Dermatology Practical & Conceptual

Guselkumab - In Psoriasis and Beyond

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Introduction

Guselkumab is a humanized monoclonal IgG1 lambda IL-23p19 antibody, and the first in this group to get approval by the US Food and Drug Administration for the treatment of moderate-to-severe chronic plaque psoriasis in adults, who are candidates for systemic therapy/phototherapy; and psoriatic arthropathy [1]. Further, guselkumab has found to be of value in treating hidradenitis suppurativa (HS), pyoderma gangrenosum (PG), pityriasis rubra pilaris (PRP) and lichen planus (LP). The level of evidence for its utility in off-label dermatologic disorders has been enumerated in Figure 1.

ABSTRACT

Introduction: Guselkumab is an interleukin 23p19 inhibitor, and the first in this group, to be approved by the US Food and Drug Administration for the management of moderate to severe psoriasis. Apart from its utility in psoriasis, there are a number of other dermatologic conditions where guselkumab has demonstrated value.

Objectives: The aim of this narrative review is to describe the utility of guselkumab in psoriasis as well as its implication in off-label dermatologic disorders.

Methods: Pubmed, Google Scholar, Scopus and ResearchGate were searched for scholarly articles related to guselkumab and its utility in dermatology using the search terms "Guselkumab" AND "Psoriasis" AND "other dermatological disorders".

Results: Guselkumab is a valuable biologic agent for the management of psoriasis and psoriatic arthropathy. It has also been used successfully for other dermatologic disorders like hidradenitis suppurativa, lichen planus, pityriasis rubra pilaris and pyoderma gangrenosum. Recently, its utility in Stewart-Treves angiosarcoma (STA) has been exemplified.

Conclusion: Guselkumab usage is not limited to psoriasis. Its benefit extends to many more dermatologic conditions. Its utility in STA could open an avenue for its application in the field of oncology. Furthermore, it has an acceptable safety profile.

Serial No.	Off-label indications in dermatology	Level of evidence for guselkumab use
1	Guttate psoriasis	D
2	Nail psoriasis	A
3	Palmoplantar psoriasis (non-pustular)	A
4	Palmoplantar psoriasis	A
5	Hidradenitis suppurativa	D
6	Pyoderma gangrenosum	D
7	Pityriasis rubra pilaris	D
8	Stewart Trevis Angiosarcoma	E

Figure 1. Level of evidence for the utility of guselkumab in off-label dermatologic indications.

A: Double blind study: At least one prospective randomized double blind controlled trial without major design flaws. **B**: Clinical trial with 20 or more subjects: Prospective clinical trials with 20 or more subjects, trials lacking adequate controls or another key facet design, which would normally be considered desirable. **C**: Clinical trial with less than 20 subjects: small trials with less than 20 subjects with significant design limitations, very large number of case reports (at least 20 such in literature). **D**. Series of 5 or less subjects: Series of patients reported to respond with at least five reports of the same in literature. **E**: Anecdotal case reports.

Objectives

The aim of this narrative review is to describe the utility of guselkumab in psoriasis as well as its implication in off-label dermatologic disorders.

Methods

We carried out a search of English language literature, regarding psoriasis, pityriasis rubra pilaris, pyoderma gangrenosum, hidradenitis suppurativa, lichen planus and other dermatological disorders, with focus on guselkumab utility for these conditions. Original articles, case series, case reports and review articles were studied using the following databases PubMed, Google Scholar, Scopus and ResearchGate. All articles published in last fifteen years were reviewed.

Results

Clinical Uses

Plaque Psoriasis

IL-23 is a proinflammatory cytokine, closely implicated in the pathogenesis of psoriasis, details of which are elucidated in figure 2 [2-8]. Guselkumab acts against the IL-23p19

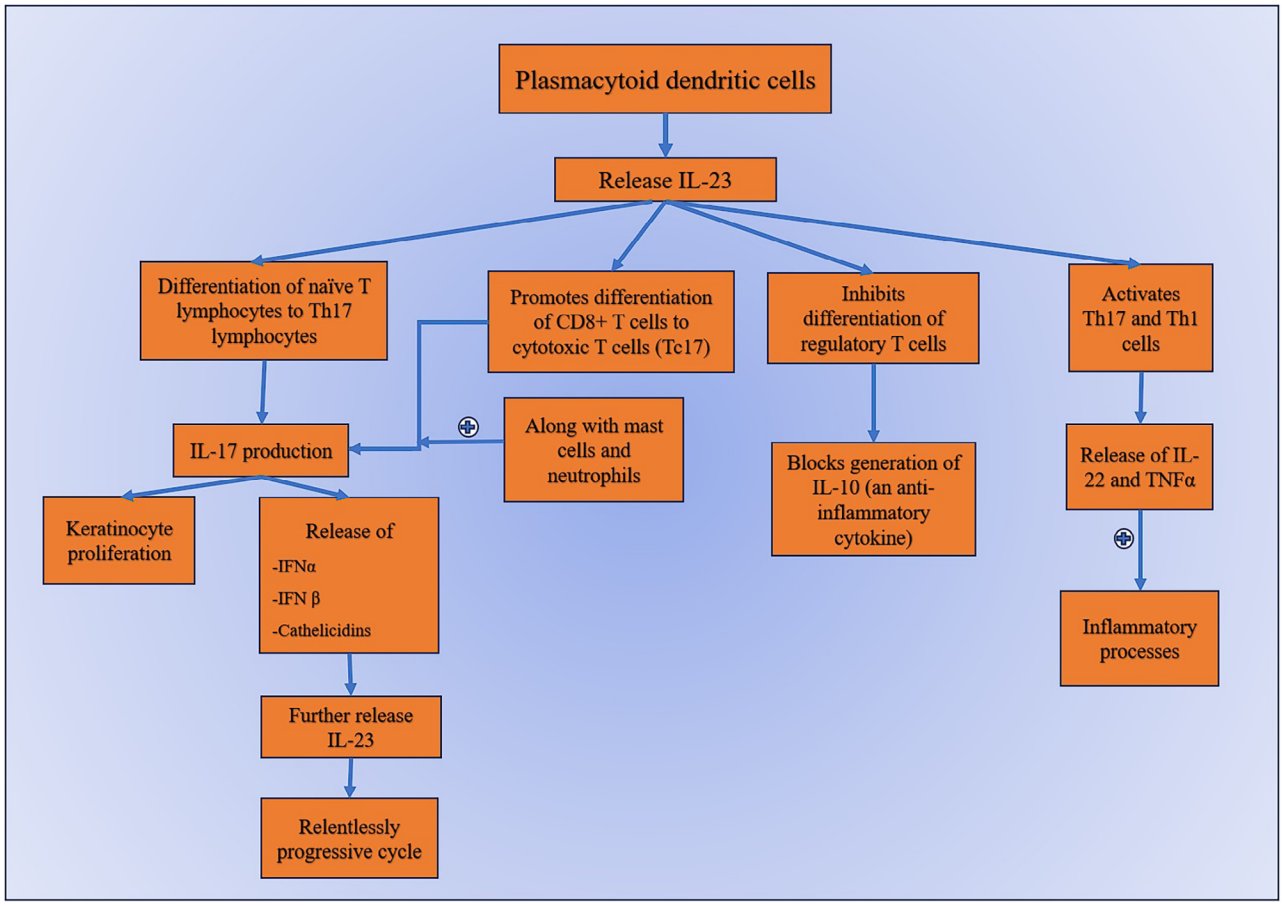

Figure 2. Role of IL-23 in psoriasis pathogenesis.

subunit of IL-23 receptor; and thus prevents IL-23 binding and subsequent progression of inflammation [9].

Guselkumab is administered subcutaneously (SC) and has a lower frequency of administration (100 mg at weeks 0, 4, and then once every 8 weeks), when compared to other biologics, with therapeutic responses persisting over time even after drug discontinuation; thus demonstrating long-term efficacy [10], that has been attributed to inhibition of IL-23p19 subunit, which has broader impact on inflammatory cytokines involved in psoriasis. Besides, tissue-resident memory T-cells that are responsible for persistence and recurrence of psoriasis are sustained in their pathogenic state by localized IL-23 produced by various subtypes of antigen presenting cells, and blocking this pathway therefore enables durable responses and low incidence of disease recurrence [11,12].

Additionally, guselkumab has lower risk of reactivation of tuberculosis and viral hepatitis, and is not associated with *de novo* onset or worsening of inflammatory bowel disease (IBD) in treated patients; making it safe and effective in these patients [13]. Furthermore, guselkumab demonstrates superiority to adalimumab, ustekinumab and secukinumab, with more consistent responses in chronic plaque psoriasis [14-16]. Moreover, significant benefit with guselkumab is observed in those patients where ustekinumab is ineffective, making guselkumab an ideal switch over drug in such scenarios [15]. In comparison with tildrakizumab however, no advantage has been observed with guselkumab. Both drugs were equally potent and safe in treating psoriasis patients [17].

Details of randomized controlled trials(RCTs) utilizing guselkumab in chronic plaque psoriasis has been described in Table 1 [14-16,18,19].

Guttate Psoriasis

Guttate psoriasis (GP) is an uncommon variant of psoriasis, classically associated with underlying streptococcal infection. However, GP has also been observed with no recent infection. Complete resolution of GP was first described by Hall et al, after one dose of guselkumab [20]. Another report illustrated complete remission of sunburn-induced guttate psoriasis following 6 doses of guselkumab, with cure maintained on drug cessation. The onset of GP in this case was connected to the activation of IL-23/IL-17 by various cytokines and keratinocytes, following sunburn in a genetically predisposed individual [21,22].

Nail Psoriasis

Nail psoriasis (NP) presents with heterogenous clinical patterns. As the nail unit is closely linked to the extensor tendon fibers and periosteum of the distal phalanx, psoriasis of nails is often associated with psoriatic arthropathy (PsA) [23]. Owing to the distinctive anatomy of the nail unit, it becomes mandatory for practitioners to have a detailed understanding regarding the therapeutic aspects in relation to NP, in order to obtain better clinical outcomes and an improved quality of life (QoL) [24,25]. Though often associated with plaque psoriasis, in 5%-10% of patients NP can present as an isolated finding [26].

Guselkumab is effective in NP, with a longer remission period following withdrawal, when compared to cutaneous psoriasis. Besides, it is seen that less severe nail disease (lower baseline Nail Psoriasis Severity Index [NAPSI]) and lower PASI scores at week 16 following treatment, are associated with greater probability of near or complete NP clearance (NAPSI 0/1) at weeks 24 and 48, thereby attributing a direct association between skin and nail responsiveness to guselkumab [27]. Additionally, cigarette smoking is associated with a negative impact on treatment response with guselkumab in NP, possibly due to local angiopathic factors, koebnerization and systemic effects of cigarette smoke [28]. Interestingly, no statistically significant association has been observed with guselkumab in relation to body mass index (BMI) and the probability of obtaining NAPSI 0/1. This caries significance because obesity is a common comorbidity in psoriasis patients, and in cutaneous psoriasis, guselkumab has demonstrated PASI 90 to be more likely in patients with BMI < 25 kg/m^2 than in those having a BMI >30 kg/m^2 [29-31]. Further, NAPSI 0/1 responses at weeks 24 and 48 with guselkumab are not impacted in patients who have previously received TNFα antagonist biologic agents, making it an ideal drug for NP even in bio-experienced individuals [19-32]. Besides, the efficacy of guselkumab in NP is similar to adalimumab, but ixekizumab has demonstrated greater profitability in NP [32,33]. Reports delineating the efficacy of guselkumab in NP are presented in Table 2 [19,32,34,35]. Currently, with this preliminary data of newer biologic drugs for NP, establishing the drug of choice would not be very practical. More data and dedicated head on comparative trials of these drugs in NP become imperative to establish an evidence-based treatment algorithm for the same.

Palmoplantar Psoriasis (Non-Pustular)

Palmoplantar psoriasis (PPP) is a variant of psoriasis characterized by hyperkeratotic and fissured plaques involving the palms and soles and often recalcitrant to treatment [36]. At present, no gold-standard therapy is recognized for PPP, despite the availability of broad and effective biologic treatment options for moderate-to-severe plaque psoriasis. Moreover, clinical trials for PPP have been challenging because many patients do not meet typical inclusion criteria needed for these trials, owing to low body surface area (BSA) involvement, often $< 10\%$ [37].

Table 1. Salient Features of Various Studies Demonstrating the Efficacy of Guselkumab in Chronic Plaque Psoriasis

Serial No.	Authors/Year	Details	Remarks

1	Blauvelt et al [14] 2017	VOYAGE 1 trial:
		• Phase III, randomized double blind trial evaluating effectiveness of guselkumab in comparison to placebo and adalimumab.
		• Patients randomized in 1:2:2 ratio for one of the 3 treatments:
		  • Placebo (weeks 0, 4 and 12), followed by guselkumab (100 mg; weeks 16, 20 and then every 8 weeks through week 44) (N=174).
		  • Guselkumab (100 mg, weeks 0, 4 and then every 8 weeks through week 44) (N=329).
		  • Adalimumab (80 mg at week 0, 40 mg at week1, and 40 mg every 2 weeks through week 47) (N=334).
			• Psoriasis Area Severity Index (PASI) 75 at week 16:
			  • Guselkumab (91.2%)
			  • Adalimumab (73.1%)
			  • Placebo (5.7%)
			• PASI 90 at week 16:
			  • Guselkumab (73.3%)
			  • Adalimumab (49.7%)
			  • Placebo (2.9%)
			• PASI 100 at week 16:
			  • Guselkumab (37.4%)
			  • Adalimumab (17.1%)
			  • Placebo (0.6%)
			• PASI 75 at week 48:
			  • Guselkumab (87.8%)
			  • Adalimumab (62.6%)
			• PASI 90 at week 48:
			  • Guselkumab (76.3%)
			  • Adalimumab (47.9%)
			• PASI 100 at week 48:
			  • Guselkumab (47.4%)
			  • Adalimumab (23.4%)
			• Investigator Global Assessment (IGA) 0/1 at 16 weeks:
			  • Guselkumab (85.1%)
			  • Adalimumab (65.9%)
			  • Placebo (6.9%)
			• IGA 0/1 at 48 weeks:
			  • Guselkumab (80.5%)
			  • Adalimumab (55.4%)
			• Dermatology life quality Index (DLQI) at 16 weeks:
			  • Guselkumab (56.3%)
			  • Adalimumab (38.6%)
			  • Placebo (4.2%)
			• DLQI at 48 weeks:
			  • Guselkumab (62.5%)
			  • Adalimumab (38.9%)

2	Langley et al [15] 2018	NAVIGATE trial
		• Patients received open label ustekinumab (45 mg for patients ≤100 kg, 90 mg for patients >100 kg) at weeks 0 and 4.
		• At week 16, 268 patients with inadequate response, considered as an IGA score of 2 or more, were randomized (double-blind) to receive:
		  a) Guselkumab (100mg; weeks 16, 20 and every 8 weeks thereafter through week 44) (N=135).
		  b) Continued with ustekinumab (week 16 and every 12 weeks after that through week 40) (N=133).
			• PASI 90 at week 52:
			  • Guselkumab (51.1%)
			  • Ustekinumab (24.1%)
			• PASI 100 at week 52:
			  • Guselkumab (20%)
			  • Ustekinumab (7.5%)
			• IGA 0/1 at week 52:
			  • Guselkumab (36.3%)
			  • Ustekinumab (17.3%)
			• DLQI at week 52:
			  • Guselkumab (35.8%)
			  • Ustekinumab (19%)

Serial No.	Authors/Year	Details	Remarks
3	Reich et al [16] 2019	ECLIPSE trial • Phase 3, randomized controlled trial. • Comparison of guselkumab (N=534) versus secukinumab (N=514) for moderate-to-severe chronic plaque psoriasis. • Guselkumab (100 mg) given by SC route at weeks 0, 4, 12 and every 8 weeks thereafter till week 44. • Secukinumab (300 mg) given by SC route at weeks 0, 1, 2, 3 and 4 and every 4 weeks thereafter till week 44.	• PASI 75 at week 12: • Guselkumab (89%) • Secukinumab (92%) • PASI 90 at week 12: • Guselkumab (69%) • Secukinumab (76%) • At week 48: • PASI 100 • Guselkumab (58%) • Secukinumab (48%) • IGA Score of 0 • Guselkumab (62%) • Secukinumab (50%) • Guselkumab has better long-term responses when compared to secukinumab.
4	Griffiths et al [18] 2020	• Extension of the VOYAGE 1 trial assessing the long-term clinical efficacy of guselkumab through 4 years in patients with moderate-to-severe psoriasis. • This publication represents data over the longest treatment period reported for an IL-23 inhibitor in psoriasis till date.	• High efficacy response rates were maintained through week 204 of treatment with guselkumab. • >80% patients maintained cleared or minimal psoriasis (PASI 90 and IGA 0/I). • >50% patients maintained cleared disease (PASI 100 and IGA 0). • Safety profile of guselkumab remained favourable with no new signals of concern revealed with longer treatment for 4 years.
5	Ohtsuki et al [19] 2018	• A phase 3, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of guselkumab in moderate-to-severe plaque-type psoriasis in Japanese patients. • Patients were randomized in 1:1:1 ratio for one of the three treatments. • Guselkumab (50 mg, weeks 0, 4 and then every 8 weeks) (N=65). • Guselkumab (100 mg, similar schedule) (N=64). • Placebo (weeks 0, 4, and 8 weekly), followed by guselkumab 50 mg/100 mg at weeks 16 and 20, and every 8 weeks thereafter (N=63).	• PASI 90 at week 16: • Guselkumab(50mg) (70.8%) • Guselkumab(100mg) (69.8%) • Placebo 0% • IGA 0/I at week 16: • Guselkumab (50mg) (92.3%) • Guselkumab (100mg) (88.9%) • Placebo (7.8%) • PASI 90 (through week 52): • Guselkumab (50mg) (75.4%) • Guselkumab (100mg) (77.8%) • Placebo guselkumab (50mg) (92.3%) • Placebo guselkumab (100mg) (73.1%) • However, with progression of time, complete clearance of psoriasis was observed in the guselkumab (100mg) group. • For most efficacy measures a dose response was not generally observed.

In a multicenter placebo-controlled trial evaluating the efficacy of guselkumab for PPP, though the primary end point of ppPASI 75 response at 16 weeks (guselkumab: 35.9%, placebo: 28.2%, P = 0.533) was not met, more pronounced numerical improvements favoring guselkumab were seen for more stringent efficacy endpoints such as ppIGA 0/1 response at week 16 (guselkumab 34.6%, placebo 15.4%) and ppPASI90 response at week 16 (guselkumab 24.4%, placebo 15.4%). Regarding the quality of life, greater proportion of subjects in the guselkumab group reported a Dermatology Life Quality Index (DLQI) 0/1 score at week 16 compared with the placebo group (19.2% versus 7.7%) respectively. Besides, significant reduction of serum IL-17A, IL-17F and IL-22 was observed at week 16 from baseline in the guselkumab group, but not in those patients receiving placebo [38]. Currently, apart from the above trial, no other publication exists on assessing guselkumab for non-pustular PPP. More studies are therefore warranted to better understand the impact of guselkumab treatment for this variant of psoriasis.

Table 2. Studies Elaborating the Role of Guselkumab in Nail Psoriasis

Serial No.	Author(s)/ Year	Study type	Details	Remarks	Adverse events
1	Ohtsuki et al [19] 2018	• Phase III, randomized double-blind placebo-controlled study.	• Patients randomized 1:1:1 to receive guselkumab 50 mg (44 patients), guselkumab 10 0mg (40 patients) and placebo (42 patients).	• Statistically significant improvement in NAPSI was seen in both guselkumab groups compared to placebo. • In the guselkumab 50mg group (p value = 0.002 versus placebo). • In the guselkumab 100mg group (P value <0.001 versus placebo).	None
2	Gerdes et al [34] 2023	• Non-interventional prospective multicentre study.	• 136 patients had ≥ 1 affected nail at baseline.	• Mean target NAPSI score reduced from 4.2 at baseline to 1 (at week 104).	None
3	Foley et al [32] 2018	• A secondary analysis of 2 randomized clinical trials.	• Of the 1829 randomized patients, 1049 (57.4%) presented with fingernail psoriasis.	• At week 16, number of patients achieving the target NAPSI score of 0 was statistically significantly higher for the guselkumab group (16%) compared with the placebo group (5.4%) (P <0.001). • At week 24, NAPSI 0 score was comparable between the guselkumab group (30.6%) and the adalimumab group (32.6%) (P = 0.50).	None
4	Jo et al [35] 2023	• Data from VOYAGE 1 and VOYAGE 2 including patients belonging to the Asian subpopulation to assess the efficacy of guselkumab and adalimumab vs placebo for fingernail psoriasis.	• 97 patients had fingernail psoriasis. o Placebo: 22 o Guselkumab: 44 o Adalimumab: 31	• Guselkumab showed greater improvement in than placebo in target NAPSI at week 16 (mean improvement 35.4% versus 10.8%) (P = 0.021). • At week 24 target NAPSI was maintained with guselkumab and was comparable to adalimumab (mean improvement 39.9% versus 35.9% (P = 0.618), respectively) • At week 24, similar proportions of patients in the guselkumab and adalimumab group achieved a 100% improvement in target NAPSI (20% versus 21% respectively) (P = 0.864).	None

NAPSI = Nail Psoriasis Severity Index.

Palmoplantar Pustulosis

Palmoplantar pustulosis presents as multiple, sterile pustules/vesiculopustules, crusting and erythema involving the palms and soles, and is considered a localized variant of pustular psoriasis [39].

The clinical efficacy of SC injections of guselkumab (200 mg at weeks 0 and 4) was assessed for moderate-to-severe palmoplantar pustulosis that had been unresponsive to topical steroids, vitamin D3 analogues, etretinate and phototherapy, in a randomized double-blind placebo-controlled

clinical trial. At week 16, there was significant reduction in the mean (SD) Palmoplantar Pustulosis Severity Index (PPSI) total scores from baseline in the guselkumab group (-3.3 [2.43]) versus placebo group (-1.8 [2.09]). This reduction was maintained at week 24 in the guselkumab group (-3.9 [2.47]) versus placebo group (-2.5 [2.78]). Regarding biomarkers, notable reduction from baseline in circulating IL-17A levels was observed at week 4 and 16 for guselkumab treated patients, while no remarkable change was noted in the placebo group [40]. In a phase 3 RCT, patients were assigned to receive guselkumab (100 mg; N = 54), guselkumab (200 mg; N = 52) or placebo (N = 53) for palmoplantar pustulosis. A significantly higher proportion of patients in the guselkumab (100 mg) group achieved a ppPASI 50 response (57.4%) at week 16, when compared to the guselkumab (200 mg; 36.5%) and placebo (34%) groups. However, the proportions of patients achieving a ppPASI 50 response increased over time, and at week 52, 83.3% patients in the guselkumab (100 mg) group and 84.6% patients in the guselkumab (200 mg) group demonstrated this change. Besides, there was remarkable improvement in the DLQI and Physician Global Assessment (PGA) scores (of cleared and almost cleared) in both guselkumab groups when compared to the placebo group [41].

In another study, guselkumab demonstrated efficacy on palmoplantar pustulosis through week 60 with sustenance of efficacy until week 84, along with considerable improvement in HR-QoL. At week 60, ppPASI 50 was 79.6%, 84.6%, 80.0% and 80.8% in the guselkumab (100 mg), guselkumab (200 mg), placebo to guselkumab (100 mg) and placebo to guselkumab (200 mg) groups respectively, which had increased to 88.9%, 95.3%, 85.7% and 87.5% respectively at week 84 [42].

The propitious effects of guselkumab in palmoplantar pustulosis is connected to significant reduction of levels of cytokines like IL-17A, IL-17F and IL-22, that are considerably elevated, and correlate with ppPASI disease scores. Guselkumab therapy results in 1.8-to-3-fold reduction of these cytokines by week 72, with greater levels of reduction in IL-22 that is crucial in bringing about an overall better ppPASI improvement [43].

Psoriatic Arthropathy

Psoriatic arthropathy (PsA) is a heterogenous inflammatory disorder associated with peripheral joint inflammation, enthesitis, dactylitis, axial disease along with cutaneous/nail involvement and significant physical and psychologic repercussions. IL-23/Th17 axis has shown to be critical in the pathogenesis of PsA (including enthesitis and dactylitis) [44]. Resident myeloid cells within the enthesis of normal human subjects are capable of producing IL-23, which in turn permits downstream IL-17A expression and induces IL-22 and TNF release, thereby eliciting articular symptoms and subsequent joint damage. Further, IL-17A has shown to have an equal role in bone remodeling by stimulating osteoclastogenesis and facilitating expression of the receptor activator of nuclear factor κβ ligand (an osteoclast differentiation factor) in osteoclast supporting cells, furthering joint destruction [45,46]. As IL-23 is involved in the regulation of numerous cytokines in the pathogenesis of PsA, targeting IL-23 individually, results in the inhibition of all other cytokines. Guselkumab, by blocking the IL-23 receptor, prevents generation of inflammatory cascades in PsA. Besides, as it selectively binds to the p19 subunit, it spares IL-12, a cytokine associated with protection from autoimmune inflammation and T cell exhaustion, giving it an added advantage [47-49].

Table 3 outlines the salient features of various studies employing guselkumab in the treatment of PsA [50-53].

Hidradenitis Suppurativa

HS is a chronic inflammatory condition of hair follicles and can severely affect patients physically and psychologically. The pathogenesis of HS occurs secondary to immune dysregulation, with increased levels of proinflammatory cytokines in lesional skin [54]. IL-23 is involved in the differentiation of Th17 cells and thus plays a major role in HS, as both IL-23 and Th17 are elevated in lesional skin of HS, and serum levels of IL-17A produced by Th17 correlate with severity of inflammation in HS [55,56]. This upregulation supports the rationale for guselkumab in the treatment of HS.

However, in many HS patients, guselkumab has not been effective, suggesting other cells(that are IL-23 independent), to be involved in the pathophysiology of HS [57]. Alternatively, despite the cellular effects of guselkumab on psoriatic lesional tissue, its uptake in lesions/fistulas of HS is generally less efficient that may account for its reduced efficacy in HS [11]. Although positive outcomes of guselkumab have been demonstrated in case reports/series, phase 2 studies have not confirmed this positive trend, suggesting guselkumab to be effective in only a subgroup of HS patients. Further details are elaborated in Table 4 [58-63].

Interestingly, guselkumab has shown to be advantageous in the management of paradoxical HS, as well as HS in patients with paradoxical psoriasiform reactions, following treatment with adalimumab [64-66]. Also, guselkumab has been effective in treating HS patients with other comorbidities like Crohn disease [67-69].

Pyoderma Gangrenosum

PG is a rare ulcerative neutrophilic dermatosis, often resistant to various forms of treatment. IL-23, a cytokine implicated in neutrophilic diseases, has shown promise as a potential target in the management of PG [70]. Additionally, IL-23 plays an essential role in advancing and bolstering

Table 3. Salient Features of Various Studies Employing Guselkumab in Psoriatic Arthropathy

Serial No.	Authors/Year	Details	Remarks

1	Deodhar et al [50] 2018	• A randomized, double-blind placebo-controlled, phase 2 study
		• Guselkumab group (N=100) given 100mg at week 0, 4 and then every 8 weeks.
		• Placebo group (N=49) given a placebo similarly till week 24, following which they received guselkumab (100mg) at week 24, 28, 36 and 44.
			At week 24:
			• American College of Rheumatology (ACR) 20 response:
			  • Guselkumab group: 58%
			  • Placebo: 9%
			• ACR 50 response:
			  • Guselkumab group: 34%
			  • Placebo group: 5%
			• Resolved dactylitis:
			  • Guselkumab:55%
			  • Placebo: 17%
			• Resolved Enthesitis:
			  • Guselkumab: 57%
			  • Placebo: 29%
			• All patients tolerated the drug well with no major adverse effects being reported.

2	Mease et al [51] 2020	• Randomized, placebo controlled, phase II study in patients with dactylitis and enthesitis in PsA.
		• Patients with enthesitis at baseline
		  - Guselkumab group (N=76)
		  - Placebo (N=31).
		• Patients with dactylitis at baseline
		  - Guselkumab group (N=58).
		  - Placebo group (N=23)
		• Guselkumab 100mg SC (label dosing) was administered.
			At week 24:
			• Proportion of patients with enthesitis resolution:
			  • Guselkumab: 56.6%
			  • Placebo: 29.0%
			• Proportion of patients with dactylitis resolution
			  • Guselkumab: 55.2%
			  • Placebo: 17.4%
			At week 56:
			• Proportions of patients with enthesitis resolution:
			  • Guselkumab: 70.8%
			  • Placebo (crossover): 62.5%
			• Proportion of patients with dactylitis resolution:
			  • Guselkumab: 93.7%
			  • Placebo (crossover): 75%

3	Mease et al [52] 2020	• A double-blind, randomized placebo-controlled phase 3 trial evaluating guselkumab in biologic naïve patients with active PsA.
		• Random allocation of patients into 3 group
		  - Guselkumab (100mg Q4 weekly) (N=246)
		  - Guselkumab (100mg Q8 weekly) (N=248)
		  - Placebo (N=247).
		• 100-week treatment phase.
		• Placebo group crossover to guselkumab from week 24 to 100.
			At week 24:
			• ACR 20 response:
			  • Guselkumab Q4W (64%)
			  • Guselkumab Q8W (64%)
			  • Placebo (33%)
			• ACR 50 response:
			  • Guselkumab Q4W (33%)
			  • Guselkumab Q8W (31%)
			  • Placebo (14%)
			• ACR 70 response:
			  • Guselkumab Q4W (13%)
			  • Guselkumab Q8W (19%)
			  • Placebo (4%)
			• Resolution of dactylitis:
			  • Guselkumab Q4W (64%)
			  • Guselkumab Q8W (59%)
			  • Placebo (42%)
			• Resolution of enthesitis:
			  • Guselkumab Q4W (45%)
			  • Guselkumab Q8W (50%)
			  • Placebo (29%)
			• Guselkumab was well tolerated with no clinically meaningful differences between dosing every 4 or 8 weeks up to 24 weeks.

Serial No.	Authors/Year	Details	Remarks

4	Deodhar et al [53] 2020	• A double-blind randomized, placebo-controlled phase 3 trial assessing the efficacy of guselkumab in PsA.
		• Randomized into 3 groups
		  • Guselkumab 100mg Q4w (N=128)
		  • Guselkumab 100mg Q8w (N=127)
		  • Placebo (N=126)
			At week 24:
			• ACR 20 response:
			  • Guselkumab Q4W (59%)
			  • Guselkumab Q8W (52%)
			  • Placebo (22%)
			• ACR 50 response:
			  • Guselkumab Q4W (36%)
			  • Guselkumab Q8W (30%)
			  • Placebo (9%)
			• ACR 70 response:
			  • Guselkumab Q4W (20%)
			  • Guselkumab Q8W (12%)
			  • Placebo (6%)

Table 4. Studies and Report Evaluating the Role of Guselkumab in Hidradenitis Suppurativa

Serial No.	Authors/year	Details	Remarks
1	Dudink et al [58] 2023	• An open-label multicenter, phase IIa trial. • 20 patients enrolled. • 2 dropped out. • Guselkumab (200 mg SC) administered at week 0, 4, 8 and 12. • Treatment given till week 16. • Follow up for 8 weeks. • Total duration 24 weeks	• 65% patients achieved Hidradenitis Suppurativa Clinical Response (HiSCR) at 24 weeks. • In 35% patients, 75% improvement of HiSCR was seen. • Median International Hidradenitis Suppurativa Score 4 (IHS4) and abscess/nodule count had significantly reduced between baseline and week 16 from 8.5 to 5. • Common adverse effects encountered were headache, nausea and upper respiratory tract infection. • The only serious adverse effect was a case of myocardial infarction (though not related to guselkumab therapy).

2	Kimball et al [59] 2023	• A phase 2, multicenter, randomized placebo controlled, double blind study.
		• 184 patients randomized as 1:1:1 to receive:
		  ➢ Guselkumab (200 mg SC) Q4W for 36 weeks (guselkumab SC group).
		  ➢ Guselkumab (1200 mg IV) Q4W for 12 weeks and then, guselkumab (200 mg SC) Q4W from 12-36 weeks (guselkumab IV group).
		  ➢ Placebo IV or SC Q4W for 12 weeks with rerandomization to:
		o Guselkumab 200mgSC Q4W from week 16 to 36 (placebo-guselkumab 200mg group)
		OR
		o Guselkumab 100mg SC at weeks 16, 20, 28 and 36, placebo at weeks 24 and 32(placebo – guselkumab 100mg) group.
			• At week 16, the proportions of patients achieving HiSCR:
			  • Guselkumab SC group (50.8%)
			  • Guselkumab IV group (45%).
			  • Placebo group (38.7%).
			• At week 40 HiSCR response rates:
			  ➢ Guselkumab SC group (45.8%).
			  ➢ Guselkumab IV group (48.3%).
			  ➢ Guselkumab 100mg group (placebo crossover) (46.4%)
			  ➢ Guselkumab 200mg group (placebo crossover) (53.6%)
			  ➢ Primary end point was not met here
			  ➢ Guselkumab was not very effective here for HS.
			• Anemia and nephrolithiasis were reported in one patient and cholelithiasis in another, though none were related to guselkumab therapy.

Table 4 continues

Table 4. Studies and Report Evaluating the Role of Guselkumab in Hidradenitis Suppurativa. *(continued)*

Serial No.	Authors/year	Details	Remarks
3	Casseres et al [60] 2019	• Retrospective chart review of 8 patients. • 4 patients: Hurley stage 3 disease • 4 patients: Hurley stage 2 disease • Previously failure of treatment with adalimumab, secukinumab, ustekinumab and ixekizumab.	• Authors reported improvement of HS in 5 patients (63%) following 4 months of therapy. • Precise data, though was lacking.
4	Montero-Vilichez et al [61] 2020	• Case series of 4 patients with HS (Hurley stage 2 and 3). • Patients were recalcitrant to biologic treatment with infliximab, adalimumab, ustekinumab and secukinumab. • Guselkumab started SC as 100 mg at week 0, and then every 4 weeks.	• Moderate reduction in HS4, visual analogue scores for pain and DLQI in 3 patients at 12 weeks of treatment. • In no patient was an improvement observed in the HS-PGA score. • In one patient HS severity had increased after treatment. • No guselkumab related adverse event was observed.
5	Kearney et al [62] 2020	• 28-year-old female with history of latent tuberculosis as a teenager, treated with rifampicin for 6 months. • Presented with HS (hurley stage 3). • Previous failed treatment with metformin and spironolactone was noted. • Guselkumab 100 mg (label dosing) given to the patient.	• By 12 weeks clear clinical and pain improvement was noted. • At 24 weeks, remission was maintained. • No therapy related adverse events were encountered.
6	Kovacs et al [63] 2019	• Case series of 3 patients with HS (Hurley stage 3). • 2 patients had failed treatment with adalimumab. • In one patient adalimumab was contraindicated due to an unclear history of SLE.	• At 12 weeks: ➢ Significant improvement in international HS score system ranging from 52.0%-60.9% was seen. ➢ VAS pain score improved by 50%-57.1%. ➢ DLQI improved by 25%-66.7%.

DLQI = Dermatology Life Quality Index; HS = hidradenitis suppurativa; PGA = Physician Global Assessment; SC = subcutaneous; SLE = Systemic lupus erythematosus; VAS = Visual Analogue Scale.

Th17 cells, resulting in IL-17 production, that further boosts neutrophilic recruitment, thus setting up a relentlessly progressive inflammatory cycle [71].

Baier and Barak were the first to demonstrate the profitability of guselkumab (100 mg, monthly dosing) in a 60-year-old woman having ulcerative PG, that was rapidly progressive with evident tendons, ligaments and muscles on inspection [72]. Prior treatment with adalimumab and infliximab was ineffective; with relapse occurring following an initial favorable response to ustekinumab (linked to the development of neutralizing antibodies). Within 3 months of guselkumab treatment, tremendous improvement of the lesion was evident with 95% reepithelization.

The use of a modified dose regimen for PG (guselkumab SC- 200 mg [week 0], 100 mg [week 4], 100 mg [week 10], and 100 mg [week 16]) was described to achieve complete healing of PG in a 49-year-old lady who had been recalcitrant to intralesional steroids, dapsone, systemic prednisolone, epifix biologic dressings, cyclosporine and adalimumab [73].

In another report, guselkumab (100mg, SC, label dosing) was highly effective in the management of ulcerative PG in a 78-year-old woman [74].

Pityriasis Rubra Pilaris

PRP is a rare idiopathic papulo-squamous disorder characterized by perifollicular keratotic papules that essentially coalesce to form orange-red scaly plaques, and palmoplantar keratoderma. [75] IL-23/Th17 axis is closely involved in the pathogenesis of PRP [76]. By blocking IL-23 release, guselkumab converts Th17 cells to regulatory T-cells (Tregs) and eventually modifies the immune disbalance [77].

Currently, there exist only case reports delineating the utility of guselkumab in PRP and is outlined in Table 5 [78-80].

Table 5. Reports Delineating the Utility of Guselkumab in Pityriasis Rubra Pilaris

Serial No.	Authors/Year	Details	Remarks
1	Pilz et al [78] 2019	Series of 2 patients with erythrodermic PRP: • Patient 1: 65-year-old male. • Patient 2: 75-year-old male. • Both patients were resistant to topical/ systemic corticosteroids. • Acitretin was ineffective in patient 1 and was contraindicated in patient 2. • Guselkumab (100 mg SC) was given at week 0, 4 and every 8 weeks. • In both patients immunohistochemical analysis of skin biopsy specimens revealed a distinct expression of IL-17.	• A rapid and drastic improvement at week 16 was witnessed in: o PGA score (80% reduction in both patients). o Body surface area (94.73% and 84.69% reduction in patient 1 and 2 respectively). o DLQI (93.3% and 89.47% reduction in patient 1 and 2 respectively).
2	Nagai et al [79] 2020	• 47-year-old woman diagnosed with PRP for a duration of 3 months with 90% BSA involvement. • Oral etretinate, and apremilast were ineffective. • Other failed treatments included bath-PUVA and topical steroids. • Guselkumab 100mg SC was administered (label dosing) after taking an informed consent from patient.	• After 4 weeks, slight reduction of erythema was noted. • At week 24, BSA had reduced to 2% from 90% and static Physician Global Assessment (sPGA) had reduced from 5 to 1. • Erythema and pruritus were completely absent 36 weeks after the last injection.
3	Nishimura et al [80] 2022	• A 60-year-old man with PRP who had failed to respond to systemic therapy that included methotrexate, retinoids and brodalumab. • Cyclosporine (100 mg/day) helped in markedly improving the skin rash after one week, but as patient was hypertensive, the dose of cyclosporine was reduced to 50 mg/day, that heralded relapse. • Guselkumab (100 mg SC, label dosing) was then started along with cyclosporine (50 mg/day)	• Improvement of PRP was evident by 12 weeks of guselkumab therapy. • Skin rash remained in complete remission at 9 months. • One year after initiation of guselkumab, cyclosporine was discontinued, and the skin rash remained well controlled.

BSA = body surface area; DLQI = Dermatology Life Quality Index; PGA = Physician Global Assessment; PRP = Pityriasis Rubra Pilaris; SC = subcutaneous.

Lichen Planus

LP is a common, chronic relapsing inflammatory disorder of the skin and mucous membranes which often poses a major therapeutic challenge due to its refractory course. IL-23 has been expounded as one of the key drivers of pro-inflammatory pathogenic Th17 cells, that are increasingly identified in lesions of both mucocutaneous and oral LP [81]. By impelling B lymphocyte-induced maturation protein 1(BLIMP 1), Th17 cells prompt the pathogenesis in LP, which if not controlled takes on a progressive course [82]. Guselkumab role in LP is linked to its inhibitory role against IL-23 release with subsequent antagonism of the entire inflammatory cascade [83].

Solimani et al reported guselkumab (100 mg SC, label dosing) to be highly effective in a 72-year-old female with recalcitrant erosive LP of the tongue for 5 years that had been unresponsive to systemic/topical corticosteroids [84]. Progressive amelioration of lesions was observed following initiation of guselkumab therapy with complete resolution by week 30.

Stewart-Treves Angiosarcoma

STA is a rare cutaneous angiosarcoma, that has a high rate of metastasis [85]. Immunohistochemical research has propounded IL-23 to have a significant role in tumor angiogenesis, via stimulating the Th17 pathway and eventual IL-17 production [86]. Additionally, IL-23 inhibits apoptosis, and recruits neutrophils and macrophages to the tumor site, promoting production of other cytokines, including vascular endothelial growth factor, that further supports tumor

progression [87,88]. By inhibiting IL-23, guselkumab may have a role here.

Esbeen and colleagues reported pronounced clinical improvement of STA of the left forearm in an 87-year-old woman following guselkumab (100 mg SC, monthly for 3 months) treatment [89]. After 3 months of therapy substantial reduction in tumor size, and forearm lymphoedema were observed. Also, satellite nodules that were attached to the lesion showed considerable regression. Apart from fatigue and headache, lasting for few days following guselkumab injection, no other side effects were encountered.

Adverse Effects

Common side effects include URTI, gastroenteritis, dermatophytes, herpes simplex, injection site reactions, arthralgia, bronchitis and diarrhea. These are usually mild, not requiring treatment interruption [90]. Rarely bullous pemphigoid and vitiligo have been encountered. [91,92] The occurrence of these cutaneous adverse effects may be due to alteration of cytokine pathways resulting in cytokine imbalances responsible for immunopathogenic mechanisms encountered here [93,94].

Monitoring Guidelines (Figure 3)

Availability, Administration and Dosing

Guselkumab injection is available as single dose (100 mg/ml) pre-filled syringes and as single dose (100 mg/ml) one-press patient-controlled injectors. It is dosed as 100 mg SC at weeks 0, 4, and then once every 8 weeks. It appears as a clear and colorless to light yellow solution that may contain small translucent particles. It needs to be stored at 2°-8°C, protected from light until use and should not be shaken. It needs to be kept out of refrigerator 30 minutes prior to injection. Injection sites include front of thighs, lower abdomen (except for a 2-inch area around the umbilicus) or, back of the arms (if administered by another person), and must not be erythematous, indurated, scaly or affected by psoriasis [90].

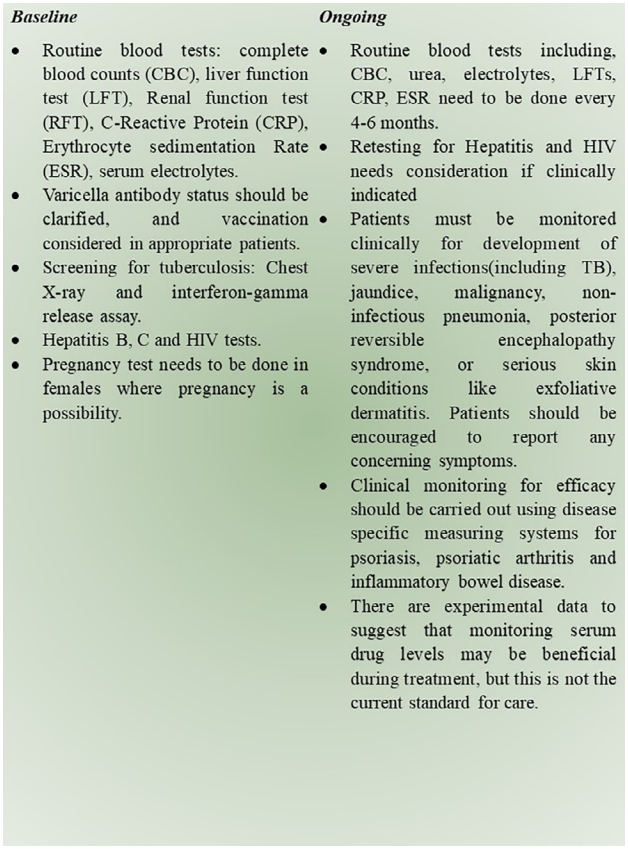

Figure 3. Monitoring guidelines for guselkumab.

Use in Specific Populations

Pregnancy

Based on available data, it is not known if taking guselkumab increases the chance of birth defects. Because guselkumab is an antibody, transfer of medication to the fetus might be low in early pregnancy, when organogenesis takes place. Further, currently it not known if guselkumab can result in any other pregnancy complications or behavioral and learning issues [95].

Lactation

At present no information is available on the clinical use of guselkumab during lactation. As guselkumab has a large molecular weight of around 144,000 Da, likelihood of its secretion in breast milk is very low [96]. Besides, guselkumab gets destroyed in the infant gastrointestinal tract making its absorption unlikely [97]. However, guselkumab still needs to be used with caution in this scenario, especially while nursing neonates. Waiting at least 2 weeks postpartum to resume treatment may minimize transfer to the infant [98].

Pediatric

To date, there are no clinical trials delineating the efficacy/safety of guselkumab in the pediatric population. Scientific evidence for the same is represented in few case reports wherein patients who were unresponsive to conventional anti-psoriasis treatment and at least one biologic drug achieved almost complete clinical remission with guselkumab without encountering any side effects [99-100]. Despite insufficient data, guselkumab can be a valuable addon in the therapeutic armamentarium of pediatric psoriasis.

Geriatric

Currently, data on guselkumab therapy for elderly patients in real world clinical practice is scant. Nonetheless, available phase III trials have demonstrated it to be effective and safe in elderly patients with no difference from younger patients [101].

Conclusions

Guselkumab is a newer agent for the management of psoriasis and PsA. It is also useful in the treatment of HS, PG, PRP and LP. Recently, its utility in STA and its propensity to reduce tumor size can have a promising role in the field of oncology.

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