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ORIGINAL ARTICLE

Real-life effectiveness and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: A 104-week multicenter retrospective study – IL PSO (ITALIAN LANDSCAPE PSORIASIS)

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Abstract

Background: Guselkumab is a fully human monoclonal antibody that binds selectively to the p19 subunit of interleukin-23, which has shown efficacy in patients with previous incomplete response to ustekinumab in the NAVIGATE clinical trial. [Correction added on [28-02-2023], after first online publication: 'humanized monoclonal antibody' has been changed to 'fully human monoclonal antibody' in the preceding sentence.]

Objectives: We conducted a 104-week multicenter retrospective study to assess the effectiveness and safety of guselkumab in patients affected by plaque psoriasis with an inadequate response to ustekinumab in a real-life setting.
Methods: Our retrospective study included 233 adults affected by moderate-to-severe plaque psoriasis, enrolled in 14 different Italian centres, and treated with guselkumab after failing therapy with ustekinumab. Patient characteristics and PASI (Psoriasis Area and Severity Index) score at each visit (baseline, weeks 16, 52 and 104) were recorded. The percentages of patients achieving 75%, 90% and 100% (PASI 75, PASI 90 and PASI 100) improvement in PASI, compared with baseline, were registered.
Results: At week 52, PASI 75 was reached by 89.88% of patients, PASI 90 by 71.43%, PASI 100 by 58.83% and absolute PASI ≤2 by 90.48%. At week 104, similar effectiveness results were observed. Compared to the NAVIGATE trial, we observed higher rates of PASI 75/90/100. Patients with the involvement of difficult-to-treat areas were significantly less likely to achieve PASI90 and PASI100 at week 16. Obese patients had significantly lower rates of PASI75 and PASI ≤2 at week 52. At week 104, comparable responses were observed among all patients' subgroups, regardless of BMI status, involvement of difficult-to-treat areas, presence of cardiometabolic comorbidities and concomitant psoriatic arthritis. No significant safety findings were reported throughout the study.
Conclusion: Our data suggest that the efficacy of guselkumab in patients with inadequate response to ustekinumab for plaque psoriasis in 'real-life' clinical practice is comparable with NAVIGATE study with higher percentages of patients achieving PASI90 and PASI100 at weeks 16, 52 and 104.

INTRODUCTION

Psoriasis is a common inflammatory disease, affecting up to 3%–4% of the general population worldwide.[1] It is well known now that psoriasis is a multisystemic inflammatory disease that can affect the joints, the immune system, the cardiovascular system and metabolism, impairing the patients' quality of life.[2]

Mild-to-moderate psoriasis is usually managed with topical corticosteroids, in monotherapy or in association with Vitamin D3 derivates, or phototherapy.[3] Regarding the treatment of moderate-to-severe cases, usually systemic disease-modifying antirheumatic drugs (DMARDs), such as cyclosporine and methotrexate, or acitretin, are needed.[3] When a patient has a contraindication or an incomplete response to conventional DMARDs, biologics are the treatment of choice.[4–7]

In particular, three selective antagonists of the p19 subunit of IL-23 have been developed (guselkumab, risankizumab and tildrakizumab).[8] Guselkumab is the first human IgG1λ monoclonal antibody that inhibits IL-23 selectively.[9] The efficacy and safety of guselkumab have been evaluated in three phase-3 clinical trials (VOYAGE1, VOYAGE2 and NAVIGATE), showing superior efficacy compared with both placebo and adalimumab.[10–12] In particular, the NAVIGATE trial demonstrated the efficacy of guselkumab in patients with an inadequate response to ustekinumab after 16 weeks of treatment.[12] However, real-life studies on long-term effectiveness and safety of guselkumab, especially on bio-experienced patients, are scarce.[13] In particular, it is necessary to evaluate guselkumab efficacy in patients who previously failed anti-IL-12/23 (ustekinumab) treatment due to their partially similar targets.[14] Moreover, despite drug antibodies being associated with ustekinumab failure, the results of both clinical trials and real-life experiences have shown that guselkumab effectiveness is not influenced by previous exposure to ustekinumab. These studies had limitations of short follow-up and limited sample size.[14–16]

Our multicentric retrospective study aimed to assess the effectiveness and safety of guselkumab in 233 patients who received this drug after failing therapy with ustekinumab.

MATERIALS AND METHODS

We conducted a non-interventional retrospective multicentre study by analysing the psoriasis database records of 14 Italian hospitals between January 2020 and September 2022. Two hundred and thirty-three patients were included in this study. All patients had previous exposure to ustekinumab before being switched to guselkumab. Patient eligibility for guselkumab treatment was assessed following the Italian adaptation of EuroGuiDerm guideline on the systemic treatment of chronic plaque psoriasis.[6]

All selected patients were switched to guselkumab because of primary or secondary failure to ustekinumab. Incomplete response to ustekinumab was defined as Dermatology Life Quality Index (DLQI) ≥ 5 and/or PASI (Psoriasis Area and Severity Index) ≥ 10 or PASI < 10 with the involvement of palms/soles, genitals, face/scalp or nails. Guselkumab was administered according to the summary of product characteristics (100 mg at weeks 0, 4 and then every 8 weeks).

Patient demographics, comorbidities, previous biologic treatments, disease characteristics and the PASI score at baseline, week 16, week 52 and week 104 were retrieved from the electronic medical records. At each time-point, the

percentages of patients achieving an improvement of 75%, 90% and 100% (PASI75, PASI90 and PASI100) in PASI, compared with baseline PASI, were registered. An additional endpoint was the percentage of patients achieving an absolute PASI ≤2, in accordance with the Italian adaptation of EuroGuiDerm guidelines.[6]

Safety was evaluated according to reported adverse events (AEs), including serious AEs, abnormal laboratory values, physical examination and local tolerability. The occurrence of AEs was collected at weeks 16, 52 and 104.

Due to the retrospective nature of this study, not all patients completed all the follow-up visits. Therefore, all 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 guselkumab. 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, PASI90 and PASI100 responses with guselkumab treatment was examined in relation to various parameters: previous failure to ustekinumab only versus multi-failure 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 and Fisher's exact test where needed. Regarding the continuous variables, the differences between two groups were analysed by the Student's *t*-test and the Mann–Whitney *U* test if the parametric test assumption were not met. The differences between more than two groups were tested with ANOVA or Kruskal–Wallis test if the distributions were not normal. All variables with a probability value (*p*-value) <0.2 on univariate analysis were included in the multivariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.

Statistical significance was defined as a *p*-value of <0.05.

RESULTS

This multicentric study included 233 patients from 14 different Italian Dermatology clinics. Their mean age was 54.27 years (SD 13.25), and they had a personal history of psoriasis for a mean of 24.20 years (SD 13.40). The mean BMI was 27.56 (SD 5.34), and 58 patients (24.89%) were obese. Among comorbidities, 122 patients (52.36%) had at least one of them; cardio-metabolic comorbidities were the most represented, with 116 patients affected (49.79%). One patient was affected by a concomitant viral hepatitis B and two had a latent tuberculosis infection. All 233 patients had failed ustekinumab, with 94 of them (40.34%) having previous exposure to at least two different biologics. Adalimumab was previously prescribed to 56 patients (24.03%), etanercept to 41 (17.60%) and infliximab to 21 (9.01%). Regarding anti-IL-17 drugs, secukinumab was previously administered to 11 patients (4.72%) and ixekizumab to six patients (2.58%). Three patients (1.29%) had also failed treatment with apremilast. Demographic characteristics of our population at baseline are summarized in Table 1.

At week 16, 178 (76.39%), 109 (46.78%) and 99 (37.77%) achieved PASI75, PASI90 and PASI100 respectively. An absolute PASI ≤2 was reached at week 16 by 181 patients (77.68%). At weeks 52 and 104, we observed higher percentages of patients achieving these endpoints, as shown in Figure 1. The mean absolute PASI scores at baseline and weeks 16, 52 and 104 are also summarized in Figure 1.

In our cohort of patients, at baseline and week 16, 58 were obese (BMI ≥ 30), 100 were overweight (25 ≤ BMI > 30) and 75 had a normal BMI (Table 2, Figure 2). Baseline PASI scores were significantly different among the three groups, as it was 12.06 among obese patients, 8.58 in the overweight group and 10.13 in normal-weight patients (*p*-value = 0.004). PASI75, PASI90 and PASI100 responses were comparable at week 16. A significantly higher percentage of overweight patients achieved an absolute PASI ≤ 2, compared with both obese and normal-weight patients (89% vs. 60.34% and 76%

TABLE 1 Demographic characteristics of the 233 patients receiving guselkumab.

Number of patients	233
Male	133/233 (56.12%)
Age (years)	54.27 SD 13.25
BMI	27.56 SD 5.34
Obese	58/233 (24.89%)
Disease duration (years)	24.20 SD 13.40
PsA	49/233 (21.03%)
Difficult-site involvement	159/233 (68.24%)
Comorbidity	122/233 (52.36%)
Cardiometabolic comorbidities	116/233 (49.79%)
Infectious disease	3/233 (1.29%)
Bio-experienced	233/233 (100%)
Previous exposure to ustekinumab only	139/233 (56.66%)
Previous exposure to ≥2 biologics	94/233 (40.34%)
Previous biologic treatments	
Adalimumab	56/233 (24.03%)
Etanercept	41/233 (17.60%)
Infliximab	21/233 (9.01%)
Secukinumab	11/233 (4.72%)
Ixekizumab	6/237 (2.58%)
Apremilast	3/233 (1.29%)

Abbreviations: BMI, body mass index; PsA, psoriatic arthritis; SD, standard deviation.

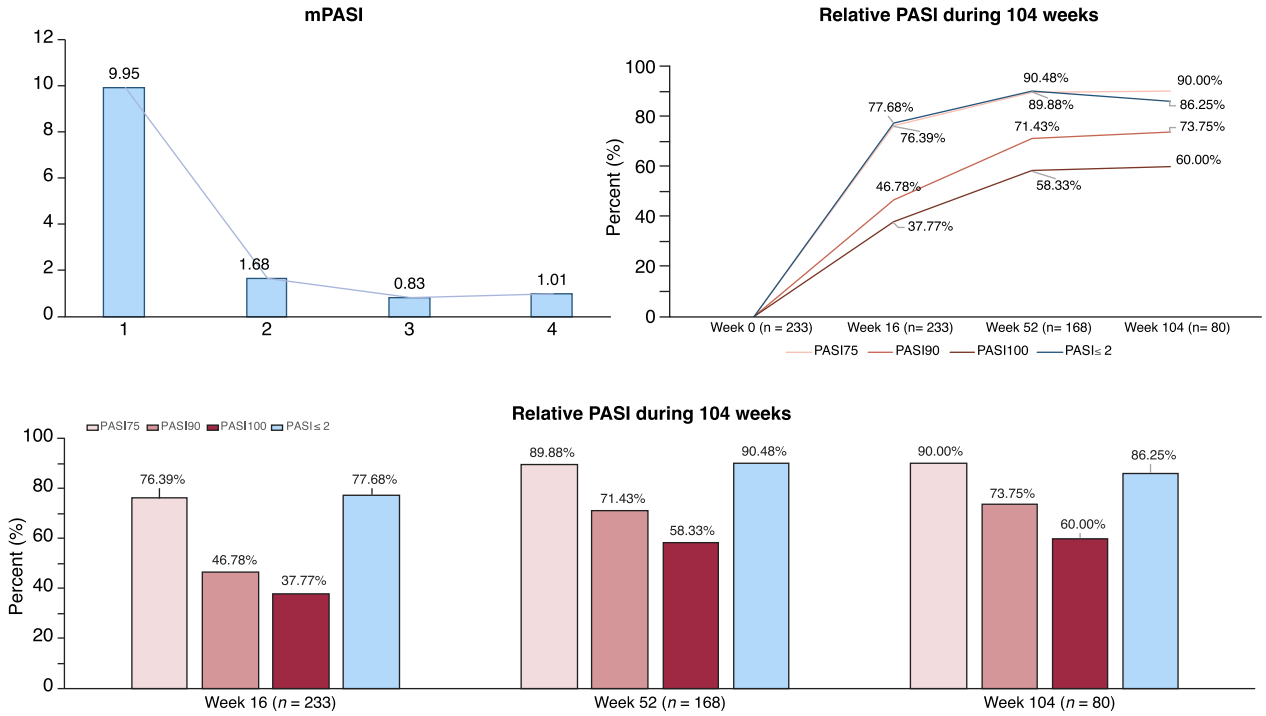

FIGURE 1 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤2 at weeks 16, 52 and 104, compared with baseline.

TABLE 2 Reduction in mean PASI score (mPASI) and percentages of patients achieving PASI 75/90/100 and ≤2 at weeks 16/52/104 in the analysed subpopulations (according to BMI and involvement of difficult-to-treat areas).

	BMI ≥ 30	25 ≤ BMI <30	BMI < 25	*p*-Value	≥1 difficult areas	No difficult areas	*p*-Value
mPASI w0	12.06	8.58	10.13	**0.004**[a]	9.84	10.17	0.712
mPASI w16	2.16	1.29	1.83	0.058	1.78	1.46	0.329
PASI75 w16	38/58 (65.52%)	81/100 (81%)	59/75 (78.67%)	0.074	120/159 (75.47%)	58/74 (78.38%)	0.627
PASI90 w16	23/58 (39.66%)	52/100 (52%)	34/75 (45.33%)	0.310	62/159 (38.99%)	47/74 (63.51%)	**<0.001**
PASI100 w16	21/58 (36.21%)	38/100 (38%)	29/75 (38.67%)	0.957	49/159 (30.82%)	39/74 (52.7%)	**0.001**
PASI ≤2 w16	35/58 (60.34%)	89/100 (89%)	57/75 (76%)	**<0.001**[a,b]	121/159 (76.10%)	60/74 (81.08%)	0.395
mPASI w52	1.58	0.44	0.74	**0.002**[a,c]	0.77	0.97	0.417
PASI75 w52	36/45 (80%)	71/74 (95.95%)	44/49 (89.8%)	**0.02**[a]	103/110 (93.64%)	48/58 (82.76%)	**0.026**
PASI90 w52	27/45 (60%)	58/74 (78.38%)	35/49 (71.43%)	0.099	77/110 (70%)	43/58 (74.14%)	0.572
PASI100 w52	23/45 (51.11%)	47/74 (63.51%)	28/49 (57.14%)	0.404	60/110 (54.55%)	38/58 (65.52%)	0.170
PASI ≤2 w52	33/45 (73.33%)	73/74 (98.65%)	46/49 (93.88%)	**<0.001**[a,c]	101/110 (91.82%)	51/58 (87.93%)	0.414
mPASI w104	1.33	0.52	1.51	0.183	0.82	1.4	0.266
PASI75 w104	21/24 (87.5%)	34/36 (94.44%)	17/20 (85%)	0.469	48/54 (88.89%)	24/26 (92.31%)	0.633
PASI90 w104	16/24 (66.67%)	29/36 (80.56%)	14/20 (70%)	0.443	39/54 (72.22%)	20/26 (76.92%)	0.654
PASI100 w104	12/24 (50%)	25/36 (69.44%)	11/20 (55%)	0.280	33/54 (61.11%)	15/26 (57.69%)	0.770
PASI ≤2 w104	18/24 (75%)	34/36 (94.44%)	17/20 (85%)	0.099	47/54 (87.04%)	22/26 (84.62%)	0.768

Abbreviations: BMI, body mass index; PASI, psoriasis area and severity index.

Significant *p*-values are highlighted in bold.

[a]Obese vs. overweight.

[b]Overweight vs. normal weight.

[c]Obese vs. normal weight.

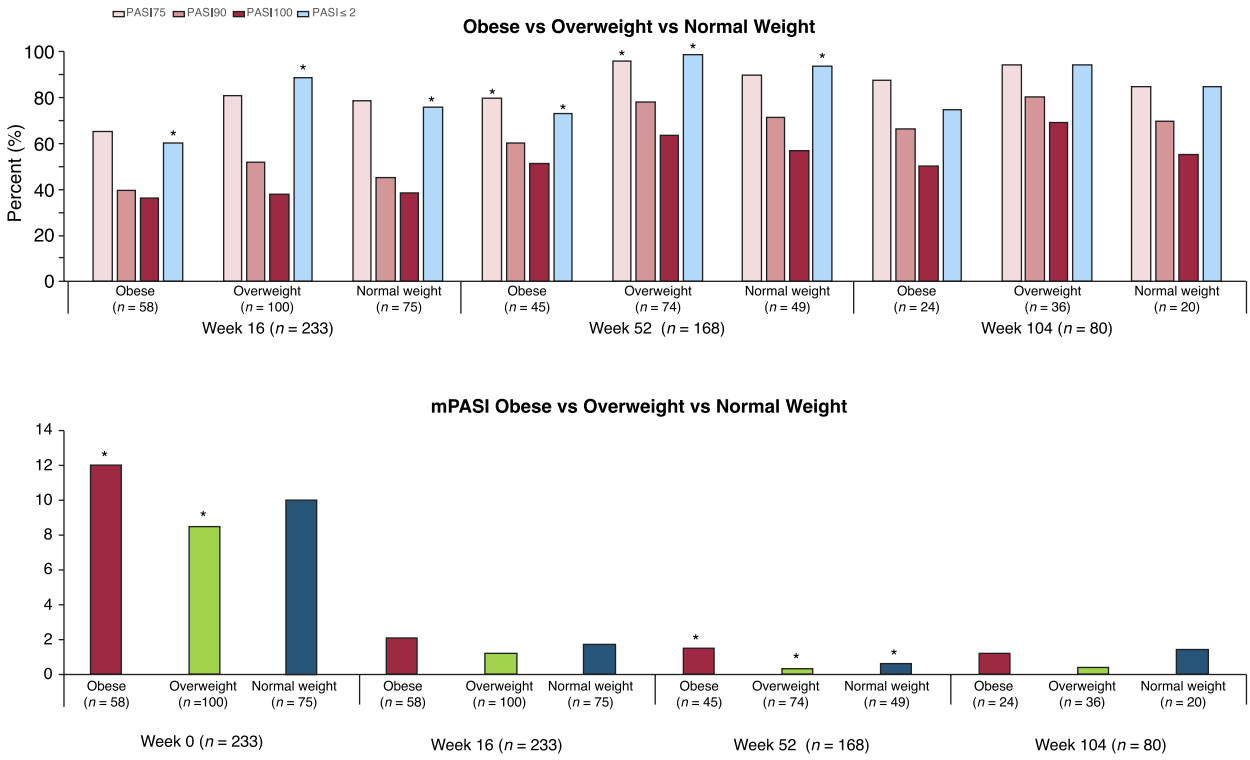

FIGURE 2 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤2 at weeks 16, 52 and 104, according to Body Mass Index.

respectively, $p < 0.001$). At week 52, mean PASI was significantly higher in obese patients, compared with both overweight and normal-weight patients (1.58 vs. 0.44 and 0.74 respectively, $p = 0.002$). Similarly, a lower PASI75 response was observed in obese patients at week 52 (80% compared with 95.95% in the overweight group and 89.8% among normal-weight patients, $p = 0.02$). However, PASI90 and PASI100 responses were comparable among obese, overweight and normal-weight patients. Regarding absolute PASI ≤2 at week 52, obese patients had a lower response compared with both the overweight and normal weight groups (73.33% vs. 98.65% and 93.88%, $p < 0.001$). At week 104, we observed comparable responses between the three groups regarding all effectiveness endpoints.

Regarding the involvement of difficult-to-treat areas, at least one of those was affected by 159 patients at baseline and week 16. At baseline, these patients had a mean PASI of 9.84, comparable with those without the involvement of difficult-to-treat areas (10.17, $p = 0.712$). At week 16, patients without psoriasis on difficult-to-treat areas had significantly better rates of PASI90 and PASI100 (63.51% vs. 38.99%, $p < 0.001$; 52.7% vs. 30.82%, $p = 0.001$ respectively). At week 52, PASI90 and PASI100 responses were comparable, regardless of the involvement of difficult-to-treat areas. At week 104, no significant differences were observed. Mean PASI and PASI ≤2 responses were comparable between the two subgroups at each week (Table 2 and Figure 3).

The improvement in PASI scores was also examined in relation to cardio-metabolic comorbidities (including the presence of cardiovascular diseases, arterial hypertension, type 2 diabetes mellitus and hyperlipidemia) (Table 3 and Figure 4). At baseline, mean PASI was comparable in patients with and without cardio-metabolic diseases (CMD) (10.51 vs. 9.38 respectively, $p = 0.179$). Mean PASI scores were also similar at weeks 16, 52 and 104 (1.84 vs. 1.51, $p = 0.282$; 1.02 vs. 0.61, $p = 0.078$; 1.26 vs. 0.68, $p = 0.245$ respectively). At week 16, patients without CMD achieved better PASI75 and PASI ≤2 responses (82.05 vs. 70.69%, $p = 0.041$, and 83.76% vs. 71.55%, $p = 0.025$). At week 16, in terms of PASI90 and PASI100, no significant differences were observed regardless of the presence of CMD. At week 52, PASI75, PASI90 and PASI100 were reached by comparable percentages of patients with and without CMD (87.91% vs. 92.91%, $p = 0.358$; 70.33% vs. 72.63%, $p = 0.732$; 57.04% vs. 61.04%, $p = 0.513$ respectively). A significantly higher proportion of patients without CMD reached an absolute PASI of two or less at week 52 (96.10% vs. 85.71%, $p = 0.022$). At week 104, no differences were observed between the two groups regarding all endpoints.

In our population, the presence of PsA did not affect baseline PASI. At week 16, patients without PsA had a lower absolute PASI (1.46 vs. 2.49, $p = 0.006$). Patients without PsA also had better PASI75 and PASI ≤2 responses at week 16 (79.89% vs. 63.27%, $p = 0.015$; 81.52% vs. 63.27%, $p = 0.006$). However, both groups achieved comparable PASI90 and PASI100 responses. At weeks 52 and 104, the presence of PsA did not have any impact on the effectiveness of guselkumab (Table 3 and Figure S1).

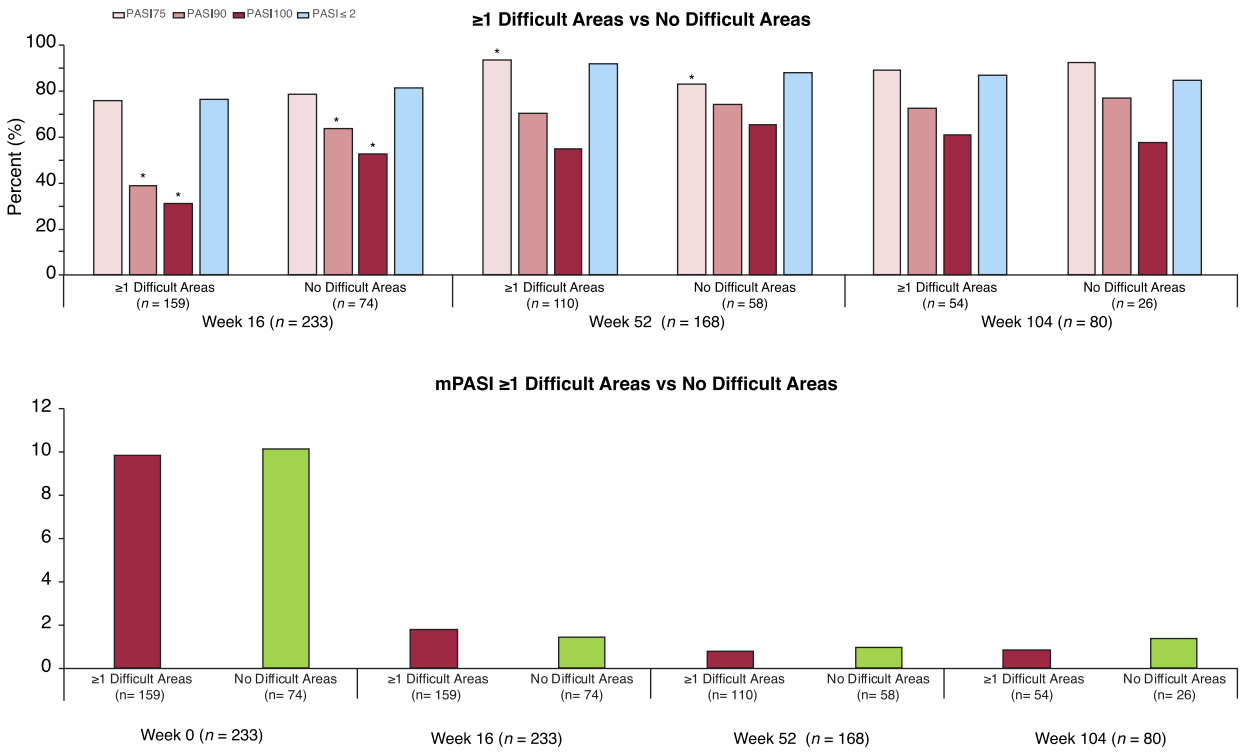

FIGURE 3 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤2 at weeks 16, 52 and 104, compared with baseline, according to the involvement of difficult-to-treat areas.

Regarding previous exposure to biologics (Table 3 and Figure S2), mean PASI at baseline was higher in patients who failed at least two biologics, compared with those who failed ustekinumab only (11.28 vs. 9.04, $p = 0.009$). At week 16, the mean PASI was still higher in multi-failure patients (2.1 vs. 1.39, $p = 0.023$). In terms of both PASI 75/PASI 90/PASI 100 and absolute PASI ≤2, guselkumab demonstrated similar effectiveness regardless of the number of previous biologics at weeks 16, 52 and 104. Moreover, at both week 52 and week 104, the mean PASI was similar in the two groups.

On multivariate analysis, at week 16, patients with PsA had a lower probability of reaching PASI75 (OR = 0.39 [95% CI 0.19–0.80], $p = 0.009$) and PASI ≤2 (OR = 0.34 [95% CI 0.15–0.74], $p = 0.007$). Compared with overweight patients both obese and normal-weight were less likely to achieve PASI ≤2 at week 16 (OR = 0.20 [95% CI 0.07–0.52], $p = 0.001$; OR = 0.30 [95% CI 0.12–0.73], $p = 0.008$). The involvement of difficult-to-treat areas was a negative predictor of PASI90 (OR = 0.38 [95% CI 0.21–0.68], $p = 0.001$) and PASI100 (OR = 0.40 [95% CI 0.23–0.70], $p = 0.002$) at week 16. At week 52, obese patients had a lower probability, compared with overweight, of reaching PASI75 (OR = 0.20 [95% CI 0.05–0.80], $p = 0.022$), PASI90 (OR = 0.43 [95% CI 0.19–0.97], $p = 0.043$) and PASI ≤2 (OR = 0.03 [95% CI 0.003–0.41], $p = 0.008$). All the other variables did not reach significance in multivariate analysis.

Regarding the safety profile of guselkumab in our study, no severe adverse events were reported (Table 4). No new safety findings were experienced by our patients. Only one patient discontinued the drug because of a psoriasis flare and was switched to an anti-IL-17 drug. Moreover, despite most patients receiving guselkumab during the apex of the COVID-19 pandemic in Italy, no COVID-19-related hospitalizations or deaths were reported. Regarding the patient with a history of viral hepatitis B, follow-up laboratory tests and periodic hepatological visits showed no signs of viral reactivation. The two patients with a positive TB Quantiferon test underwent annual pneumologic visits and chest X-rays, with no evidence of active tuberculosis.

DISCUSSION

Our retrospective study is one of the largest real-life studies on guselkumab use in patients who failed ustekinumab, with a population of 233 patients. Our study confirmed data from both clinical trials and real-life studies on the effectiveness of guselkumab in daily clinical practice in patients affected by moderate-to-severe plaque psoriasis with previous exposure to ustekinumab.[12,14,16,17] Compared with the Phase 3 clinical trial NAVIGATE,[12] which evaluated the effectiveness of guselkumab in patients with inadequate response to ustekinumab in 135 patients, our cohort was larger at baseline. Our population was slightly older (with a mean age of 54.27 years vs. 44.2 years), with a lower BMI (27.56 vs. 30.3) and also included patients with previous exposure to anti-IL-17 drugs. Our patients also had a longer history of psoriasis, with a

TABLE 3 Reduction in mean PASI score (mPASI) and percentages of patients achieving PASI 75/90/100 and ≤2 at weeks 16/52/104 in the analysed subpopulations (according to the presence of cardio-metabolic comorbidities, diagnosis of PsA and previous exposure to biologics).

	CMD	Non-CMD	*p*-Value	PsA	Non-PsA	*p*-Value	One previous biologic	≥2 previous biologics	*p*-Value
mPASI w0	10.51	9.38	0.179	10.13	9.9	0.824	9.04	11.28	**0.009**
mPASI w16	1.84	1.51	0.282	2.49	1.46	**0.006**	1.39	2.1	**0.023**
PASI75 w16	82/116 (70.69%)	96/117 (82.05%)	**0.041**	31/49 (63.27%)	147/184 (79.89%)	**0.015**	109/139 (78.42%)	69/94 (73.4%)	0.377
PASI90 w16	53/116 (45.69%)	56/117 (47.86%)	0.740	17/49 (34.69%)	92/184 (50%)	0.056	66/139 (47.48%)	43/94 (45.74%)	0.794
PASI100 w16	42/116 (36.21%)	46/117 (39.32%)	0.624	15/49 (30.61%)	73/184 (39.67%)	0.245	55/139 (39.57%)	33/94 (35.11%)	0.491
PASI ≤2 w16	83/116 (71.55%)	98/117 (83.76%)	**0.025**	31/49 (63.27%)	150/184 (81.52%)	**0.006**	112/139 (80.58%)	69/94 (73.4%)	0.197
mPASI w52	1.02	0.61	0.078	0.61	0.89	0.323	0.94	0.69	0.289
PASI75 w52	80/91 (87.91%)	71/77 (92.21%)	0.358	32/35 (91.43%)	119/133 (89.47%)	0.733	82/94 (87.23%)	69/74 (93.24%)	0.200
PASI90 w52	64/91 (70.33%)	56/77 (72.73%)	0.732	25/35 (71.43%)	95/133 (71.43%)	1.000	62/94 (65.96%)	58/74 (78.38%)	0.077
PASI100 w52	51/91 (56.04%)	47/77 (61.04%)	0.513	22/35 (62.86%)	76/133 (57.14%)	0.542	53/94 (56.38%)	45/74 (60.81%)	0.563
PASI ≤2 w52	78/91 (85.71%)	74/77 (96.10%)	**0.022**	31/35 (88.57%)	121/133 (90.98%)	0.666	85/94 (90.43%)	67/74 (90.54%)	0.980
mPASI w104	1.26	0.68	0.245	0.89	1.04	0.799	1.07	0.96	0.822
PASI75 w104	41/46 (89.13%)	31/34 (91.18%)	0.762	14/16 (87.5%)	58/64 (90.63%)	0.709	37/40 (92.5%)	35/40 (87.5%)	0.456
PASI90 w104	35/46 (76.09%)	24/34 (70.59%)	0.581	11/16 (68.75%)	48/64 (75%)	0.611	29/40 (72.5%)	30/40 (75%)	0.799
PASI100 w104	28/46 (60.87%)	20/34 (58.82%)	0.853	8/16 (50%)	40/64 (62.5%)	0.361	22/40 (55%)	26/40 (65%)	0.361
PASI ≤2 w104	37/46 (80.43%)	32/34 (94.12%)	0.079	13/16 (81.25%)	56/64 (87.5%)	0.516	36/40 (90%)	33/40 (82.5%)	0.330

Abbreviations: CMD, cardio-metabolic diseases; PsA, psoriatic arthritis.

Significant *p*-values are highlighted in bold.

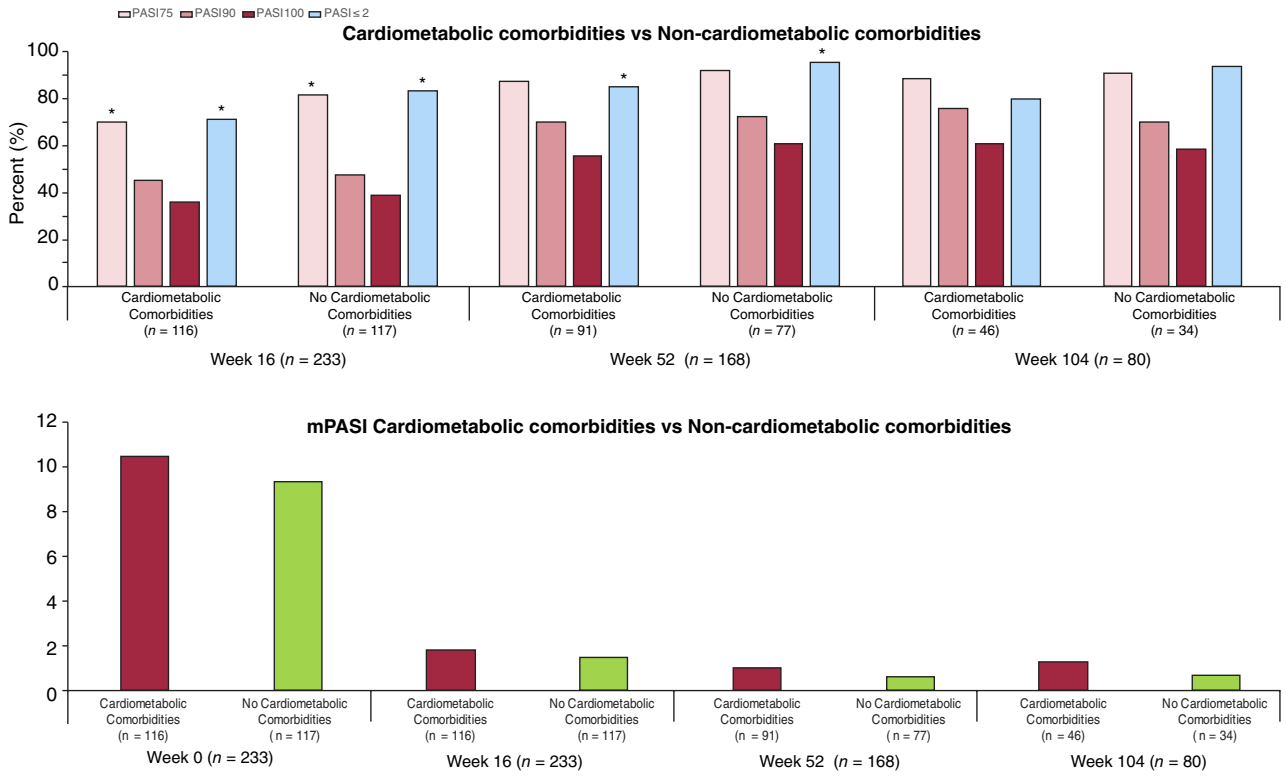

FIGURE 4 Mean PASI (mPASI) reduction and percentages of patients achieving PASI 100/90/75 and PASI ≤2 at weeks 16, 52 and 104, compared with baseline, according to the presence of cardio-metabolic comorbidities.

TABLE 4 Reported adverse events during the treatment with guselkumab.

Adverse events	*N* (% on total population)
Upper respiratory tract infectious	2 (0.85%)
Headache	3 (1.2%)
Reaction at injection site	3 (1.29%)
Diarrhoea	1 (0.43%)
Flare of Psoriasis	1 (0.43%)
Total	9 (3.86%)
Severe AE	0 (0%)
AE leading to discontinuation	1 (0.43%)

mean of 24.20 (SD 13.40), compared with 18.20 (SD 12.70) in patients receiving guselkumab in the NAVIGATE study. Our patients had a lower mean PASI at baseline due to the strict inclusion criteria of Phase 3 clinical trials.[12]

Compared with data from the NAVIGATE trial, we observed better clinical responses to guselkumab in our real-life study. At week 52, PASI90 was achieved by 71.43% of our patients, compared with 51.1% from NAVIGATE study, while PASI100 was reached by 58.33% of our patients (vs. 20%). These findings could be explained by a higher mean PASI at baseline in the NAVIGATE population. It has been shown that ustekinumab failure is associated with increased levels of drug antibodies.[15] Despite ustekinumab and guselkumab sharing IL-23 as target, our real-life experience confirmed the results of clinical trials, showing that the effectiveness of guselkumab is not influenced by previous ustekinumab treatment.

In our study, obese patients experienced lower rates of PASI ≤2 at weeks 16 and 52. These findings are consistent with a recent analysis of pooled data from VOYAGE-1 and VOYAGE-2 studies, which identified a subgroup of 'super-responders' to guselkumab.[18] According to this study, patients with a lower BMI are more likely to achieve better responses when treated with guselkumab. However, in our experience, no significant differences were observed after 2 years of continuous treatment.

Regarding the involvement of difficult-to-treat areas, at week 16, we observed lower PASI90 and PASI100 responses in patients who presented psoriasis on those sites. In contrast, at weeks 52 and 104, those differences were not significant. The effectiveness of guselkumab on scalp, hands and feet and nails has been evaluated in a clinical trial from Foley et al.,[19] showing superior efficacy compared with adalimumab at weeks 16 and 24. Our data, showing comparable effectiveness of guselkumab in patients with and without the involvement of difficult-to-treat areas after 2 years of treatment, confirm the results of a real-life study on the effectiveness of anti-IL-23 and anti-IL-17 drugs in psoriasis of the scalp.[20]

Regarding the impact of cardio-metabolic comorbidities on the effectiveness of guselkumab, at week 16, we observed lower

rates of PASI75 and PASI ≤2 in patients with CMD. However, the multivariate analysis did not show any significant differences between the groups. Interestingly, PASI90 and PASI100 responses were comparable at all timepoints. Anti-IL-23 drugs have shown effectiveness and safety in both clinical trials and real-life studies in patients with cardio-metabolic comorbidities.[21–25] In our study, guselkumab demonstrated a slower impact, in terms of relative PASI reduction, on patients with CMD up to week 52. However, at week 104, no differences were observed between these two groups.

Guselkumab has recently received approval also for the treatment of psoriatic arthritis.[26] At week 16, patients with PsA were less likely to achieve a PASI75 and absolute PASI ≤ 2. However, after 1 year of treatment, patients with and without PsA achieved comparable responses, showing slower effectiveness of guselkumab in those with concomitant joint involvement.

In our study, the previous exposure to two or more biologics did not interfere with the achievement of PASI 75/PASI 90/PASI 100/PASI ≤ 2 at all timepoints. These findings are consistent with other real-life studies which evaluated the effectiveness of guselkumab in a cohort of multi-failure patients (including patients with previous exposure to anti-IL-17 drugs).[14,16,17,27,28] Guselkumab, along with other anti-IL-23 drugs, could also represent a valid therapeutic option in patients who failed several biologics.

Regarding the safety of guselkumab, in our study, no significant safety findings were shown after 104 weeks of treatment, in accordance with both clinical trials and real-life studies.[12,29] No data on severe forms of COVID-19 infections were recorded, as observed in other real-life studies evaluating the safety of biological drugs in plaque psoriasis.[23–25] The safety of guselkumab was also confirmed in patients with serological evidence of viral hepatitis, as no viral reactivation was reported.[30]

Our study has some limitations, the first being its retrospective design, which does not allow the retrieval of missing data. Other limitations include the smaller sample size at week 104, the lack of a randomized controlled setting and the heterogeneity of clinical evaluations among different centres.

CONCLUSION

Our results at weeks 52 and 104 confirm the long-term effectiveness of guselkumab in patients with inadequate response to ustekinumab. Compared with the NAVIGATE trial, we observed better PASI90 and PASI100 responses, showing the high effectiveness of guselkumab in a real-life setting with one of the largest populations to date.

Guselkumab was effective in both patients with previous exposure to guselkumab only and multi-failure patients (including failure to anti-IL-17 drugs) at both week 52 and week 104. Moreover, at week 104, we also observed comparable responses among all patient subgroups, regardless of BMI status, involvement of difficult-to-treat areas, presence of cardiometabolic comorbidities and concomitant diagnosis of psoriatic arthritis. Guselkumab demonstrated effectiveness in our real-life cohort of patients with several comorbidities and a longer history of psoriatic disease, compared with NAVIGATE trial.

Guselkumab was well tolerated, as no significant safety findings emerged after 2 years of therapy. Larger and longer prospective studies and retrospective analyses of patient databases are needed to further assess the effectiveness and safety of guselkumab in real-life bio-experienced patients.

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CONFLICT OF INTEREST STATEMENT

P. Malagoli has been a speaker for AbbVie, Lilly, Novartis, Janssen-Cilag, Celgene, Leopharma and Almirall. F. Bardazzi has been a consultant adviser and clinical study investigator for Eli Lilly, Abbvie, Novartis, Leo Pharma, Sandoz, Bristol Myers, Abiogen-Pharma, Celgene and Janssen. M. Burlando has acted as a speaker and consultant for AbbVie, Janssen, Amgen, Novartis, Eli Lilly, UCB Pharma. C. G. Carrera has served as a board participant or speaker for Abbvie, Lilly, Janssen, Novartis, Celgene, Almirall and Leopharma. A. Chiricozzi has served as advisory board member and/or consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Incyte, Janssen, Leo Pharma, Lilly, Novartis, Pfizer and Sanofi Genzyme. P. Dapavo has been a speaker for Novartis, Abbvie, Sanofi, UCB, Janssen, Lilly and LeoPharma. G. Fabbrocini acted as a speaker or consultant for Abbvie, Amgen, Eli Lilly, Janssen, Leo-Pharma, Almirall, Novartis and UCB. F. M. Gaiani acted as a speaker or consultant for Novartis, Abbvie, Eli Lilly, Celgene, LeoPharma and Almirall. C. Giofrè has been a member of scientific board/speaker/clinical study investigator for AbbVie, Celgene, Janssen, Novartis, Sanofi. C. Guarneri has been a scientific consultant/speaker/clinical study investigator for Abbvie, Celgene, Janssen, Eli Lilly, Novartis, Pfizer, Sanofi, Almirall, LEO Pharma. F. Loconsole served on advisory boards and/or received honoraria for lectures from Abbvie, Janssen-Cilag, Novartis, Lilly, Sanofi. G. Malara has received honoraria as a speaker and consultant for Janssen, Sanofi, Abbvie, Eli Lilly, Novartis and Celgene. M. Megna acted as a speaker or consultant for Abbvie, Eli Lilly, Janssen, Leo-Pharma and Novartis. S. Piaserico has consulted (includes advisory boards, editorial advice, podium presentations and travel grants) for AbbVie, Almirall, Celgene, Janssen-Cilag, Lilly, MSD, Novartis and Pfizer. M. Talamonti has served as a scientific adviser and/or clinical study investigator for Abbvie, Amgen, Janssen, LEO Pharma, Lilly, Novartis, Sanofi Genzyme, and as paid speaker for Janssen, Novartis and Sanofi Genzyme. 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. 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. L. Gargiulo, L. Ibba, R. G. Angileri, N. Bernardini, V. Dini, M. Galluzzo and L. Marcelli have nothing to declare.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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