Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Long-Term Real-World Effectiveness and Drug Survival of Guselkumab in Patients with Psoriasis: A 5-Year Retrospective Study

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Background: Clinical trials have demonstrated the efficacy of guselkumab in psoriasis, however, limited data are available from real-life studies evaluating the long-term effectiveness and drug survival (DS) of guselkumab.

Objective: This multicenter study assessed the 5-year efficacy, DS, and predictors of treatment response in a large cohort of patients with psoriasis.

Methods: In this retrospective, longitudinal study, we analyzed data from 1024 patients with moderate-to-severe psoriasis treated with guselkumab between 2019 and 2024. PASI scores were evaluated at baseline, 6 months, and 1–5 years. DS (ie, duration of continuous treatment with guselkumab without discontinuation) was assessed using Kaplan-Meier analysis, and logistic regression analysis was used to identify predictors of PASI response.

Results: Mean PASI decreased from 14.3±8.8 at baseline to 1.3±2.4 at 6 months, with sustained improvement from 12–60 months (PASI values ranging from 1.0±2.2 to 1.3±3.5). Bioexperienced (ie having previous biological treatment) patients and obese individuals had lower PASI response. Subgroup analyses revealed significantly lower PASI response rates in obese patients, those previously treated with biologics, and those switched from anti-IL-17 agents ($p<0.05$).

Multivariate logistic regression analysis revealed that previous biologic exposure and obesity remained significant negative predictors of achieving PASI 75, PASI 90, and PASI 100 across different time points. Cardiovascular disease emerged as a negative predictor for PASI 90 at 3 months (OR 0.64, 95% CI: 0.42–0.97, p=0.035). The probability of remaining on treatment at 12, 24, 36, 48, and 60 months were 95.85%, 91.73%, 89.74%, 87.08%, and 85.76% respectively. Female sex, ≥3 prior biologics, longer disease duration, and previous anti-IL-17 therapy increased the risk of treatment discontinuation. No significant differences in drug discontinuation were noted between patients with or without comorbidities.

Conclusion: This real-world study demonstrates the sustained long-term efficacy and DS of guselkumab in patients with psoriasis. Prior biologic exposure, obesity, and patient history are important factors to consider when initiating treatment for long-term management.

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Plain Language Summary: This study looked at how well guselkumab, a medication for psoriasis, works over five years in real-world patients. Guselkumab is a type of biologic drug (immune-targeted therapy) that blocks a protein called interleukin-23 (IL-23), which plays a key role in causing inflammation and skin symptoms seen in psoriasis. It is administered by injection and used to treat people with moderate-to-severe disease.

In this study, over 1,000 people with psoriasis were treated with guselkumab between 2019 and 2024. Most patients saw marked improvements in their skin within six months, and these benefits continued for up to five years. However, people who were obese, had tried other biologic drugs before, or had heart disease did not respond as well. Women and those with longer disease history were more likely to stop treatment. Still, most patients (>85%), stayed on the drug for the full five years. This study shows that guselkumab can be an effective long-term option for psoriasis, especially when tailored to individual patient needs.

Keywords: guselkumab, effectiveness, long-term, drug survival, psoriasis, comorbidities

Introduction

Psoriasis is a chronic, immune-mediated dermatological condition affecting approximately 2–3% of the population worldwide,[1] severely impacting upon patients quality of life.[2] Once thought to be limited to the skin, psoriasis is now recognized as a systemic inflammatory disease associated with a range of cardiometabolic comorbidities, including obesity, hypertension, type-2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease.[3]

At the molecular level, psoriasis is characterized by T-cell-driven inflammation, with interleukin (IL)-23 playing a central role in regulating Th17 cell activity and contributing significantly to the pathogenesis of the disease.[4–6] In recent years, new immune-targeted therapies have been developed.[7] Among these, biologic agents have revolutionized psoriasis management, demonstrating both safety and efficacy.[8] IL-23-targeted biologics such as ustekinumab, guselkumab, tildrakizumab, and risankizumab have been approved for treating moderate-to-severe psoriasis in both the US and Europe.[9]

Guselkumab is a fully human immunoglobulin G1k (IgG1k) monoclonal antibody targeting the p19 subunit of IL-23, inhibiting intracellular pathways involved in Th17 lymphocyte survival and differentiation.[10,11]

The efficacy and safety of guselkumab has been evaluated in multiple Phase III clinical trials.[12–15] The randomized, double-blind, phase III trials VOYAGE-1 and VOYAGE-2 demonstrated the superiority of guselkumab over adalimumab, a monoclonal antibody targeting TNF-alpha.[12,13] The NAVIGATE study showed superior efficacy of guselkumab compared to ustekinumab, an IL-12/IL-23 inhibitor.[14] In addition, the ECLIPSE study assessed long-term efficacy of guselkumab versus secukinumab, an IL-17A inhibitor.[15]

While clinical trials provide critical evidence of efficacy and safety, real-world evidence (RWE) is essential to understand the performance of guselkumab in routine clinical practice.[16–18] The characteristics of clinical trial participants often differ from real-life patients due to strict exclusion criteria, comorbidities, polypharmacy, and prior treatment failures.[16–18] Real-world data on guselkumab are emerging, though many analyses are limited to relatively short follow-up periods, typically around one year.[19–21] However, two recent studies extended follow-up to three years, involving 112 and 122 patients with psoriasis.[22,23] More recently, two larger real-life studies provide valuable RWE from cohorts of 200 and 849 patients, respectively, with follow-up durations of up to four years.[24,25]

Data from real-world experiences vary across studies but generally align with clinical trial results at 28–48 weeks (6–11 months), with PASI 90 response rates ranging from 37–95.2% in real-life studies versus 84–90% in VOYAGE 2 and ECLIPSE trials.[15] These findings confirm guselkumab as a highly effective, well-tolerated long-term option.

Drug survival (ie, the length of time a patient remains on therapy without discontinuation) can be considered as a reliable indicator of overall treatment effectiveness in observational studies, as it is mainly determined by drug efficacy and safety profile.[26]

To address the need for long-term RWE, this study presents real-world data on the efficacy, drug survival (DS), and predictors of treatment response in patients with moderate-to-severe psoriasis. To our knowledge, this is the largest real-life cohort treated with guselkumab and the longest follow-up (up to 5 years) reported to date.

Materials and Methods

Study Design and Population

This retrospective, multicenter study was conducted in 10 Italian centers to assess the long-term outcomes, efficacy, and treatment persistence of guselkumab in patients with moderate-to-severe psoriasis, including those with comorbidities. A total of 1,024 patients treated between 2019–2024 were included. All patients received guselkumab according to standard protocol, consisting of an induction phase with 100 mg administered subcutaneously at weeks 0 and 4, followed by maintenance doses every 8 weeks. Patients were eligible if they had a Psoriasis Area and Severity Index (PASI) >10 or, in cases of involvement of sensitive areas (eg, face, scalp, hands, or genital regions), a PASI score <10, and had shown inadequate response, contraindications, or intolerance to at least one conventional systemic therapy or phototherapy.

Baseline demographic and clinical data, including age, sex, disease onset and duration, PASI scores, psoriatic arthritis (PsA) status, prior biologic exposure (ie bioexperienced), and comorbidities (eg, hypertension, dyslipidemia, obesity, cardiovascular disease; CVD, thyroid disorders, diabetes, and psychiatric illnesses), were collected from medical records and entered into a dedicated database. All patients underwent appropriate screening and monitoring for infectious comorbidities (hepatitis B, HBV; hepatitis C, HCV; tuberculosis, TB, and HIV) and, when indicated, oncological evaluation.

Individuals with concomitant autoimmune or inflammatory disorders, such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, and ankylosing spondylitis, were not included. In addition, patients who had undergone treatment with biologic agents, systemic therapies, or phototherapy within the four weeks prior to their initial evaluation, or who had received these treatments in combination with biologics, were excluded. Furthermore, individuals presenting with guttate, erythrodermic, or pustular psoriasis were deemed ineligible. Written informed consent was obtained from all participants, and the study was performed in accordance with the Declaration of Helsinki.

Outcome Measures

Drug survival (retention rate), was retrospectively defined as the interval from the initiation of guselkumab therapy until permanent discontinuation. This included patients who discontinued treatment due to primary inefficacy (failure to achieve PASI 75 after 16 weeks of treatment) or secondary inefficacy (loss of PASI 75 after 16 weeks of treatment), those lost to follow-up, and those who experienced adverse events (AEs). Clinical efficacy was assessed by evaluating the proportion of patients achieving PASI 75, PASI 90, and PASI 100 responses, corresponding to a 75%, 90%, and 100% reduction in PASI score, at 6 months, 12 months, and annually up to 5 years. For the overall cohort, both PASI response and retention rates were calculated over a 5-year follow-up period.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation and categorical variables were reported as number and percentage. Baseline characteristics were compared using two-tailed t-tests (continuous data) and Chi-square tests (categorical data). Drug survival was assessed using Kaplan–Meier survival analysis, with subgroup comparisons based on sex, obesity status, prior biologic exposure, previous anti-IL-17 use and the number of previous biologic treatments. Differences between curves were assessed using the Log rank test. Multivariate logistic regression was used to identify predictors of PASI 75, 90, and 100 at 6, 12, 24, 36, 48, and 60 months and results reported as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value ≤ 0.05 indicated statistical significance. All analyses were performed using STATA 11.2 (Statacorp LP).

Results

Baseline Clinical Characteristics of Patients

A total of 1,024 patients (mean age: 57, range: 20–92) were included in the study, with 61.3% being male and 38.7% female (Table 1). The median age of psoriasis onset was 32 years (range: 1–83), and the median disease duration was 21 years (range: 0–71). PsA was present in 23.2% of patients, with a higher proportion in females than in males (26% vs 21.4%, p=0.038). The median baseline PASI score was 12 (range: 3–60), and there was no significant difference between males and females (p=0.371).

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Table 1 Baseline Clinical Characteristics of Psoriasis Patients, Stratified by Sex

Clinical Characteristics	Total (N=1024)	Male (N=628)	Female (N=396)	p-value
General				
Age, median (range), years	57 (20–92)	56 (20–92)	58 (23–90)	0.21
BMI, median (range), kg/m^2	26.2 (17–52.7)	26.8 (17–52.7)	25.1 (17–42.7)	0.013
Current cigarette smoker, n (%)	379 (37.1)	236 (37.5)	134 (36.1)	0.89
Disease characteristics				
Age at disease onset, median (range)	32 (1–83)	32 (1–83)	33 (1–78)	0.17
Disease duration, median (range)	21 (0–71)	22 (1–69)	19 (0–71)	0.57
PsA, n (%)	238 (23.2)	135 (21.4)	103 (26)	0.038
PASI at baseline, median (range)	12 (3–60)	12 (3–60)	12 (4–53)	0.37
Biologic therapy, n *(%)*				
Biologic naïve	392 (38.3)	240 (38.3)	152 (38.4)	0.92
Previous biologic therapy	632 (61.7)	388 (61.7)	244 (61.6)	0.95
1 biologic	377 (36.8)	228 (36.3)	149 (37.6)	0.37
2 biologics	163 (15.9)	103 (16.4)	60 (15.1)	0.54
≥3 biologics	92 (8.9)	57 (9)	35 (8.8)	0.91
Last therapy anti-TNF	159 (25.1)	88 (22.6)	71 (29.1)	0.29
Last therapy ustekinumab	278 (44)	187 (48.1)	91 (37.2)	0.008
Last therapy anti-IL-17	187 (29.6)	109 (28.1)	78 (31.9)	0.17
Last therapy anti-IL-23	8 (1.3)	4 (1)	4 (1.6)	0.51
Comorbidities, n *(%)*				
Hypertension	394 (38.4)	248 (39.4)	146 (36.8)	0.41
Dyslipidemia	283 (27.6)	180 (28.6)	103 (26)	0.17
Obesity (BMI ≥30 kg/m^2)	251 (24.5)	157 (25)	94 (23.7)	0.71
Heart disease	191 (18.6)	134 (21.3)	57 (14.3)	0.006
Diabetes mellitus	145 (14.2)	92 (14.6)	53 (13.3)	0.52
Thyroid diseases	65 (6.3)	16 (2.5)	49 (12.3)	<0.001
Psychiatric illness	31 (3)	18 (2.8)	13 (3.2)	0.71
Follow up, median months (range)	140.8 (8.9–616.3)	140.9 (8.9–616.3)	140.7(9.0–305.4)	0.73

Notes: Data are presented as median (range) or number (percentage).
Abbreviations: BMI, Body Mass Index; PsA, Psoriatic Arthritis; PASI, Psoriasis Area and Severity Index; TNF, Tumor Necrosis Factor; IL, Interleukin.

Prior to initiating guselkumab, 38.3% of patients were biologic-naïve, while 61.7% had been previously treated with biologics. The distribution of prior biologic exposure did not significantly differ between sexes. However, more females had been treated with ustekinumab compared to males (48.1% vs 37.2%, p=0.008). The most common comorbidities were hypertension (38.4%), dyslipidemia (27.6%), and obesity (24.5%). Heart disease was more frequent in males (21.3% vs 14.3%, p=0.006), while thyroid disorders were more common in females (12.3% vs 2.5%, p<0.001). No significant differences were observed in the prevalence of diabetes or psychiatric illnesses. The median follow-up duration was 140.8 months (range: 8.9–616.3), with no significant differences by gender (p=0.734).

PASI Response Over 5 Years

The efficacy of guselkumab was evaluated using PASI scores over a 5-year follow-up period. The mean PASI at baseline was 14.3±8.8, which decreased to 1.3±2.4 at 6 months and further improved to 0.9 at 12 months (Figure 1A). This improvement was sustained over time, with mean PASI values of 1.0±2.2, 1.2±3.2, 1.1±3.2, and 1.3±3.5 at 24, 36, 48, and 60 months, respectively.

The proportion of patients achieving PASI 75, PASI 90, and PASI 100 followed a similar trend (Figure 1B). At 6 months, 87.5% of patients reached PASI 75, 69.9% achieved PASI 90, and 57.6% attained complete clearance (PASI 100). These response rates were maintained or improved over time, with PASI 75, PASI 90, and PASI 100 rates of 89.3%, 80.5%, and 70.6%, respectively, at 60 months.

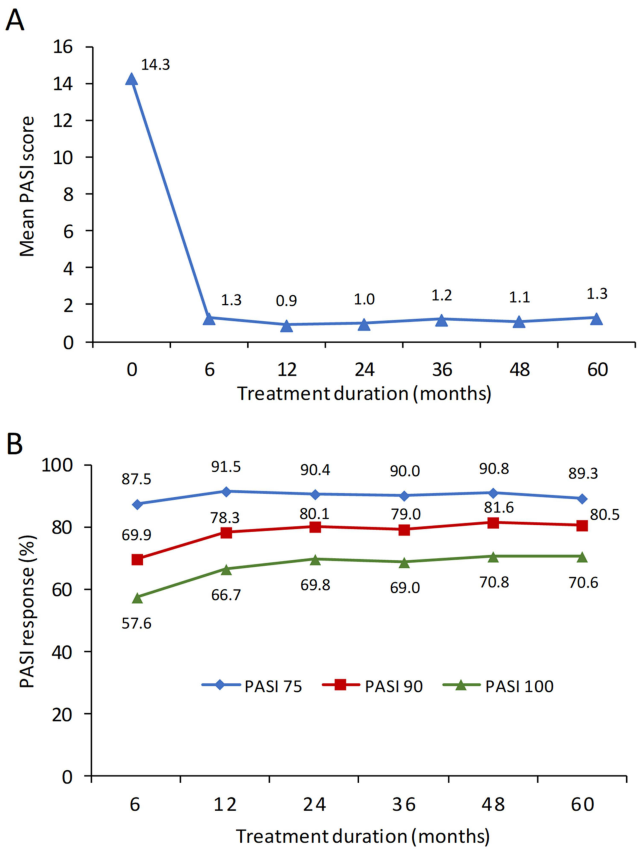

Figure 1 Effect of guselkumab in psoriatic patients on PASI score and achievement of PASI 75, 90 and 100 response over 5 years. (**A**) PASI is presented as mean values. (**B**) % patients achieving PASI 75, 90 and 100 response. Mean PASI score, and % patients achieving PASI 75, 90 and 100 response are presented for each time point. The number of patients included at each yearly follow-up, based on the last observation carried forward (LOCF) method, was as follows: Year 0 = 1008; Year 1 = 931; Year 2 = 752; Year 3 = 548; Year 4 = 381; Year 5 = 252.

Subgroup analyses revealed significant differences in some sub populations, particularly in the early phases of treatment, with lower PASI response rates in patients with previous biologic treatment (Figure 2A) and obese patients (Figure 2B), as well as in those previously treated with anti-IL-17 agents (Figure 2C). These differences remained statistically significant at multiple time points during the follow-up period ($p<0.05$), highlighting the potential impact of prior biologic exposure and BMI on treatment response.

Factors Associated with Enhanced PASI Response

Univariate logistic regression was used to identify factors associated with PASI response. The analyzed variables included demographic and clinical characteristics such as sex, age, smoking status, disease onset and duration, body weight, BMI, baseline PASI, comorbidities, PsA, prior biologic treatments, and the last biologic class used.

Logistic regression models assessed their impact on PASI 75, PASI 90, and PASI 100 at different time points (Tables 2–4). Previous exposure to biologics and the number of prior biologic treatments were consistently associated with a reduced likelihood of achieving PASI 75, PASI 90, and PASI 100 at multiple time points. The presence of obesity also emerged as a significant negative predictor (OR ranging from 0.45–0.73) across all response criteria, particularly at 6 months and beyond. Although higher baseline PASI emerged as a positive predictor of PASI 75 response at 6, 12, and 24 months it was a negative predictor of PASI 100 response at 6 months. The use of anti-IL-17 therapy strongly emerged (OR ranging from 0.44–0.64) as a negative predictor of treatment response at early as well as long-term time points (Tables 2–4).

Previous treatment with anti-IL-12/23 biologics also emerged as a negative predictor of achieving complete remission (PASI 100) at 60 months (Table 4).

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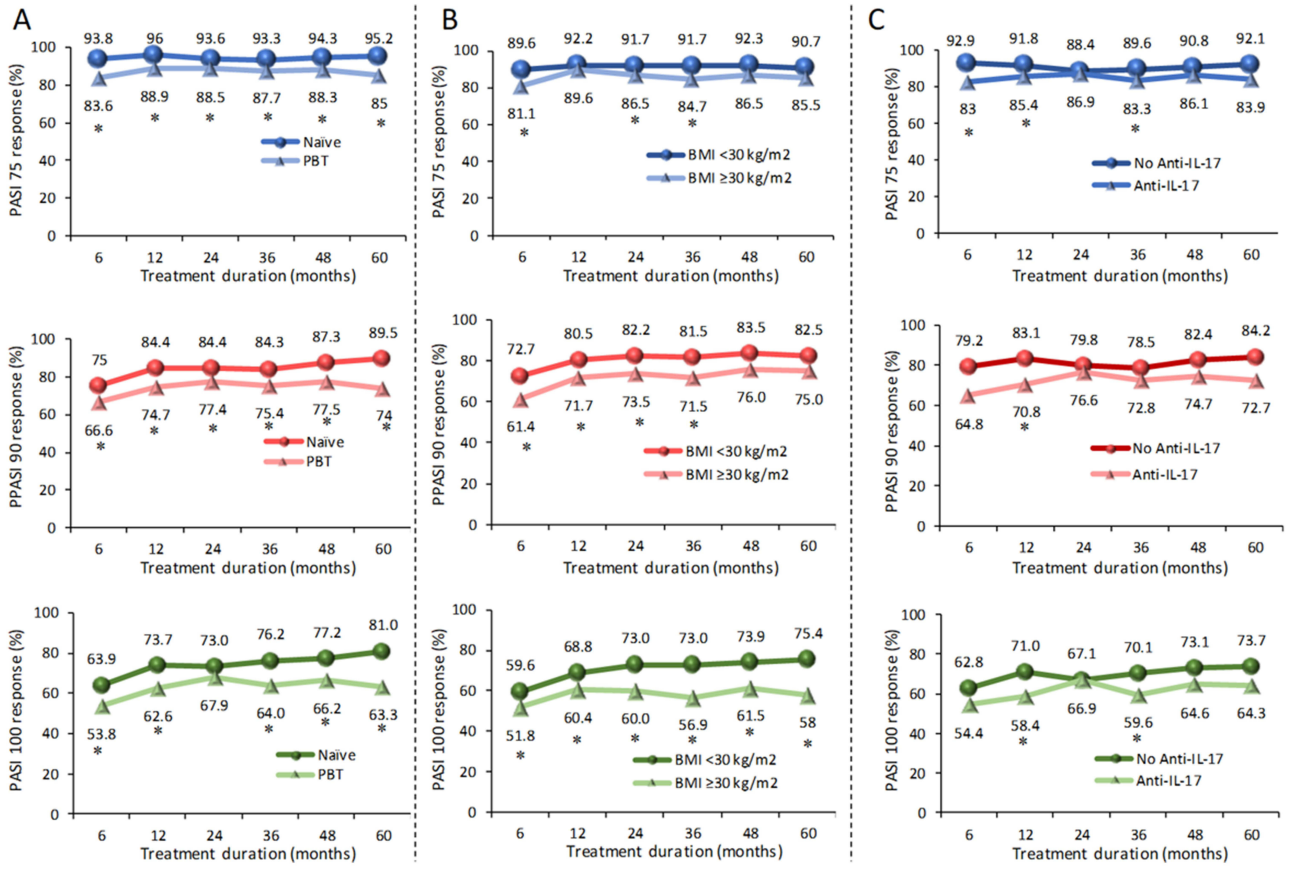

Figure 2 Effect of guselkumab in psoriatic patients on achievement of PASI 75, 90 and 100 response in patient subgroups over 5 years: (**A**) role of previous biological therapy, (**B**) presence of obesity, and (**C**) previous anti-IL-17 therapy. The % patients achieving PASI 75, 90 and 100 response are presented for each time point. The number of patients lost to follow-up at 0, 1, 2, 3, 4, and 5 years, calculated using the last observation carried forward (LOCF) method, was as follows: 623, 585, 470, 325, 222, and 147 in the PBT group; 385, 346, 223, 158, and 105 in naive group; 249, 230, 185, 137, 96, and 69 in the obese group; 759, 701, 567, 411, 284, and 183 in the non-obese group; 182, 178, 145, 114, 79, and 356 in patients switched from IL-17; and 828, 753, 607, 434, 301, and 196 in those not switched from IL-17. * = p<0.05.

Following stepwise multivariate logistic regression analysis (Table 5), previous biologic exposure and obesity remained significant negative predictors of achieving PASI 75, PASI 90, and PASI 100 across different time points. Higher baseline PASI emerged as a positive predictor for PASI 75, while negative for PASI 100 at multiple time points.

Table 2 Univariate Logistic Regression Analysis of Variables Significantly Associated with PASI 75 Response

Time Point	Variable	OR (95% CI)	p-value
3 months	Previous exposure to biologics	0.57 [0.38–0.85]	0.006
	Number of prior biologic treatments	0.77 [0.66–0.90]	0.001
	Last therapy with anti-IL-17	0.65 [0.43–0.98]	0.041
6 months	Obesity (BMI ≥30 kg/m^2)	0.50 [0.34–0.74]	0.001
	Previous exposure to biologics	0.34 [0.21–0.54]	0.0001
	Number of prior biologic treatments	0.75 [0.64–0.88]	0.0001
	Last therapy with anti-TNFα	0.59 [0.38–0.94]	0.027
	Last therapy with anti-IL-17	0.63 [0.41–0.98]	0.042
	Baseline PASI	1.05 [1.03–1.08]	0.0001

(*Continued*)

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Table 2 (Continued).

Time Point	Variable	OR (95% CI)	p-value
12 months	Previous exposure to biologics	0.34 [0.19–0.61]	0.0001
	Number of prior biologic treatments	0.74 [0.61–0.89]	0.001
	Last therapy with anti-IL-17	0.44 [0.27–0.73]	0.001
	Baseline PASI	1.07 [1.03–1.11]	0.0001
24 months	BMI	0.96 [0.92–0.99]	0.039
	Obesity (BMI ≥ 30 kg/m^2)	0.58 [0.35–0.97]	0.038
	Previous exposure to biologics	0.53 [0.30–0.92]	0.023
	Last therapy with anti-TNFα	0.49 [0.27–0.87]	0.014
	Baseline PASI	1.06 [1.02–1.11]	0.002
36 months	Obesity (BMI ≥ 30 kg/m^2)	0.50 [0.29–0.90]	0.019
	Previous exposure to biologics	0.51 [0.28–0.95]	0.035
	Last therapy with anti-IL-17	0.45 [0.25–0.82]	0.009
48 months	BMI	0.94 [0.89–0.99]	0.026
	Previous exposure to biologics	0.46 [0.21–1.00]	0.050
60 months	Previous exposure to biologics	0.28 [0.10–0.78]	0.014

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; BMI, Body Mass Index; PASI, Psoriasis Area Severity Index; IL, Interleukin.

Table 3 Univariate Logistic Regression Analysis of Variables Significantly Associated with PASI 90 Response

Time points	Variables	OR (95% CI)	p-value
3 months	Cardiovascular disease	0.63 [0.42–0.95]	0.029
	Number of previous biologics	0.88 [0.77–1.00]	0.055
6 months	Obesity (BMI ≥ 30 kg/m^2)	0.60 [0.44–0.81]	0.001
	Previous exposure to biologic drugs	0.65 [0.49–0.87]	0.003
	Number of previous biologics	0.88 [0.78–0.99]	0.039
12 months	Obesity (BMI ≥ 30 kg/m^2)	0.62 [0.44–0.87]	0.006
	Number of previous biologics	0.85 [0.74–0.97]	0.019
	Previous exposure to biologic drugs	0.55 [0.39–0.77]	0.001
	Last anti-IL-17 therapy	0.60 [0.42–0.87]	0.007
24 months	Obesity (BMI ≥ 30 kg/m^2)	0.60 [0.41–0.89]	0.011
	Previous exposure to biologic drugs	0.63 [0.43–0.94]	0.022
36 months	Obesity (BMI ≥ 30 kg/m^2)	0.57 [0.36–0.89]	0.014
	Previous exposure to biologic drugs	0.57 [0.37–0.89]	0.012
	Number of previous biologics	0.84 [0.70–0.99]	0.043
48 months	Previous exposure to biologic drugs	0.50 [0.28–0.88]	0.016
	Number of previous biologics	0.80 [0.65–0.99]	0.043
60 months	Previous exposure to biologic drugs	0.33 [0.16–0.69]	0.003
	Number of previous biologics	0.78 [0.61–1.00]	0.05

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; BMI, Body Mass Index; PASI, Psoriasis Area Severity Index; IL, Interleukin.

CVD emerged as an independent negative predictor for PASI 90 at 3 months (OR 0.64, 95% CI: 0.42–0.97, p=0.035), while prior treatment with anti-IL-17 agents was associated with a reduced likelihood of achieving PASI 75 at 12 and 36 months (OR 0.43–0.45, 95% CI: 0.25–0.62, p<0.01).

Table 4 Univariate Logistic Regression Analysis of Variables Significantly Associated with PASI 100 Response

Time Point	Variable	OR (95% CI)	p-value
3 months	Baseline PASI	0.95 [0.94–0.97]	0.0001
6 months	Obesity (BMI ≥30 kg/m^2)	0.73 [0.55–0.97]	0.032
	Previous exposure to biologic drugs	0.66 [0.51–0.85]	0.002
	Number of previous biologics	0.87 [0.78–0.98]	0.026
	Baseline PASI	0.97 [0.96–0.99]	0.0001
12 month	Obesity (BMI ≥30 kg/m^2)	0.69 [0.51–0.95]	0.02
	Previous exposure to biologic drugs	0.59 [0.44–0.80]	0.001
	Number of previous biologics	0.83 [0.73–0.94]	0.004
	Last anti-IL-17 therapy	0.64 [0.46–0.90]	0.010
24 months	Number of previous biologics	0.87 [0.76–1.00]	0.046
	Obesity (BMI ≥ 30kg/m^2)	0.55 [0.39–0.78]	0.001
	BMI	0.96 [0.93–0.99]	0.005
36 months	Obesity (BMI ≥ 30kg/m^2)	0.49 [0.33–0.73]	0.0001
	Comorbidities	0.66 [0.45–0.97]	0.035
	Number of previous biologics	0.78 [0.67–0.91]	0.002
	Previous exposure to biologic drugs	0.55 [0.38–0.81]	0.003
	Last anti-IL-17 therapy	0.59 [0.39–0.91]	0.016
48 months	Obesity (BMI ≥ 30kg/m^2)	0.56 [0.34–0.92]	0.021
	Previous exposure to biologic drugs	0.58 [0.36–0.92]	0.021
	Number of previous biologics	0.79 [0.65–0.95]	0.013
60 months	BMI	0.92 [0.88–0.97]	0.001
	Obesity (BMI ≥ 30kg/m^2)	0.45 [0.25–0.81]	0.007
	Previous exposure to biologic drugs	0.41 [0.22–0.73]	0.003
	Number of previous biologics	0.76 [0.61–0.95]	0.016
	Last anti-IL-12/23 therapy	0.48 [0.26–0.88]	0.018

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; BMI, Body Mass Index; PASI, Psoriasis Area Severity Index; IL, Interleukin.

Table 5 Multivariate Logistic Regression (Stepwise Analysis) of Predictors for PASI 75, PASI 90, and PASI 100 Response After Guselkumab Treatment

Time Point	PASI Response	Variable	OR (95% CI)	p-value
3 months	PASI 75	Number of previous biologics	0.76 [0.66–0.89]	0.0001
	PASI 90	Number of comorbidities	0.53 [0.34–0.84]	0.007
		Cardiovascular disease	0.64 [0.42–0.97]	0.035
	PASI 100	Number of comorbidities	0.53 [0.34–0.84]	0.007
		Baseline PASI	0.95 [0.93–0.97]	0.0001
6 months	PASI 75	Previous exposure to biologic drugs	0.38 [0.24–0.62]	0.0001
		Baseline PASI	1.04 [1.01–1.07]	0.004
		Obesity (BMI ≥30 kg/m^2)	0.49 [0.33–0.74]	0.001
	PASI 90	Previous exposure to biologic drugs	0.64 [0.48–0.86]	0.003
		Obesity (BMI ≥30 kg/m^2)	0.61 [0.45–0.82]	0.001
	PASI 100	Previous exposure to biologic drugs	0.57 [0.44–0.75]	0.0001
		Obesity (BMI ≥30 kg/m^2)	0.74 [0.55–0.99]	0.043
		Baseline PASI	0.96 [0.95–0.98]	0.0001

(*Continued*)

Table 5 (Continued).

Time Point	PASI Response	Variable	OR (95% CI)	p-value
12 months	PASI 75	Baseline PASI	1.07 [1.03–1.10]	0.001
		Last anti-IL-17 therapy	0.43 [0.26–0.73]	0.002
	PASI 90	Obesity (BMI ≥30 kg/m^2)	0.61 [0.43–0.87]	0.006
		Previous exposure to biologic drugs	0.56 [0.39–0.80]	0.001
	PASI 100	Previous exposure to biologic drugs	0.51 [0.37–0.69]	0.0001
		Obesity (BMI ≥30 kg/m^2)	0.70 [0.51–0.96]	0.027
		Baseline PASI	0.97 [0.96–0.99]	0.001
24 months	PASI 75	Baseline PASI	1.06 [1.02–1.10]	0.003
	PASI 90	Obesity (BMI ≥30 kg/m^2)	0.60 [0.40–0.89]	0.012
		Previous exposure to biologic drugs	0.64 [0.43–0.96]	0.03
	PASI 100	Obesity (BMI ≥30 kg/m^2)	0.55 [0.39–0.78]	0.001
36 months	PASI 75	Last anti-IL-17 therapy	0.45 [0.25–0.82]	0.01
		Obesity (BMI ≥30 kg/m^2)	0.52 [0.29–0.93]	0.028
	PASI 90	Obesity (BMI ≥30 kg/m^2)	0.57 [0.36–0.89]	0.014
		Previous exposure to biologic drugs	0.59 [0.38–0.92]	0.019
	PASI 100	Obesity (BMI ≥30 kg/m^2)	0.46 [0.31–0.70]	0.0001
		Previous exposure to biologic drugs	0.57 [0.38–0.85]	0.006
48 months	PASI 75	BMI	0.94 [0.88–0.99]	0.024
		Previous exposure to biologic drugs	0.45 [0.20–0.99]	0.046
	PASI 90	Previous exposure to biologic drugs	0.50 [0.28–0.88]	0.016
48 months	PASI 100	Obesity (BMI ≥30 kg/m^2)	0.57 [0.35–0.94]	0.026
		Number of previous biologics	0.79 [0.66–0.96]	0.017
60 months	PASI 75	Previous exposure to biologic drugs	0.29 [0.10–0.78]	0.015
	PASI 90	Previous exposure to biologic drugs	0.33 [0.16–0.69]	0.003
	PASI 100	BMI	0.92 [0.87–0.97]	0.001
		Previous exposure to biologic drugs	0.39 [0.20–0.72]	0.003

Abbreviations: CI, Confidence Interval; OR, Odds Ratio; BMI, Body Mass Index; PASI, Psoriasis Area Severity Index; IL, Interleukin.

Drug Survival

Over the 5-year follow-up, 102 patients (10%) discontinued guselkumab treatment due to primary inefficacy (N=14; 1.4%), loss of efficacy (N=43; 4.2%), or AEs (N=13; 1.3%). AEs included 1 case of Hodgkin's lymphoma, 3 eczematous reactions, 1 case of oral lichen planus, 2 cases of lung cancer, 2 cases of uncontrollable PsA, 2 injection site reactions, and 2 deaths. Lung cancer and death were unrelated to guselkumab treatment. Additionally, 24 patients (2.3%) were lost during follow-up, 5 patients (0.5%) suspended treatment for personal reasons, and 3 patients discontinued treatment due to pregnancy-related reasons.

The probability of remaining on treatment at 12, 24, 36, 48, and 60 months were 95.85%, 91.73%, 89.74%, 87.08%, and 85.76% respectively (Figure 3A). Female patients (compared to males) had a significantly lower probability of remaining on guselkumab treatment (Log-rank text, p=0.025) (Figure 3B). No significant difference in retention rate was observed between patients with obesity (vs patients with BMI <30 kg/m^2) (Figure 3C) or those that were bioexperienced (vs naïve) (Figure 3D). However, patients who switched from anti-IL-17 therapy showed a significantly lower probability of remaining on treatment compared to those who did not switch (Log rank test, p=0.0276; Figure 3E. Lastly, a significant difference in treatment survival was observed between patients who had received fewer than three biologic therapies and those treated with at least three (Log rank test, p=0.0001; Figure 3F). The long-term efficacy and retention of guselkumab was also observed in patients with pre-existing conditions and psoriasis in difficult-to-treat areas. In a representative case, a 33-year-old male with chronic, treatment-resistant psoriasis affecting difficult areas and comorbid anemia achieved sustained remission for over 6 years with guselkumab after failure with multiple therapies. This

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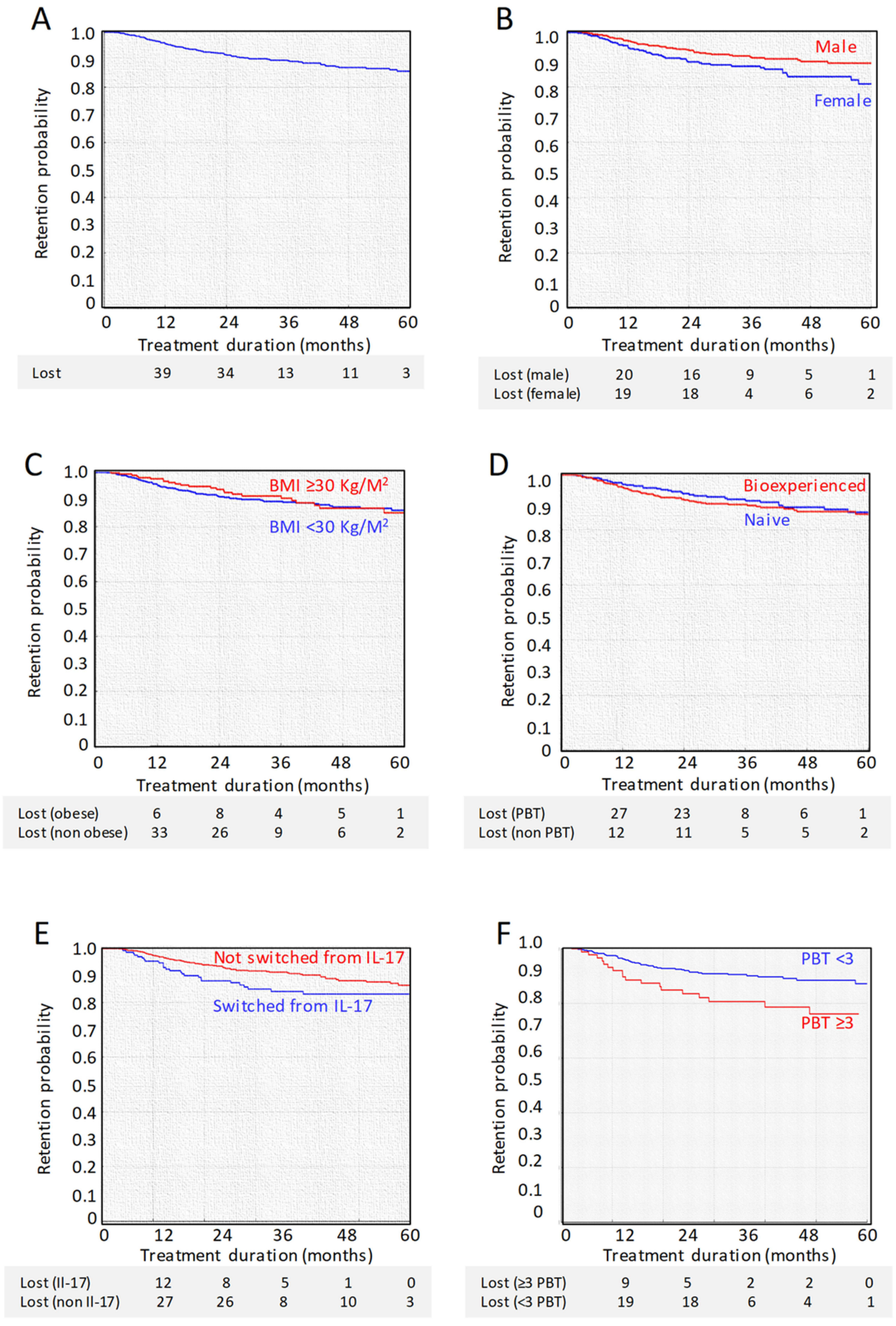

Figure 3 Retention rate in psoriatic patients and different subgroups treated with guselkumab. Kaplan–Meier curves show cumulative retention probability of ustekinumab in psoriatic patients. (**A**) Shaded areas represent upper and lower 95% confidence intervals. (**B**–**F**) Comparison between retention probability curves between subgroups was calculated using the Log rank test: (**B**) male vs female: p=0.025; (**C**) obese vs non-obese: p=0.66; (**D**) bioexperienced vs naive: p=0.46; (**E**) switched from anti–IL-17 vs not switched from anti–IL-17: p=0.0276; (**F**) <3 PBT vs ≥3 PBT: p=0.0001. PBT = previous biological treatment. The number of patients lost to follow up in sub-groups is shown in grey below each Kaplan–Meier curve.

Table 6 Univariate and Multivariate Logistic Regression Analysis of Variables Associated with Drug Discontinuation

Analysis Type	Variable	OR (95% CI)	p-value
Univariate analysis	Number of previous biologics	1.27 [1.05–1.54]	0.013
	Therapy with at least 3 previous biologics	2.46 [1.32–4.59]	0.005
	Last anti-IL-17 therapy	2.09 [1.26–3.48]	0.004
	Disease duration	1.02 [1.01–1.03]	0.006
*Multivariate analysis	Disease duration	1.02 [1.00–1.03]	0.013
	Last anti-IL-17 therapy	2.04 [1.22–3.40]	0.007

Notes: *Stepwise (multivariate) logistic regression after removing number of previous biologics therapy (p=0.74) and at least 3 previous biologics (p=0.14).
Abbreviations: CI, Confidence Interval; OR, Odds Ratio; BMI, Body Mass Index; IL, Interleukin; PASI, Psoriasis Area Severity Index.

highlights the long-term safety and tolerability of guselkumab even in complex cases with pre-existing conditions (Supplementary Figure S1).

Both univariate and multivariate logistic regression analyses were next performed to identify predictors associated with drug discontinuation. In the univariate model, number of previous biologics, having at least three prior biologics, prior treatment with anti-IL 17 and longer disease duration were all significantly increased the likelihood of treatment cessation (Table 6). In various stepwise multivariate logistic regression models, the best model associated with a higher probability of drug discontinuation was characterized by a longer disease duration and having received anti-IL-17 biologics as the last therapy prior to starting guselkumab (Table 6).

Discussion

This study presents the largest real-world cohort (N=1,084) of psoriasis patients treated with guselkumab over a 5-year period. Guselkumab demonstrated rapid and sustained improvements in PASI scores. Prior biologic exposure was negatively associated with achieving PASI 75, 90, and 100, while obesity reduced the likelihood of achieving complete or near-complete skin clearance. Despite these factors, DS remained high throughout the 5 years. The broad effectiveness of guselkumab across patients with diverse comorbidities highlights its versatility in managing complex psoriasis cases, although prior use of ≥3 biologics, longer disease duration, and female sex increased the risk of discontinuation.

The clinical efficacy of guselkumab in improving psoriasis is well-established in clinical trials[12,14,15] and supported by various real-world studies.[22,23,25,27–30] Our findings reinforce this, showing a rapid reduction in mean PASI scores from 14.3±8.8 at baseline to 1.3±2.4 at 6 months that was sustained over time, with mean PASI scores remaining low (1.3 ±3.5) at 5 years. Other real-world studies have reported similar PASI reductions for follow-up periods of up to 3 years.[22,23,28] Recently, a 4-year follow-up study documented a significant PASI reduction from 10.9±5.8 at baseline to 0.5 ±0.8.[24] Although baseline PASI in that study was lower than in ours, the decrease aligns with our results, confirming the sustained efficacy of guselkumab.

At 5 years, PASI 75, 90, and 100 response rates were 89.3%, 80.5%, and 70.6%, respectively, in our cohort, comparable with prior real-world studies reporting shorter follow-up periods.[20,21,23,31–33] Megna et al reported PASI 75 and 90 rates of 87.5% and 81.3% at 3 years.[22] Our findings are also in line with clinical trials: VOYAGE 1 and 2 reported 5-year PASI 90 rates of 84.1% and 82.0%, alongside PASI 100 rates of 52.7% and 53.0%.[2]

Obesity and prior biologic exposure were linked to reduced guselkumab efficacy.[23] Gargiulo et al observed a reduced response in obese patients after 2 years,[30] and the PERSIST study found lower response rates in patients with previous biological treeatment.[34] Similarly, the BIOREP study reported higher PASI 90 and 100 rates in bio-naïve and normal-weight individuals compared to bioexperienced and obese patients, further supporting our results.[28] It is important to note that although obese individuals tend to show a reduced response to treatment, particularly in achieving PASI 90 and 100, our survival analysis indicates that their discontinuation rate is not higher than that of patients with normal BMI.

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CVD also emerged as a negative predictor for PASI 90 at 3 months. These findings suggest that the presence of CVD may act as a negative predictor of treatment response in the early stage, possibly because these patients take multiple medications. However, after 3 months, this variable no longer influenced the response. Gargiulo et al observed that patients without cardiometabolic comorbidities had higher PASI 75 rates at week 16.[30] However, no significant differences were observed for PASI 90 and 100, and by year 2. In contrast, Mastorino et al found CVD to be advantageous in achieving PASI 100 at 3 years.[24] This discrepancy may result from differences in patient populations or follow-up duration, highlighting the need for further investigation into the impact of CVD impact on guselkumab response.

In addition to strong long-term efficacy, our analysis also reports a high rate of DS, with approximately 86% of patients remaining on treatment after 5 years. These results align with prior short-term studies reporting high guselkumab survival rates.[23,28,35–37] Gargiulo et al documented a 4-year DS of 82.4%, similar to our 87.08% at 4 years, though slightly lower.[30] In contrast, Mastorino et al[24] reported a 68.5% DS at 4 years, likely due to differences in patient populations; their cohort was younger and had a lower baseline PASI compared to ours. Our findings also align with the VOYAGE trials, which reported discontinuation rates below 20% over 5 years.[2]

Discontinuation rates appeared to be influenced by gender and previous biologic treatments, with women and patients with ≥3 prior biologics exhibiting higher discontinuation rates. In a shorter follow-up study, Torres et al found that female sex and prior biologic exposure significantly increased the risk of discontinuation.[38] However, specific data on this is limited, and those available indicate that DS was not significantly affected by previous biologic treatments or by sex.[23,28] The favourable retention rates in our study were observed even among patients with various comorbidities, including viral infections, cancer, and CVD, consistent with the favourable safety profile of guselkumab.[39–41]

AEs were observed in a small number of patients (N=13; 1.3%). Cases of oral lichen planus and eczematous reactions resolved following discontinuation of therapy. All oncological cases were reviewed by respective specialists, who, although they did not consider the events to be related to the therapy, did not authorize continuation of guselkumab treatment. Patients with uncontrolled PsA were switched to a different pharmacological class, as indicated by the treating specialist. Despite low rates of AEs, strategies to reduce risk with guselkumab include baseline cancer screening, smoking cessation, regular skin monitoring, managing PsA via multidisciplinary care, and educating patients on injection techniques. A proactive, personalized approach supports safer long-term use in patients with complex profiles or comorbid conditions.

We also observed that variables such as undergoing three or more biologic therapies, having an anti-IL-17 agent as the most recent treatment, and a longer disease duration were identified as negative prognostic factors for treatment retention. Moreover, multivariate stepwise logistic regression revealed that the strongest negative predictive model for retention was the combination of anti-IL-17 as the last therapy and a longer disease history. This supports previous findings regarding PASI response but not drug survival.[23] One hypothesis is that prior IL-17 inhibition fails to correct the Treg/TRM imbalance, creating an "immunologic scar" that leads to persistent inflammation.[42] Although IL-23 blockers typically reset the Treg/TRM balance, this mechanism may be impaired in skin previously treated with IL-17 inhibitors, potentially explaining the poorer drug survival.[43]

Limitations

Despite the strengths of this study including the large sample size (N=1,084) and a 5-year follow-up, this retrospective analysis has limitations that need to be considered. As a real-world retrospective design, it is subject to selection bias and documentation inaccuracies compared to clinical trials. Although we adjusted for confounders, residual confounding cannot be excluded. The single-center design limits generalizability to other demographics or healthcare settings. The observed associations between obesity, prior biologic exposure, and reduced PASI response, and higher baseline PASI affecting complete remission require further investigation. Conflicting findings regarding CVD also necessitate additional research with standardized definitions and longer follow-up. Finally, the identification of female sex and ≥3 prior biologics as risk factors for discontinuation highlights the need for tailored management strategies in these subgroups. Future multicenter studies are needed to confirm these findings.

Conclusion

This real-world study shows that guselkumab provides rapid and sustained PASI improvements over 5 years, with high drug survival across diverse patient populations. While obesity and prior biologic exposure were associated with reduced response, the safety profile remained favourable. Our findings, consistent with previous clinical trials and real-world evidence, support guselkumab as an effective long-term psoriasis treatment. The impact of cardiovascular comorbidities on treatment outcomes requires further investigation.

Data Sharing Statement

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

Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for patient consent to review medical records was waived by the Ethics Committee (Comitato Etico Territoriale Lazio Area 2) due to the retrospective observational nature of the study and the use of anonymized data. Patient confidentiality was rigorously maintained throughout the study. Data were de-identified prior to analysis to ensure privacy and prevent the identification of individual patients. All procedures complied with applicable data protection regulations and institutional policies governing the use of medical records for research purposes.

Consent to Participate

Informed consent was obtained from all participants to participate in the study. Written informed consent was provided by the patient to have their case details and any accompanying images published (Supplementary Figure S1).

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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