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Research Article

A Retrospective Study of Time to Relapse following Guselkumab Withdrawal in Patients with Psoriasis

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Background. Psoriasis is a chronic immune-mediated skin disease requiring long-term management. However, for various reasons such as financial issues, treatment cessation is common among psoriasis patients who have achieved clinical remission. Currently, only few studies have assessed the time to relapse after guselkumab withdrawal in the real-world setting. *Objective*. The study aimed at assessing the time to relapse after remission following guselkumab discontinuation in patients with moderate-to-severe plaque psoriasis in the real-world setting. *Materials and Methods*. Eligible adult moderate-to-severe plaque psoriasis patients received at least 2 doses of administration of guselkumab treatment between March 2020 and March 2022 were enrolled. The study included patients who achieved PASI < 3 at week 12. Relapse was defined as restart of systemic therapy upon guselkumab withdrawal. Time to relapse was defined as the time interval between the last guselkumab administration and restart of systemic therapy. *Results*. Totally, 76 patients were enrolled. Relapse was found in 60.5% of patients, with a median PASI score at relapse of 4.6 (IQR: 1.6, 8.4) and median time to relapse was 201 (IQR: 159, 314) days. The proportion of patients with comorbidities significantly differed between the relapse and nonrelapse groups at baseline ($P < 0.05$). Compared with patients with PASI < 3, those with PASI ≥ 3 at relapse had longer time to relapse ($P < 0.001$). *Conclusions*. Guselkumab provides durable maintenance of response after discontinuation of therapy in the real-world setting. Higher PASI score at relapse was associated with longer time to relapse. This trial is registered with Chinese Clinical Trial Registry: ChiCTR2000041398.

1. Introduction

Psoriasis is an immune-mediated chronic inflammatory skin disease requiring long-term management with increasing trends in incidence and prevalence worldwide [1, 2]. In the past few years, therapeutic options for psoriasis have multiplied with many new biologics and nonbiologic systemic treatments for moderate to severe psoriasis. It is important to follow algorithms for the choice of therapy since optimal treatment selection and management are meant to reduce morbidity caused by psoriasis and to improve the health-related quality of life of affected individuals [3, 4]. Multiple reports have demonstrated the efficacy and safety of IL-23 inhibitors, especially guselkumab, in the treatment of moderate-to-severe psoriasis [5, 6]. The superior efficacy of guselkumab was established over adalimumab in two major phase 3 studies, VOYAGE 1 and VOYAGE 2 [7, 8]. In addition, guselkumab showed improved long-term efficacy based on PASI 90 at week 48 compared with secukinumab, an IL-17A inhibitor, in a phase 3 and randomized controlled trial [9]. However, psoriatic lesions relapse eventually or within a time period after drug discontinuation, so more clinical studies evaluating long-term control of biological agents following withdrawal are needed.

The patient's desire for complete skin clearance and stable, long-term control is generally more important than an early response. Given the expectation of patients for long-time maintenance following discontinuation, studies evaluating long-term control upon guselkumab withdrawal are urgently required. In a recent longitudinal, retrospective analysis in the real-world setting with moderate-severe chronic plaque psoriasis, guselkumab showed to maintain its efficacy for up to 12 months [10]. However, studies assessing the maintenance time after guselkumab

withdrawal are still scarce. Here, we performed a retrospective study, investigating the time at relapse following guselkumab withdrawal in patients with psoriasis in the real-world setting.

2. Materials and Methods

We performed a retrospective analysis of patients with moderate-to-severe plaque psoriasis administered guselkumab in Dermatology Hospital of Southern Medical University, Guangzhou, China, from April 2020 to March 2022. Inclusion criteria were as follows: (1) age ≥ 18 years; (2) standard treatment with guselkumab (100 mg administered by subcutaneous injection at weeks 0 and 4, then every 8 weeks) as the only treatment; and (3) PASI < 3 in 12 weeks. Sex, age, body mass index (BMI), psoriasis duration, comorbidities, and previous treatments for every patient were collected at baseline. As for disease index, psoriasis area and severity index (PASI) and physicians' global assessment (PGA) were assessed by dermatologists, and dermatology life quality index (DLQI) was determined by the patients themselves at baseline. Furthermore, PASI was recorded at 12 weeks and at relapse. Relapse was defined as restart of systemic treatments more than 3 months after the last injection of guselkumab. Systemic treatments included but were not limited to biologics, systemic acitretin, and immune suppressive drugs. Time to relapse was defined as the time (days) from the last guselkumab administration to relapse. In cases determined to have relapsed by the date of data cutoff (31/3/2022), time to withdrawal was recorded and defined as the time (days) from the last administration to the date of data cutoff. This retrospective study aimed to primarily assess the time to relapse after remission following guselkumab withdrawal in patients with moderate-to-severe plaque psoriasis and to identify potential contributing factors.

Data normalization was assessed by the Shapiro–Wilk method. Measurement data with normal distribution were presented as mean ± standard deviation (SD) and compared by the independent sample t test and ANOVA for group pairs and multiple groups, respectively. Those with skewed distribution were presented as median and interquartile range (IQR) and compared between groups by the Mann–Whitney U test. Count data were presented as frequency (N) and percentage (%) and compared between groups by the chi-square test or Fisher exact test. Correlation analysis was performed by the Spearman method. Two-sided $P < 0.05$ was considered statistically significant. R (version 4.2.0) was used for data analysis.

3. Results

In this retrospective study, totally 76 patients with at least two doses of guselkumab were analyzed. Out of these, 46 patients (60.5%) relapsed after remission of psoriasis lesions; meanwhile, 30 (39.5%) cases were assigned to the nonrelapse group, who had not restarted to receive systemic therapy. The baseline patient characteristics of the relapse and nonrelapse groups are presented in Table 1. The proportion of patients with comorbidities was significantly higher in the relapse group compared with the nonrelapse group (71.7% versus 40.0%, $P < 0.05$). The median PASI score at relapse was 4.6 (IQR: 1.6, 8.4), with an average improvement of 60.7% versus baseline. Among individuals who experienced disease relapse, 28 (60.9%) and 14 (30.4%) had PASI scores of 50 and PASI 75, respectively, at the time of relapse. The median follow up time in all patients ($N = 76$) was 204 days. In the relapse group ($n = 46$), the median time to relapse was 201 days, including the shortest and longest times of 78 days and 475 days, respectively. In the nonrelapse group ($n = 30$), the median time to withdrawal was 235 days, including the shortest and longest times of 126 days and 581 days, respectively.

Spearman's correlation analysis was performed to assess the correlation of PASI score at relapse with the time to relapse. In the relapse group, PASI score at relapse was positively correlated with the time to relapse after withdrawal ($r = 0.392$, $P < 0.01$, Figure 1). Besides, to further examine the correlation of PASI at relapse with the time to relapse, the patients were divided into two subgroups based on PASI score at relapse and whether they had PASI 50 and PASI 75 versus baseline (Table 2). These findings demonstrated compared with patients with PASI < 3, those with PASI ≥ 3 at relapse had longer time to relapse ($P < 0.05$). Moreover, compared with patients still maintaining PASI 75 at disease relapse, those with PASI 75 had longer time to relapse ($P < 0.05$).

4. Discussion

Current data assessing the time to relapse after guselkumab withdrawal in the real-world setting are limited. In a retrospective, multicenter study of Spanish patients who completed the ECLIPSE study (NCT03090100), median time from the last dose of biologics and restart of a new systemic treatment was 282 (IQR: 180, 333) days for guselkumab, versus 192.5 (IQR: 107, 308) days for secukinumab, and median PASI score at relapse in patients administered guselkumab was 9.0 [11]. This must be interpreted with caution since all patients in the Spanish study received 48 weeks of guselkumab treatment, while in this study most patients only had a short time (mostly 2 or 4 doses) of guselkumab treatment. A longer follow-up time is required to examine whether long-term guselkumab treatment would show longer time to relapse. Another research conducted in the same hospital as our study revealed a median time to relapse after secukinumab discontinuation of 6 weeks (range, 3–22 weeks) in 11 patients, although median PASI score at relapse was unknown [12]. Disease relapse was defined distinctly in the latter study, as topical or systemic treatment after drug withdrawal.

Indirectly compared with conventional systemic treatments with methotrexate and/or cyclosporine, tumor necrosis factor (TNF) antagonists, interleukin-17 (IL-17) antagonists, IL-12/23 antagonists, and small molecule inhibitors such as tofacitinib and apremilast, IL-23 antagonists have longer time to relapse despite distinct criteria defining relapse [13]. In an 8-year multicenter retrospective study, median time to relapse (PASI 50) after ustekinumab

Table 1: Patient characteristics.

Characteristic	Total ($N = 76$)	Relapse group ($n = 46$)	Nonrelapse group ($n = 30$)	P value
Male, n (%)	53 (69.7)	30 (65.2)	23 (76.7)	>0.05
Age (years)	38.0 (28.8, 48.2)	42.0 (31.2, 48.8)	33.0 (26.0, 46.8)	>0.05
BMI (kg/m^2)	24.4 ± 3.5	24.8 ± 3.4	23.8 ± 3.8	>0.05
Disease duration (years)	9.0 (4.8, 13.0)	9.5 (5.0, 13.0)	8.0 (4.2, 10.0)	>0.05
Age at disease onset (years)	28 (21.0, 39.2)	30 (24.2, 42.8)	23.5 (18.0, 36.0)	>0.05
Comorbidities, n (%)				
Psoriatic arthritis	6 (7.9)	5 (10.9)	1 (3.3)	>0.05
Obesity	11 (14.5)	8 (17.4)	3 (10)	>0.05
Hypertension	8 (10.5)	5 (10.9)	3 (10.0)	>0.05
Dyslipidemia	19 (25.0)	13 (28.3)	6 (20.0)	>0.05
Diabetes	6 (7.9)	5 (10.9)	1 (3.3)	>0.05
Hepatitis B	7 (9.2)	6 (13.0)	1 (3.3)	>0.05
Latent tuberculosis	9 (11.8)	3 (6.5)	6 (20.0)	>0.05
Depression	3 (3.9)	1 (2.2)	2 (6.7)	>0.05
Comorbidities, n (%)				0.006
Yes	45 (59.2)	33 (71.7)	12 (40.0)	
No	31 (40.8)	13 (28.3)	18 (60.0)	
Prior biologic therapy, n (%)	9 (11.8)	8 (17.4)	1 (3.3)	>0.05
Duration of guselkumab treatment, n (%)				>0.05
4 weeks (2 doses of injections)	39 (51.3)	22 (47.8)	17 (56.7)	
12 weeks (3 doses of injections)	5 (6.6)	4 (8.7)	1 (3.3)	
20 weeks (4 doses of injections)	31 (40.8)	19 (41.3)	12 (40.0)	
28 weeks (5 doses of injections)	0	0	0	
36 weeks (6 doses of injections)	1 (1.3)	1 (2.2)	0	
PASI score at baseline	11.7 (7.5, 20.5)	11.9 (7.9, 18.5)	11.6 (7.2, 21.0)	>0.05
PGA score at baseline	3 (3, 4)	3 (3, 4)	3 (3, 4)	>0.05
DLQI score at baseline	12.0 ± 4.8	11.7 ± 4.8	12.4 ± 5.0	>0.05
PASI score at relapse	NA	4.6 (1.6, 8.4)	NA	—
Duration of relapse (days)	203.5 (167, 338)	201 (159, 314)	235 (173, 377)	>0.05

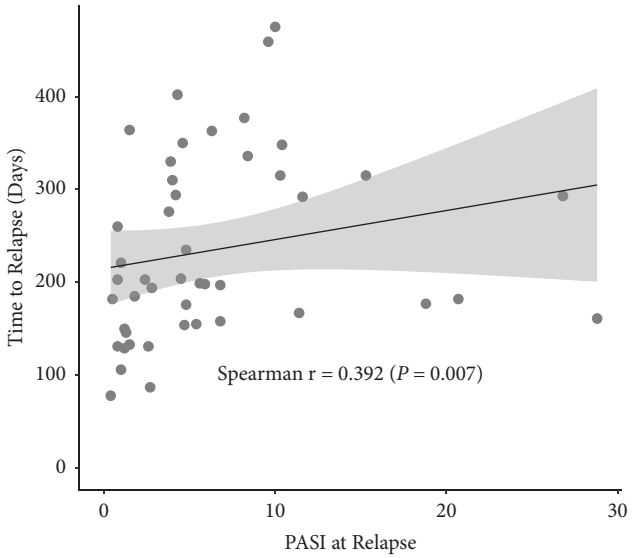

Figure 1: Spearman's correlation analysis between PASI at relapse and the time to relapse.

treatment was 6.7 ± 4.1 months and biologics-naivety, absence of arthritis or chronic kidney disease, shorter psoriasis duration, absence of family history of psoriasis, and higher and more rapid response to treatment were potential predictors of longer relapse time [14].

Table 2: Differences in time to relapse between different subgroups.

	Patients, n (%)	Time to relapse (days)	P value
PASI score			<0.001
<3.0	17 (37.0)	150 (78, 364)	
≥3.0	29 (63.0)	292 (154, 475)	
PASI 75			0.004
Maintained	14 (30.4)	165.5 (78, 364)	
Lost	32 (69.6)	255.5 (87, 475)	

Disease recurrence after guselkumab discontinuation was associated with elevated amounts of serum IL-23 signaling cytokines, including IL-17A, IL-17F, and IL-22 [15]. The ability of guselkumab to reduce disease-and mechanism-associated biomarkers in psoriasis and IL-23 blockade in psoriasis had a greater impact on effector cytokines and transcriptional profiles associated with the IL-23/Th17 axis compared with TNF-α blockade [16]. Besides, epidermal resident memory T (TRM) cells producing IL-17A upon skin stimulation are considered key contributors in psoriatic lesion recurrence, especially at the originally affected sites [17–19]. The rate of CD8+ TRM cells decreased significantly after administration of guselkumab, but not secukinumab, as described in a subanalysis of lesion biopsy specimens from patients administered guselkumab

and secukinumab, respectively, in the ECLIPSE study [9, 20], which may account for the superior long-term control of skin inflammation with guselkumab.

According a recent report of the GUIDE study (NCT03818035), participants with PASI < 3 at week 68 will be withdrawn from guselkumab treatment and further mechanistic biomarker subanalyses will be performed, aiming to explore the mechanism by which guselkumab modifies the disease course by altering molecular and cellular drivers causing relapse after drug withdrawal, and the results are expected soon [21].

Furthermore, it brings another issue which treatment cessation is common among psoriasis patients who have achieved clinical remission, especially in countries without public health care and with low socio-economic levels. Among the reasons for the suspension, there are financial issues. Dose tapering is successfully described for adalimumab in a retrospective 7-year study [22]. In consideration of the durable maintenance of the response of guselkumab, after discontinuation of therapy, it should be important to evaluate dose tapering as therapeutic option to reduce the risk of drug-exposure and to increase cost-effectiveness in the further studies.

5. Conclusions

Guselkumab provides durable maintenance of response after discontinuation of therapy in psoriatic patients in the real-world setting. Higher PASI score at relapse was associated with longer time to relapse.

Data Availability

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

Disclosure

This trial is registered with Chinese Clinical Trial Registry: ChiCTR2000041398. Jia-Yi Zhuang and Fang-Fei Zhang are co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yong-Feng Chen gave substantial contributions to the conception or design of the work and final approval of the version to be published. Jia-Yi Zhuang and Fang-Fei Zhang drafted the work and analysed the data for the work. Yuan-Qiu Zhong collected the data. Jia-Yi Zhuang and Fang-Fei Zhang contributed equally to this work.

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