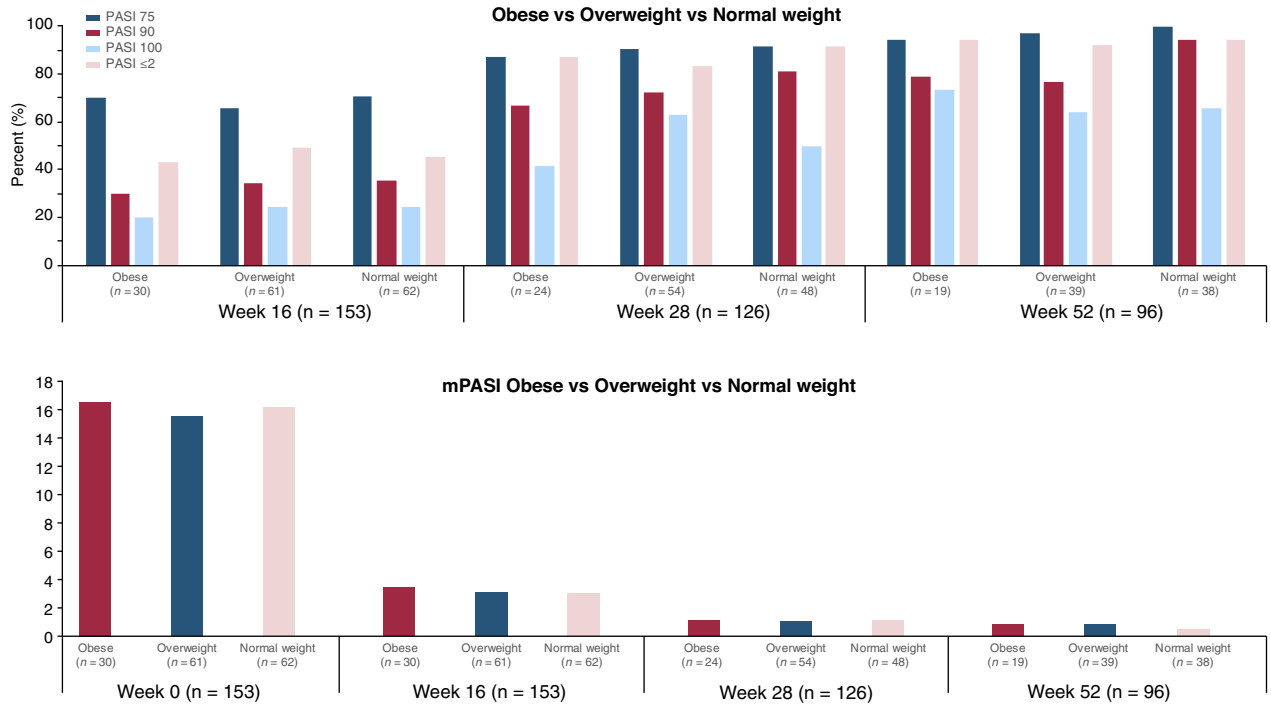

FIGURE 2 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤ 2 at Weeks 16, 28 and 52, according to body mass index.

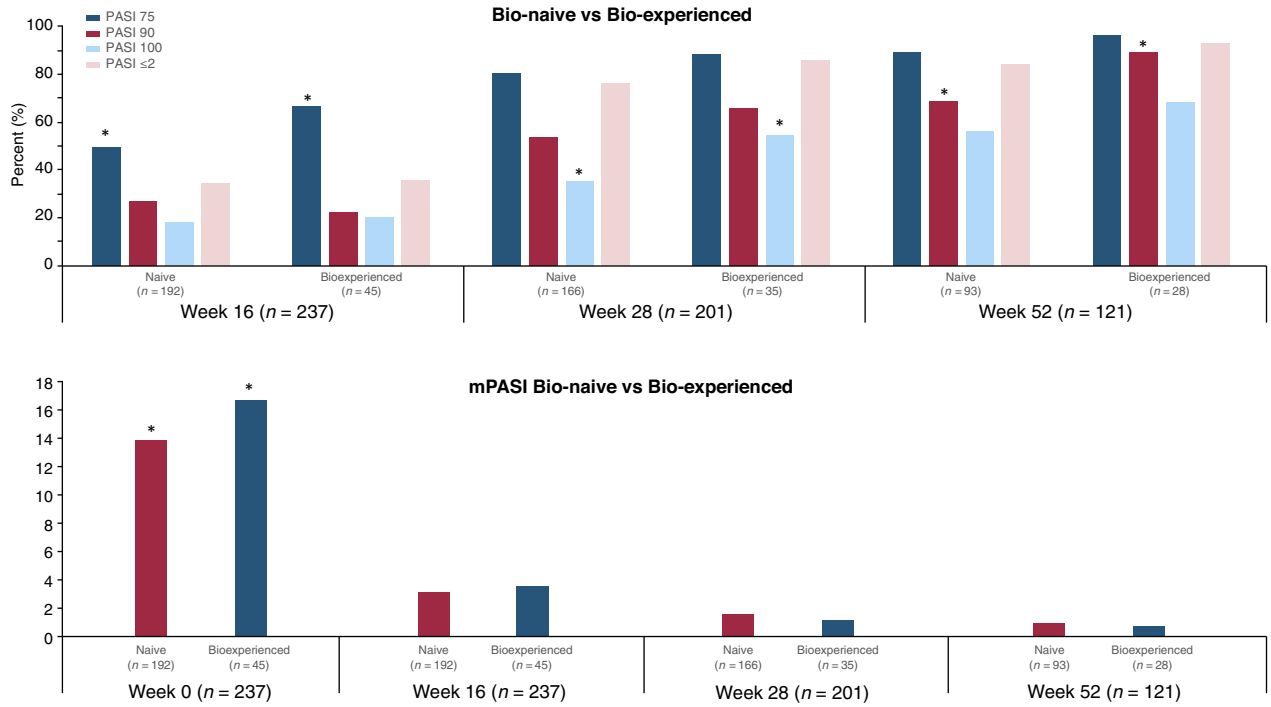

FIGURE 3 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤ 2 at Weeks 16, 28 and 52, compared with baseline, according to previous exposure to biologic drugs.

differences regarding the effectiveness of tildrakizumab were observed between patients with and without a diagnosis of PsA.

Our study clearly differentiated patients without previous exposure to biologics from those that had been previously treated with biologics. The bio-experienced

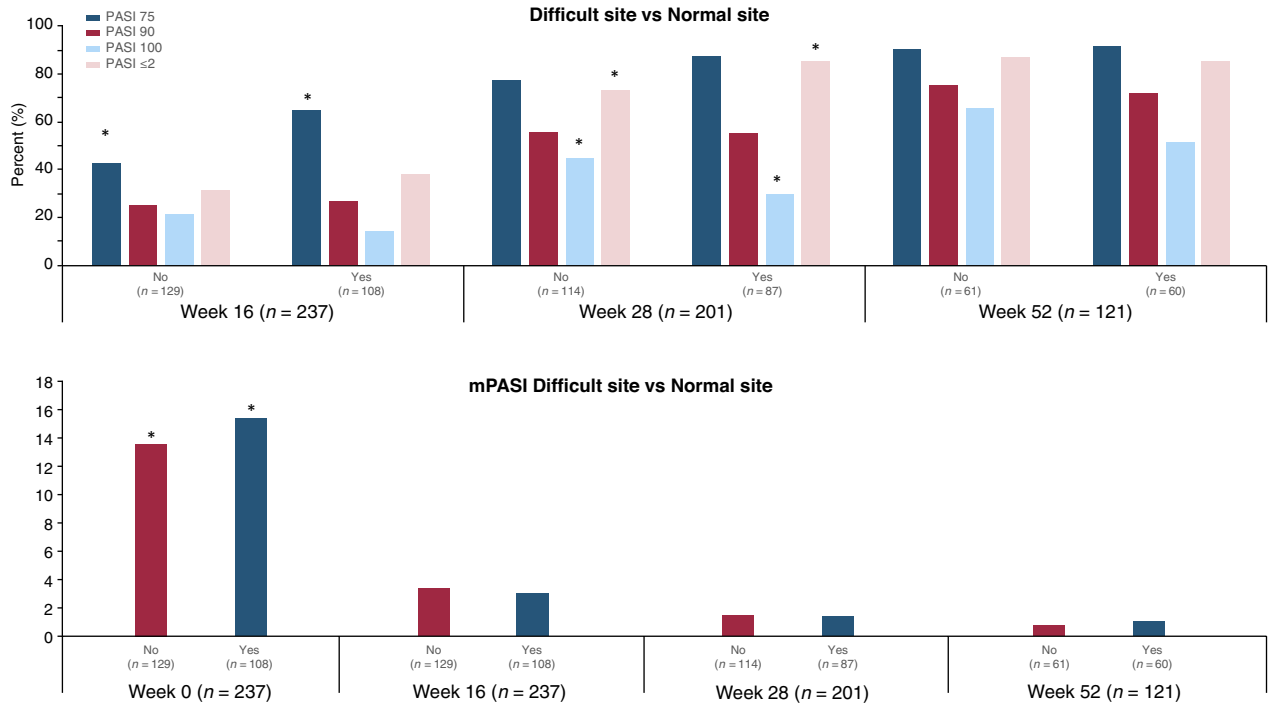

FIGURE 4 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤ 2 at Weeks 16, 28 and 52, compared with baseline, according to the involvement of difficult-to-treat areas.

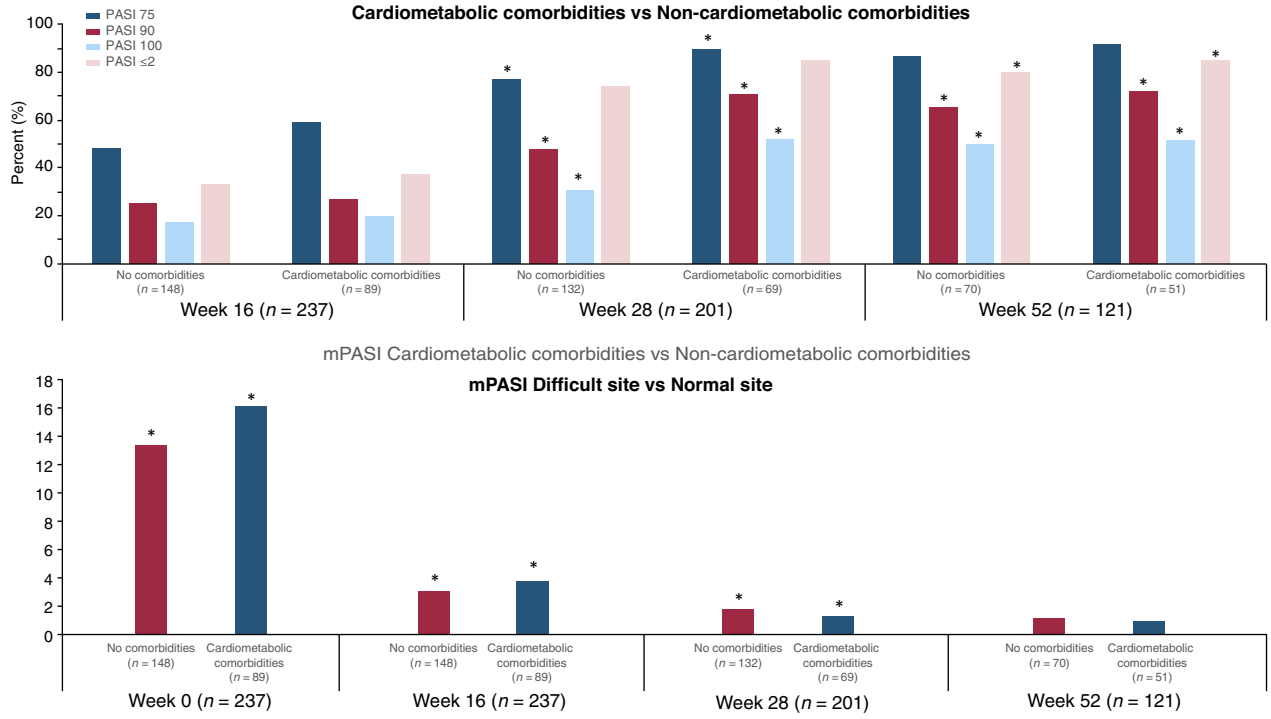

FIGURE 5 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤ 2 at Weeks 16, 28 and 52, compared with baseline, according to the presence of cardio-metabolic comorbidities.

patients had higher absolute PASI scores at baseline. This may indicate that they had somewhat more intense or prolonged disease. Several efficacy endpoints were reached by significantly higher percentages of bio-experienced patients at various time points (PASI 75 at Week 16, PASI 100 at Week 28 and PASI 90 at Week 52). These results can be

TABLE 3 Reported adverse events during the treatment with tildrakizumab.

Adverse events	*N* (% on total population)
Nasopharingitis	6 (2.5%)
Upper respiratory tract infections	3 (1.3%)
Cefalea	1 (0.4%)
Nausea	1 (0.4%)
Reaction at injection site	1 (0.4%)
Total	12 (5%)
Severe AE	0 (0%)
AE leading to discontinuation	0 (0%)

partially explained by the higher mean PASI at baseline of these patients, but they also show the high efficacy of tildrakizumab in this population. Tildrakizumab, as the other anti-IL-23 drugs, can represent a valid therapeutic option also in patients who failed other biologic drugs (including anti-IL-17 s).[27]

Difficult-to-treat areas were involved in almost half of our patients. Tildrakizumab proved to be effective also in this subset of patients, with slower rates of responses (especially regarding PASI 100 at Week 28). However, at Week 52, no significant differences were detected. Data from our analysis shows that tildrakizumab is an effective option for the management of psoriasis in difficult-to-treat areas, confirming the observations of *Galluzzo* et al.[28]

Regarding the impact of the presence of cardiovascular diseases and/or metabolic comorbidities on the response to tildrakizumab of patients with moderate-to-severe plaque psoriasis, surprisingly, our data showed significant better responses for several efficacy endpoints (PASI 75/90/100 at Week 28, PASI 90/100 and PASI ≤ 2 at Week 52). This is the first study that has observed similar data. However, the high efficacy of tildrakizumab in patients with cardio-metabolic diseases has been already described in pooled analyses from the extension open-label studies, where no significant differences were observed in patients with and without metabolic syndrome.[29] Our data showed higher percentages of PASI 75/90/100 responses at various time points, suggesting that these patients could benefit more than other of the treatment with tildrakizumab.

In our study, tildrakizumab showed no significant safety findings, and up to Week 52, no relevant side-effects were reported among all patients receiving tildrakizumab, in accordance with other real-life studies.[26–29] Moreover, despite the current data being collected during the first outbreak of the COVID-19 pandemic, in an area strongly affected by SARS-CoV-2, none of the patients experienced severe forms of COVID-19, consistent with previously reported data on safety of biologics.[30,31] None of the 9 patients with serological evidence of viral hepatitis, experienced viral reactivation during tildrakizumab therapy, as previously published by *Gargiulo* et al.[32] regarding the safety of anti-IL-17 and anti-IL-23 drugs in this population.

This study has some limitations, the first one being its retrospective design, which does not allow retrieval of missing data. Other significant limitations are the small size of the sample at Week 52 (which was 50% smaller than at baseline), the lack of a randomized controlled setting, the exclusion of patients with PASI lower than 10 at baseline, and the heterogeneity of clinical assessment among clinicians from different centres.

CONCLUSIONS

Our results at Week 52 confirm that the effectiveness of tildrakizumab is maintained over time, with higher therapeutic responses at Week 28 and Week 52 compared with Week 16. Our data demonstrate the high effectiveness of tildrakizumab in daily clinical practice in a large cohort of patients with moderate-to-severe plaque psoriasis, with the longest real-life follow-up to date.

Compared with Phase-3 RCTs, our study found comparable PASI 75/90 responses at Weeks 16, 28 and 52, supporting tildrakizumab as an effective therapeutic option in real-world conditions. Moreover, we observed higher percentages of patients achieving complete skin clearance (PASI 100) at all time points compared with pooled analyses from reSURFACE 1 and 2 studies. Tildrakizumab was more effective at Weeks 28 and 52 in patients with cardio-metabolic comorbidities, with comparable responses among patients with different BMI classes. The effectiveness of tildrakizumab was comparable also among bio-naive and bio-experienced patients, confirming the results of other real-life studies on anti-IL-23 drugs.

Tildrakizumab was well tolerated, with no significant safety findings reported throughout the study. Larger and longer prospective studies and retrospective analyses of patient registries are needed to evaluate the safety and effectiveness of tildrakizumab further in a real-life setting.

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None.

CONFLICT OF INTEREST

A. Narcisi has served on advisory boards, received honoraria for lectures and research grants from Almirall, Abbvie, Leo Pharma, Celgene, Eli Lilly, Janssen, Novartis, Sanofi-Genzyme, Amgen and Boehringer Ingelheim. Federico Bardazzi has been consultant, adviser and clinical study investigator for Eli Lilly, Abbvie, Novartis, LEO Pharma, Sandoz, Bristol Myers, Abiogen-Pharma, Celgene and Janssen-Cilag. C.Guarneri has been a scientific consultant/speaker/clinical study investigator for Abbvie, Celgene, Janssen, Eli Lilly, Novartis, Pfizer, Sanofi, Almirall, LEO Pharma. M.

Burlando has acted as a speaker and consultant for AbbVie, Janssen, Amgen, Novartis, Eli Lilly, UCB Pharma. Carrera CG has served as a board participant or speaker for Abbvie, Lilly, Jannsen, Novartis, Celgene, Almirall and Leopharma. P. Dapavo has been a speaker for Novartis, Abbvie, Sanofi, UCB, Janssen, Lilly and Leopharma. Francesco Loconsole served on advisory boards and/or received honoraria for lectures from Abbvie, Janssen-Cilag, Novartis, Lilly, Sanofi. G. Girolomoni served as consultant and/or speaker for AbbVie, Abiogen, Almirall, Amgen, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Celltrion, Eli-Lilly, Genzyme, Leo Pharma, Menlo therapeutics, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi and UCB. P. Malagoli has been a speaker for AbbVie, Lilly, Novartis, Janssen-Cilag, Celgene, Leopharma and Almirall. A. Costanzo has served as an advisory board member, consultant and has received fees and speaker's honoraria or has participated in clinical trials for Abbvie, Almirall, Biogen, LEO Pharma, Lilly, Janssen, Novartis, Pfizer, Sanofi-Genzyme, and UCB-Pharma. L. Gargiulo, L. Ibba, M. Valenti, F. Amoruso, G. Argenziano, G. Damiani, V. Dini, C. Franchi, F. Sampogna, M. Travaglini, have nothing to declare.

DATA AVAILABILITY STATEMENT

All the patients' data and information supporting the findings of this study are available from thecorresponding author upon reasonable request.

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