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Original Research Article

Efficacy and safety of guselkumab for the treatment of patients with moderate-to-severe plaque psoriasis: A meta-analysis of randomized clinical trials

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Abstract

Purpose: *To conduct a systematic analysis on data from randomized controlled trials (RCTs) on different doses of guselkumab, and provide high-quality evidence for its use in the treatment of patients with moderate-to-severe plaque psoriasis (PsO).*
Methods: *Related studies were searched using online search engines including MEDLINE, PubMed, and central registry of Cochrane controlled trials from January 2001 to October 2017. Only randomized, placebo-controlled, double-blind clinical trials involving guselkumab- and placebo-treated PsO subjects were included.*
Results: *Five eligible double-blind, randomized, and placebo-controlled trials involving patients with moderate-to-severe PsO subjects treated with guselkumab were included. Compared with the placebo groups, the proportion of patients with improvements in Psoriasis Area and Severity Index (PASI) 75 (RR= 12.14; 95% CI= 9.11-16.16; p < 0.001); PASI 90 (RR= 23.26; 95% CI =14.57-37.13; p < 0.001), and PASI 100 (RR = 37.66; 95% CI = 15.81-89.69; p < 0.001) were significantly higher than those in guselkumab-treated groups. Furthermore, the guselkumab-treated groups showed significant decreases in Physician's Global Assessment (PGA) score (RR = 10.46; 95% CI = 7.96-13.83; p < 0.001) and the Dermatology Life Quality Index (DLQI) score (SMD = -1.3; 95% CL = -1.4 to -1.19; p < 0.001), when compared with the placebo groups. However, there were no significant differences in adverse events (AEs) (RR = 1.01; 95% CL = 0.93-1.11; p > 0.05); severe adverse events (SAEs) (RR = 1.32; 95% CI =0.69-2.54; p > 0.05) and study discontinuations (RR = 0.79; 95% CI = 0.42-1.48; p > 0.05) between the two groups.*
Conclusion: *This meta-analysis summarizes available evidence for the use of guselkumab in psoriasis. The results suggest that guselkumab is superior to placebo in moderate-to-severe psoriasis, and is well-tolerated, effective, and safe in improving the severity of disease and quality of life.*

Keywords: *Guselkumab, Effectiveness, Safety, Plaque psoriasis, Meta-analysis, Quality of life*

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INTRODUCTION

Psoriasis is an autoimmune skin disease which occurs in about 2% of humans [1]. It is accompanied by several comorbidities such as coronary disease, metabolic syndrome, malignancies, and emotional problems [2-4]. Plaque psoriasis (PsO), the most common subtypes of psoriasis, occurs in 90% of psoriasis cases, mostly in children and adolescents [5]. It has serious effect on patients' psychology, productivity and life quality. Therefore, there is a dire need for development of effective treatment strategies for psoriasis.

Over the past two decades, novel therapies for psoriasis have been rapidly developed, particularly biological agents, including tumor necrosis factor (TNF) inhibitors, interleukin-12/23 inhibitors, and IL-17 inhibitors [6]. Studies have demonstrated the implication of Il-23 in the etiology of psoriasis [6-8]. A dimeric protein, it comprises p19 and p40 subunits, the latter of which is present in Il-12, while the former is a special component of IL-23 [6]. The role of IL-23 in the pathogenesis of psoriasis is linked to the activation of some cytokines and congenital T-helper (Th) 17 cells [8]. In recent years, several new biological agents such as IL-23 inhibitors guselkumab, tildrakizumab and risankizumab have been approved for treatment of PsO, and are currently undergoing clinical tests [9,10]. Guselkumab (CNTO 1959, Janssen Research and Development) is human IgG1 monoclonal antibody which suppresses intracellular IL-23 signal transduction by binding to p19 component [11,12].

Currently, phases I-III clinical trials have revealed that guselkumab, at different doses resulted in significant clinical responses in patients with moderate-to-severe PsO [13-17]. However, the effectiveness and safety associated with the use of guselkumab and placebo for PsO have not been systematically investigated in RCTs to date. The aim of this study was to carry out a meta-analysis-based review of data from RCTs with different doses of guselkumab, and provide high-quality evidence for its clinical use.

METHODS

Literature search strategy

From January 2001 to October 2017, a systematic literature search was carried out using 5 electronic databases (Pubmed, Medline, Embase, Web of Science, and Cochrane Library). The key word used were "guselkumab psoriasis" or "guselkumab psoriatic". Moreover, original and review studies were manually searched to avoid missing some articles during the database search process. As a result, only randomized trials published in peer-reviewed journals were considered eligible. Observational studies, abstracts, case series, and case reports were not considered. There were no language restrictions with respect to selection of articles.

Selection criteria

The included studies were independently reviewed by two researchers (XBT and YHZ) using the study search strategy to judge if they met the criteria for inclusion. The inclusion criteria for studies used in this meta-analysis were as follows: (1) multicenter and double-blind RCTs and trials incorporating placebo controls; (2) studies in which experimental groups were given guselkumab while control group was given placebo; (3) studies that evaluated indices of effectiveness and safety, and (4) studies where outcome assessment indices included PASI score, PGA score and DLQI score, as well as incidence of AE, SAE, and study discontinuations.

Investigation of heterogeneity and publication bias

The I^2 test was employed to assess heterogeneity of doses and administration durations among different clinical trials. High heterogeneity was defined as I^2 value higher than 50%, or p value less than 0.1 [18]. For values with statistical significance, meta-regression was done through stepwise deletion of individual studies to determine if the results were consistent and of good quality. Furthermore, Galbraith radical plot was employed to ascertain the impact of each study on the overall results. Publication bias was determined with Begg funnel plot. Each study outcome was shown using an independent datum point and a middle regression line in forest plot.

Data extraction and quality assessment

In this meta-analysis, two reviewers (XBT and BH) independently extracted data from included studies. Differences between them were resolved through discussion and agreement. The study data were listed in an EXCEL form. The information included authors, year, type, study name, country, Clinicaltrials.gov identification number, guselkumab dose, number of guselkumab-treated patients and placebo-treated patients, duration of study, and outcome assessment indices. The indices of effectiveness

were 75, 90 or 100% reduction in PASI score; PGA score of zero or 1, and DLQI score of 0 or 1. Safety indices were associated with AEs, SAEs, and AE-linked study discontinuation. The main indices were PASI score (75%, 90%, and 100%); PGA score, DLQI score, adverse events and serious adverse events, while the others were considered as secondary indices. For each enrolled study, quality was assessed using Cochrane collaboration tool. Based on the Cochrane Handbook, it was believed that the risk of bias for each included study was either low, high, or uncertain.

Statistical analysis

Review manager version 5 was used for quality evaluation and publication bias analysis of included literature. STATA/SE 15.1 manager version was used for all statistical analyses. All standardized mean differences (SMDs), risk ratios (RRs), and their 95% confidence intervals (CIs) were calculated for included clinical outcomes using random-effects model. Statistical significance was assumed at $p < 0.05$.

RESULTS

Study characteristics

A total of 398 articles were searched, among which were 373 potentially eligible articles initially identified through electronic databases, and 25 articles identified using the Cochrane Central. Following screening of the publications, 151 articles were excluded due to duplication, while the 247 articles remaining were saved. Then, 179 irrelevant articles were excluded because they did not meet the eligibility criteria for inclusion, while 68 articles were re-assessed for eligibility. Eventually, the following categories of articles which did not meet the criteria for inclusion were excluded: (1) articles that were not associated with effectiveness and toxicity of guselkumab in PsO subjects (43 papers); (2) articles that were reviews or meta-analysis (n=17), and (3) those that were not double-blinded RCTs on guselkumab (n = 3). As a result, only the 5 remaining independent articles met the criteria for inclusion. They were 5 RCTs involving two phase-I trials, one phase-II trial and two phase-III trials, with a total of 1592 enrolled patients comprising 1109 guselkumab-administered subjects and 483 patients treated with placebo. The study selection process is presented in Figure 1, while Table 1 shows the characteristics of the included studies.

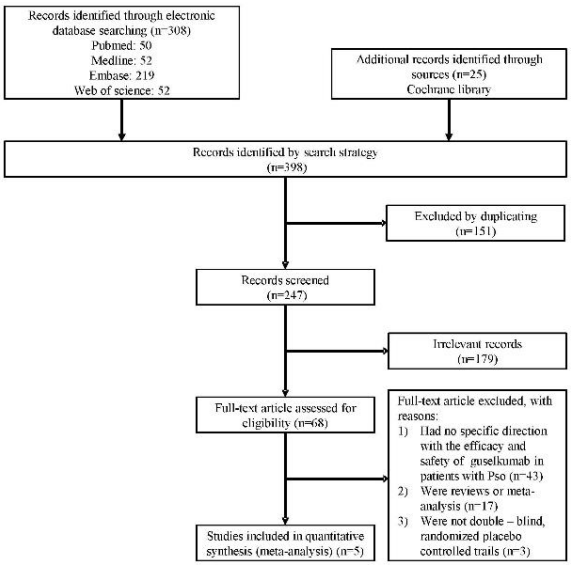


Figure 1. Study selection process for this meta-analysis

Risk of publication bias assessment

Figure 2 shows the results of evaluation of the study quality of each RCT. There was acceptable random sequence in the chosen articles. Moreover, there was a low risk of bias in terms of allocation concealment. Furthermore, all included studies were RCTs. Thus, ‘‘blinding of participants and personnel’’ and ‘‘blinding of outcome assessment’’ were deemed at a low risk of bias. Meanwhile, given the completeness of the reported data and the absence of selectivity bias, the included studies were still considered to be at low risk. Overall, all the 5 RCTs manifested low risks of bias (Supplementary Figure 1). Interestingly, the patients and researchers were blinded through employment of placebo, and their baselines were similar. The results of funnel plot visually revealed that studies with larger samples were plotted near the average, while studies with smaller samples were evenly distributed on both sides, thereby forming a roughly funnel-shaped distribution (Supplementary Figure 1 A). In addition, as revealed in Begg test, there were no appreciable bias in publications used (Supplementary Figure 1B).

Test of heterogeneity and sensitivity analysis

In a pooled analysis of the 5 clinical trials, meta-regression was used to determine the origins of heterogeneity. There was no heterogeneity in the included studies in all outcome assessment indices, except for high heterogeneity in DLQI score (I^2=55.1%, p=0.037; Figure 2 E).

Table 1: The basic characteristics of the included studies in the meta-analysis

Reference	Year	Type	Study name	Country	CTG	Phase	Doses of guselkumab (mg)	T/C, n	Outcome assessment indexes
Sofen et al[13]	2014	mRCT	NA	USA	NCT01483599	I	SC (10, 30, 100, 300 mg), for 24 weeks	4/20	Efficacy: PASI 75, PASI 90 Safety: AE
Zhuang et al[14]	2016	mRCT	NA	USA	NCT00925574	I	Part 1: IV (0.03, 0.1, 0.3, 1, 3, 10 mg/kg), SC (3 mg/kg) Part 2: SC (10, 30, 100, 300 mg) for 24 weeks	56/15	Efficacy: PASI 75 Safety: AE
Gordon et al[15]	2015	mRCT	NA	Multinational	NCT01483599	II	SC [5 mg (at week 0, 4, then q12w), 15 mg (q8w), 50 mg (at week 0,4, then q12w), 100 mg (q8w), 200 mg (at week 0,4, then q12w)], for 40 weeks	208/42	Efficacy: PASI 75, PASI 90, PASI 100, PGA (0, 0/1), Change in DLQI, DLQI 0/1 Safety: AE, SAE, Study discontinuations
Blauvelt et al[17]	2017	mRCT	VOYAGE 1	Multinational	NCT02207231	III	SC 100 mg (at week 0 and 4, then q8w; at weeks 16 and 20, then q8w;) for 48 weeks	329/174	Efficacy: PASI 75, PASI 90, PASI 100, PGA (0, 0/1), Change in DLQI, DLQI 0/1 Safety: AE, SAE, Study discontinuations
Reich et al[18]	2017	mRCT	VOYAGE 2	Multinational	NCT02207244	III	SC 100 mg (at week 0, 4, then q8w) for 48 weeks	496/248	Efficacy: PASI 75, PASI 90, PASI 100, PGA (0, 0/1), Change in DLQI, DLQI 0/1 Safety: AE, SAE, Study discontinuations

mRCTs: Multicenter randomized controlled trials; CTG: Clinicaltrials.gov identification number; PASI: Psoriasis area and severity index; PGA: Physician's Global Assessment; DLQI: Dermatology Life Quality Index; AEs: Adverse events; SAEs: Severe adverse events; Study discontinuation: Discontinued study agent because of AEs

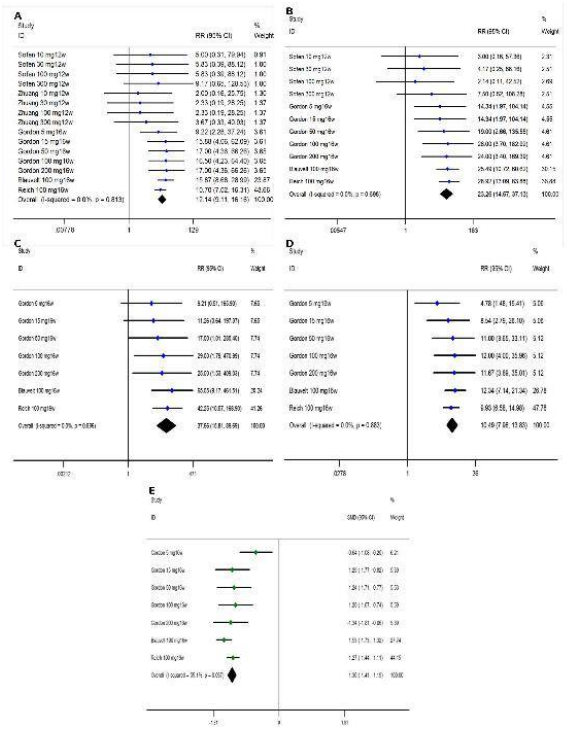
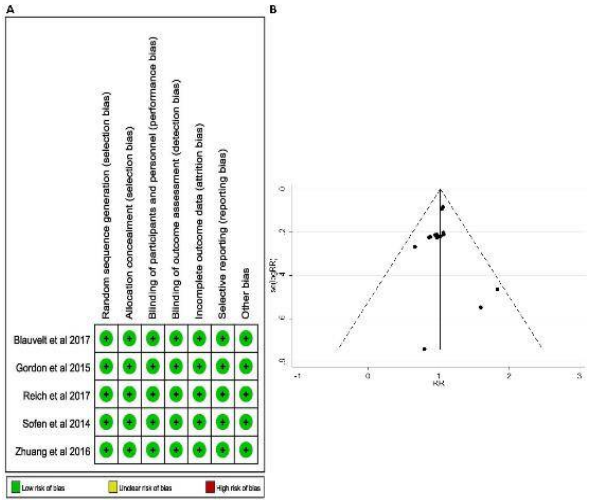


Figure 2: Forest plot of efficacy outcomes of 5 RCTs with guselkumab- and placebo-treated patients with moderate-to severe PsO. A, The PASI 75 score. B, The PASI 90 score. C, The PASI 100 score. D, The PGA score. E, The DLQI score.



Supplementary Figure 1: Studies included in this meta-analysis showed a low risk of bias. A, Risk of bias for each included study. B, Begg funnel plot.

There were no statistically significant differences among AE, SAE and study discontinuation (Figure 3). The L'Abbe plot was used to assess the contribution of guselkumab doses (5, 10, 15, 30, 50, 100, 200 and 300 mg) to the heterogeneity of the results. Low heterogeneity and high reproducibility were seen in the overall outcome (Supplementary Figure 2 in the Supplementary material). Furthermore, the Galbraith radial plot was used to assess heterogeneity among different doses in guselkumab treatment groups. The results showed that the group given 10 mg of guselkumab in phase I trial (Sofen 10 mg 24 w) was the major source of heterogeneity (Supplementary Figure 3 in the Supplementary material). Finally, after excluding the major source of heterogeneity and pooling all data, a sensitivity analysis was carried out to determine whether the bias still had an impact on the treatment effects. A stable result from meta-analysis random-effects estimates was revealed, which was close to the real effect (Supplementary Figure 4 in the Supplementary material).

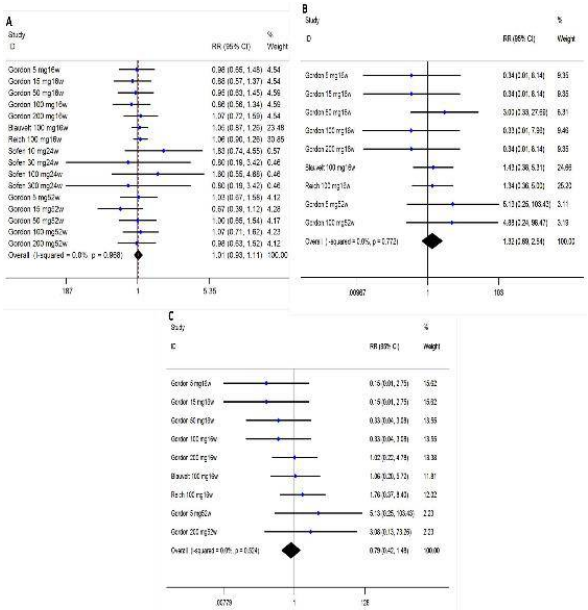
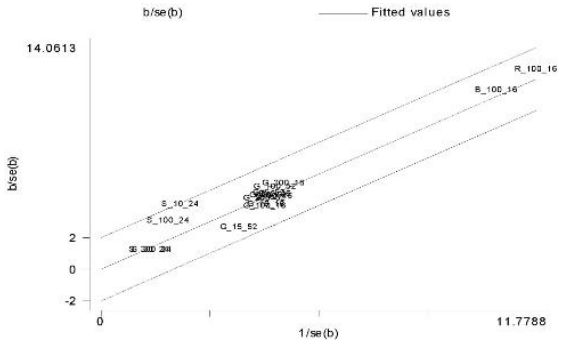
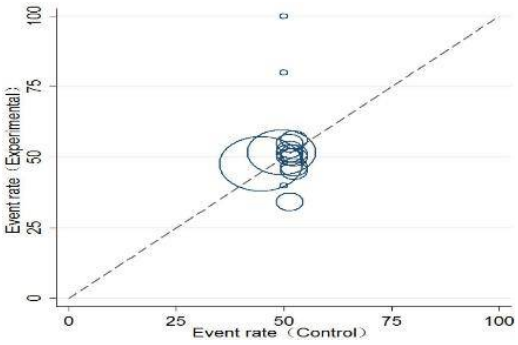


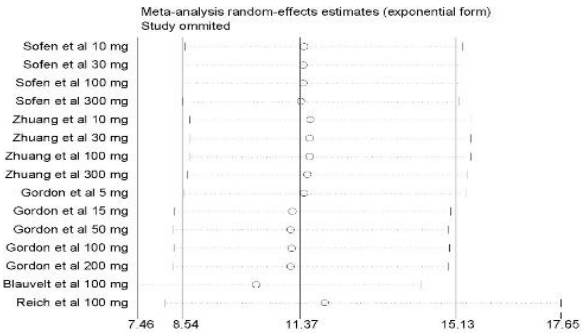
Figure 3. Forest plot of safety outcomes of 5 RCTs with guselkumab- and placebo-treated patients with moderate-to-severe PsO. A, AE rates and RR of AE rates between guselkumab- and placebo-treated patients. B, SAE rates and RR of SAE rates between guselkumab- and placebo-treated patients. C, Rates of study discontinuation and RR of study discontinuation between guselkumab- and placebo-treated patients.



Supplementary Figure 2. L'Abbe plot of meta-analysis



Supplementary Figure 3. Galbraith radical plot of meta-analysis



Supplementary Figure 4. Sensitivity analysis plot of meta-analsysis

Efficacy of guselkumab treatment on PsO

The efficacy of guselkumab was evaluated from the scores of PASI, PGA, and DLQI during the placebo-controlled period (follow-up at weeks 16 and 24). Compared with the placebo controls, the percentages of patients with PASI 75 improvement (RR = 12.14; 95% CI = 9.11-16.16; $p < 0.001$; Figure 2 A); PASI 90 improvement (RR = 23.26; 95% CI = 14.57-37.13; $p < 0.001$; Figure 2 B), and PASI 100 improvement (RR = 37.66; 95% CI =15.81-89.69; $p < 0.001$; Figure 2 C) were significantly higher than those of guselkumab-treated patients at week 16 and week 24. During the 16-week follow-up, patients in the guselkumab group experienced a significant decline in PGA score, when compared to the placebo group (RR = 10.46; 95% CI = 7.96-13.83; $p < 0.001$; Figure 2 D). In addition, the DLQI scores of patients given guselkumab were significantly lower than those of patients who received placebo at week 16 (SMD = -1.3; 95% CI = -1.4 to -1.19; p <0.001; Figure 2 E), which indicated that the use of guselkumab treatment effectively improved the life quality of the subjects. (Supplementary Figure 4).

Safety of guselkumab treatment on PsO

The safety of guselkumab was assessed based on the prevalence of AEs, SAEs and study discontinuation during the placebo-controlled period (follow-up within 16 weeks). The most-frequently reported AEs in guselkumab-treated patients were nasopharyngitis, headache, and upper respiratory tract infection. At weeks 16, 24 and 52, there were no statistically significant differences in AEs between guselkumab-treated patients and placebo-treated patients (RR = 1.01; 95% CI = 0.93-1.11; $p > 0.05$; Figure 3 A). By the end of weeks 16 and 52, there were no marked differences in SAEs such as myocardial infarction, stroke and cardiovascular death between guselkumab-treated patients and the placebo control (RR = 1.32; 95% CI= 0.69-2.54; $p > 0.05$; Figure 3 B). Furthermore, the prevalence AE-associated disengagement from the study did not differ significantly between the guselkumab-treated patients and placebo controls at weeks 16 and 52 (RR = 0.79; 95% CI = 0.42-1.48; $p > 0.05$; Figure 3 C).

DISCUSSION

Across all the included studies, most patients with moderate-to-severe PsO who received guselkumab treatment had more significant relief than those given placebo, as assessed using PASI score, PGA score and DLQI score. This demonstrates that guselkumab treatment significantly reduced the severity of moderate-to-severe PsO and patient's life quality, when compared with placebo at weeks 12 and 16. Furthermore, there were no statistically significant differences in incidence of AEs, SAEs and study discontinuations between guselkumab- and placebo-treated PsO patients. There were mild AEs in guselkumab-administered moderate-to-severe PsO subjects, suggesting that guselkumab was well-tolerated. These results indicate that guselkumab produced significant and positive benefits in the treatment of moderate-to-severe PsO patients, and they are consistent with the findings in several published reviews [18-20]. However, some of the findings are not in agreement with those of obtained in earlier studies [13, 21, 22]. This may be due to the small study size, inconsistent sample sizes, and under-representation (< 30), which were also the fundamental reason for the meta-analysis. It is worthy of note that although there were no significant differences in the incidence of AEs and SAEs between the two groups, the incidence of infections increased. To our knowledge, treatment-related infections are not usually serious. However, further studies are needed to investigate the pathogenesis of the infection.

This study has revealed that the results of the five independent investigations were not heterogenous, and were very reproducible,

although the studies involved PsO subjects with variabilities in seriousness of the disease and pre-conditioning requirements. This shows that guselkumab is reliable and produces reproducible effects in patients with PsO.

Study limitations

This study has several limitations. First, only 5 RCTs were used for meta-analysis. These RCTs had relatively small overall sample sizes and inconsistent factors in baseline characteristics of some patients in multiple treatment groups, which may bias the overall results. Secondly, there was a high heterogeneity in DLQI score across the included studies, which may have some influence on the overall results. Thirdly, subgroup analysis could not be performed due to inconsistent doses used from phases I to III. Thus, the optimal effective dose could not be determined.

CONCLUSION

In general, based on the results of this meta-analysis and clinical practice perspective, this meta-analysis demonstrates that guselkumab improves PASI, PGA, and DLQI score, and has a side effect profile similar to that of placebo. Guselkumab is well tolerated, effective and safe in reducing the severity of illness while improving the quality of life.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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