Guselkumab for Active Psoriatic Arthritis: Results from Systematic Literature Review and Network Meta-Analyses

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Background

- Psoriatic arthritis (PsA) is a progressive, chronic inflammatory disease characterized by irreversible joint damage.[1-3] A variety of treatments are currently recommended for the treatment of PsA, including non-steroidal anti-inflammatory drugs, glucocorticoids, conventional systemic agents (eg, methotrexate, sulfasalazine), and targeted or biologic therapies.
- Guselkumab (GUS) is a monoclonal antibody that binds with high affinity and specificity to the p19 subunit of interleukin (IL)-23, disrupting IL-23-mediated signaling.
- The safety and efficacy of GUS for PsA has recently been demonstrated in two Phase 3 trials (DISCOVER-1 & -2) but has not been evaluated versus existing targeted therapies for PsA. Given a lack of head-to-head data, indirect comparisons are needed to inform the comparative efficacy of GUS versus other targeted therapies.

Objective

- To compare GUS to other targeted therapies for active PsA through network meta-analysis (NMA).

Methods

- A systematic literature review was performed to identify randomized controlled trials (RCTs) from 2000 to 2018 meeting eligibility criteria from a pre-specified PROSPERO protocol (**Table 1**) available online at: CRD42020152614.

Table 1. SLR Inclusion Criteria

Item	Inclusion Criteria
Population	Adults (aged 18 years and older) with active PsA
Intervention	• Guselkumab 100 mg at weeks 0 and 4, then every 8 weeks • Guselkumab 100 mg every 4 weeks
Comparators	Searches included any targeted or biologic therapies for treatment of PsA, including: • TNF inhibitors (golimumab, certolizumab, etanercept, adalimumab, infliximab) • IL-12/23 inhibitors (ustekinumab) • IL-17 inhibitors (secukinumab, ixekizumab, brodalumab, bimekizumab) • IL-23 inhibitors (risankizumab, tildrakizumab) • PDE4 inhibitors (apremilast) • JAK inhibitors (tofacitinib, upadacitinib) • CTLA-4 inhibitors (abatacept) • Biologic biosimilar agents • Placebo and no treatment
Outcomes	• ACR 20, ACR 50, ACR 70, PASI 75, PASI 90, PASI 100, HAQ-DI score, resolution of enthesitis, resolution of dactylitis, adverse events, and serious adverse events
Study Design	Published RCTs • English language

Abbreviations: ACR = American College of Rheumatology; CTLA-4 = Cytotoxic T-lymphocyte-associated protein 4; HAQ-DI = Health Assessment Questionnaire Disability Index; IL = interleukin; JAK = Janus Kinase; NMA = network meta-analysis; PASI = Psoriasis Area Severity Index; PDE4 = Phosphodiesterase 4; PsA = psoriatic arthritis; RCT = randomized controlled trial; SLR = systematic literature review; TNF = tumor necrosis factor-alpha; vdH-S = van der Heijde-Sharp.

- Search strategies were developed in collaboration with an information specialist and peer reviewed using the PRESS checklist.[4]
- Two reviewers performed study selection and data collection. Conflicts between reviewers were resolved via consensus or involvement of a third reviewer.
- Bayesian NMAs were performed to estimate comparisons between treatments for outcomes of interest, including American College of Rheumatology (ACR) 20/50/70 response, Psoriasis Area Severity Index (PASI), Health Assessment Questionnaire Disability Index (HAQ-DI), resolution of enthesitis (RoE), resolution of dactylitis (RoD), adverse events (AEs), and serious adverse events (SAEs).
- Although searches were not limited by study phase or treatment approval status, only Phase 3 studies evaluating approved targeted or biologic therapies were included in NMAs given the robustness of efficacy assessments in such trials.
- Prior to analyses, a thorough assessment of between-study heterogeneity was performed. Unadjusted and baseline risk-adjusted NMAs, which account for between-trial variation in placebo response, were performed when feasible and the best-fitting model was selected based on model fit statistics according to National Institute for Health and Care Excellence Technical Support Documents.[5]

Methods

- Random effects models using vague prior distributions for treatment effects, trial baselines, and the between-study variance parameter were fit unless unfeasible due to data limitations and structures of evidence networks, in which case weakly informative priors were used to inform parameters.
- Primary analyses focused on efficacy outcomes reported at the primary timepoint of included studies (varying from 12 to 24 weeks) in the overall population of each study. For safety outcomes, the latest placebo-controlled timepoint was used. Sensitivity analyses were performed to control for variation in timepoint (ie, 12-16 week and 24 week) and previous exposure to biologics (ie, bio-naïve and bio-experienced), when feasible.
- Results for key outcomes are presented in forest plots (**Figures 2-8**) evaluating the comparative efficacy of active treatments versus placebo through pairwise relative risk (RR) ratios for dichotomous outcomes or mean differences (MD) for continuous outcomes with associated 95% credible intervals (CrI). Additional results are summarized using the surface under the cumulative ranking (SUCRA) scores (**Figure 1**), which reflects the proportion of treatments that a given intervention is estimated to be better than.

Results

- After review of 2,659 unique citations and 534 full-text publications, 47 publications describing 24 unique Phase 3 RCTs were identified and included in the NMAs. Data were not available for all treatments and outcomes. No trials were identified evaluating biosimilar agents.
- Because of the cross-trial differences in patient and study characteristics identified, a baseline risk-adjusted, random effects NMA, which adjusted for variations in placebo group response rates, was performed for all ACR, PASI, AE, and SAE outcomes. Analyses for HAQ-DI, RoE, and RoD were better fit by – and therefore assessed using – an unadjusted, random effects model.
- For ACR 20 response, GUS Q8W and Q4W ACR 20s were comparable to IL-17 and subcutaneous TNF inhibitors versus placebo (**Figure 2**). Intravenous TNF inhibitors demonstrated higher likelihood of achieving ACR 20 response than other (ie, oral and subcutaneous) agents. Similar conclusions were also obtained for ACR 50 and 70 (**Figure 1**).
- For PASI 90, GUS Q8W and Q4W had the highest probabilities of achieving a response and were better than most other comparators versus placebo (**Figure 3**). Similar results were observed for PASI 75, with GUS Q8W and Q4W retaining the highest SUCRA scores and demonstrating improvement over most other comparators (**Figure 1**). For PASI 100, GUS Q4W had the highest SUCRA score, but low event rates and lack of data for most comparators made comparative analyses uncertain (**Figure 1**).
- For change in HAQ-DI score, RoE, and RoD, conclusions were similar to ACR analyses, with GUS Q8W and Q4W showing comparable improvement versus placebo to IL-17 and subcutaneous TNF inhibitors (**Figures 4-6**).
- For both AEs and SAEs, GUS Q8W and Q4W had among the highest SUCRA scores (**Figure 1**) and were comparable to or better than other agents (**Figures 7 & 8**).
- Conclusions were broadly aligned in sensitivity analyses controlling for timepoint of outcome evaluation, although SUCRA scores for GUS Q8W and Q4W were often lower when restricting to data at 12-16 weeks (results not shown). Notably, SUCRA scores were better-aligned with primary analyses when restricting to data at 24 weeks (results not shown). Similarly, conclusions were broadly consistent in sensitivity analyses that controlled for exposure to previous biologics but were occasionally limited by sparse networks (results not shown).

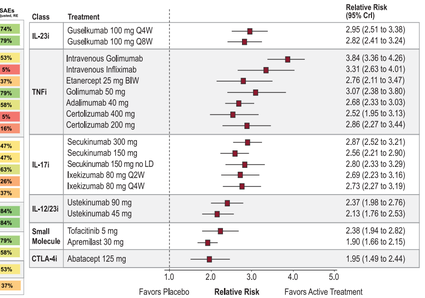
Figure 1. SUCRA Scores Across Outcomes

Class	Treatment	ACR 20 Adjusted, RE	ACR 50 Adjusted, RE	ACR 70 Adjusted, RE	PASI 75 Adjusted, RE	PASI 90 Adjusted, RE	PASI 100 Unadjusted, RE	HAQ-DI Unadjusted, RE	RoE Unadjusted, RE	RoD Unadjusted, RE	AEs Adjusted, RE	SAEs Adjusted, RE
IL-23i	Guselkumab 100 mg Q4W	79%	53%	53%	100%	93%	88%	68%	42%	42%	83%	74%
	Guselkumab 100 mg Q8W	68%	37%	47%	95%	93%	75%	47%	58%	33%	89%	79%
TNFi	Intravenous Golimumab	100%	95%	89%	68%	57%	25%	100%	92%	92%	89%	53%
	Intravenous Infliximab	95%	84%	53%	74%	NA	NA	89%	NA	NA	0%	5%
	Etanercept 25 mg BIW	58%	84%	16%	11%	0%	NA	89%	NA	NA	NA	37%
	Golimumab 50 mg	84%	74%	37%	26%	NA	NA	58%	NA	NA	17%	79%
	Adalimumab 40 mg	53%	63%	74%	37%	36%	38%	47%	67%	58%	78%	58%
	Certolizumab 400 mg	37%	47%	32%	42%	14%	NA	42%	NA	NA	17%	5%
	Certolizumab 200 mg	68%	63%	89%	42%	21%	NA	68%	NA	NA	28%	16%
IL-17i	Secukinumab 300 mg	68%	74%	74%	74%	71%	NA	47%	83%	75%	56%	47%
	Secukinumab 150 mg	42%	42%	68%	53%	56%	NA	16%	67%	58%	50%	47%
	Secukinumab 150 mg no LD	63%	42%	47%	53%	36%	NA	21%	17%	50%	56%	63%
	Ixekizumab 80 mg Q2W	53%	84%	89%	89%	86%	75%	74%	58%	75%	11%	26%
	Ixekizumab 80 mg Q4W	58%	74%	89%	74%	79%	75%	74%	83%	100%	22%	37%
IL-12/23i	Ustekinumab 90 mg	26%	26%	32%	68%	64%	38%	53%	NA	NA	50%	84%
	Ustekinumab 45 mg	16%	16%	21%	53%	43%	25%	32%	NA	NA	39%	84%
Small Molecule	Tofacitinib 5 mg	26%	32%	53%	21%	NA	NA	37%	33%	25%	78%	79%
	Abatacept 125 mg	11%	11%	21%	5%	NA	NA	11%	33%	17%	72%	58%
CTLA-4i	Apremilast 30 mg	11%	5%	5%	11%	NA	NA	21%	17%	8%	28%	53%
	Placebo	0%	0%	0%	0%	7%	0%	0%	0%	0%	72%	37%

SUCRA Score

0% SUCRA 100%

Figure 2. Forest Plot of Active Treatments Versus Placebo for ACR 20



Abbreviations: ACR = American College of Rheumatology; AEs = adverse events; BIW = biweekly; CrI = credible interval; CTLA-4i = cytotoxic T-lymphocyte-associated protein 4; GUS = guselkumab; IL-17i = interleukin-17 inhibitor; IL-12/23i = interleukin-12/23 inhibitor; IL-23i = interleukin-23 inhibitor; IV = intravenous; LD = loading dose; MD = mean difference; PASI = Psoriasis Area Severity Index; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RR = relative risk; SAEs = serious adverse events; TNFi = tumor necrosis factor inhibitor.

Figure 3. Forest Plot of Active Treatments Versus Placebo for PASI 90

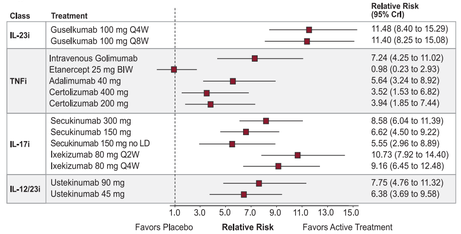


Figure 4. Forest Plot of Active Treatments Versus Placebo for HAQ-DI Score

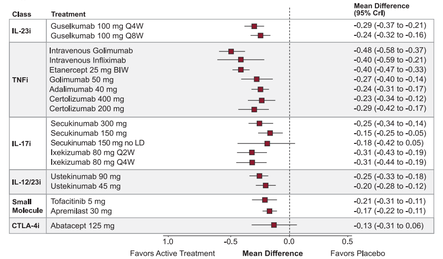


Figure 5. Forest Plot of Active Treatments Versus Placebo for Resolution of Enthesitis

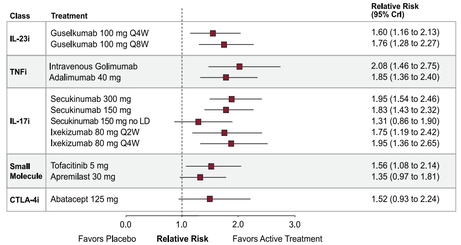


Figure 6. Forest Plot of Active Treatments Versus Placebo for Resolution of Dactylitis

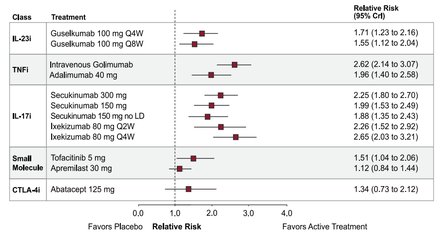


Figure 7. Forest Plot of Active Treatments Versus Placebo for Adverse Events

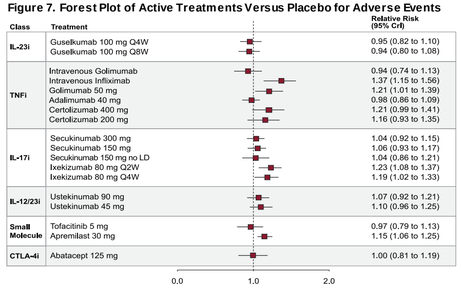
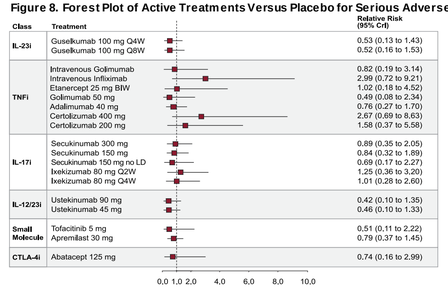


Figure 8. Forest Plot of Active Treatments Versus Placebo for Serious Adverse Events



Conclusions

- This analysis presents evidence of the comparative effectiveness of GUS, a novel p19 subunit IL-23 inhibitor that provides a new alternative for the treatment of patients with PsA.
- GUS Q8W and Q4W offer joint arthritis efficacy and physical function outcomes that are comparable to subcutaneous TNF inhibitors and IL-17 inhibitors.
- GUS Q8W and Q4W offer better PASI skin outcomes compared to most other agents available to treat PsA.
- GUS Q8W and Q4W have favorable safety profiles, with occurrence of AEs and SAEs comparable to other agents.

References

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