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REVIEW

Positioning Guselkumab in The Treatment Algorithm of Patients with Crohn's Disease

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Abstract: Guselkumab, a selective interleukin-23 (IL-23) inhibitor, has emerged as a promising biologic therapy for the management of patients with moderate-to-severe Crohn's disease (CD) and has been recently approved for its treatment. Unlike conventional therapies, guselkumab offers a different mechanism of action by selectively inhibiting IL-23, a key cytokine implicated in the pathogenesis of CD. IL-23 drives intestinal inflammation through activation of the Th17 cell pathway and other immune processes, positioning IL-23 inhibition as a critical therapeutic approach. In randomized Phase III clinical trials, guselkumab proved to be effective in inducing clinical and endoscopic remission both in patients naive to biologics and in patients already exposed to advanced therapies. Furthermore, no safety issues were found, supporting the well-characterized safety in other indications and its use in clinical practice also in IBD. Moreover, guselkumab has been approved for other immunomediated inflammatory disease moderate to severe plaque psoriasis, psoriatic arthritis and ulcerative colitis. This review summarizes the available evidence on efficacy and safety of guselkumab in patients with moderate to severe CD, focusing on its positioning in the treatment algorithm.

Keywords: guselkumab, Crohn's disease, IL-23, selectivity, inflammatory bowel disease

Introduction

Crohn's disease (CD) is a progressive and relapsing inflammatory bowel disease (IBD) requiring long-term therapeutic management.[1] Over the past two decades, treatment targets have evolved significantly shifting from symptomatic relief to clinical, biochemical, and endoscopic remission, with the ambition of reaching deeper targets such as transmural healing.[2,3] Despite the development of new molecules, approximately 50% of patients have suboptimal disease control.[4,5] Moreover, while anti-TNF agents are effective, their use is limited by immunogenicity and infection risk.[2] Vedolizumab and ustekinumab offer improved safety profiles but show slower onset or limited efficacy in some patients.[2] Upadacitinib shows rapid symptom control but raises concerns regarding safety.[6] This unmet need has driven interest in novel therapeutic targets with increasingly selective mechanisms of action in order to obtain greater effectiveness while reducing the risk of adverse events.

Interleukin-23 (IL-23) is recognized as a central cytokine in the pathogenesis of CD, contributing to the activation and maintenance of Th17 cells and promoting a cascade of inflammatory processes that sustain mucosal inflammation.[7] Ustekinumab, a monoclonal antibody targeting the shared p40 subunit of IL-12 and IL-23, was the first drug in class to be approved for the treatment of CD.[8] A head-to-head trial, the SEAVUE trial, demonstrated the non-inferiority of

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ustekinumab compared to TNFα inhibitors in terms of efficacy and safety, supporting its use as first line treatment in biologic-naïve patients with CD.[9] Guselkumab is a new IL-23 inhibitor that selectively binds to the p19 subunit showing promising efficacy and safety results in CD clinical trials.[10,11] Despite the similar mechanism of action, guselkumab differs from other IL-23 inhibitors in molecular structure.[12]

This review summarizes the available evidence on guselkumab's efficacy and safety in CD, examining its mechanism of action and its potential role within the evolving therapeutic landscape. We will also discuss how guselkumab could be integrated into current treatment algorithm, its potential advantages and limitations, and ongoing research that may further clarify its positioning in CD management.

Materials and Methods

We conducted a comprehensive search of the PubMed, Embase, and Scopus databases up to March 2025, with the aim of identifying studies regarding patients with IBD treated with guselkumab. To achieve this, we employed specific search terms such as 'guselkumab', in conjunction with "Crohn's disease", "CD", "inflammatory bowel disease", "IBD", "Immunomediated inflammatory diseases", "IMIDs". We limited our search to articles published in the English language.

Our screening process involved two independent reviewers (SB and FD) who initially assessed titles and abstracts to identify potentially relevant studies. Subsequently, we examined the full texts of these selected articles to determine their eligibility for inclusion. Additionally, we manually scrutinized the reference lists of these articles to ensure that no relevant studies were overlooked during the electronic search. The final inclusion of abstracts and articles was based on their relevance to our research objectives.

Mechanism of Action

IL-23 is a cytokine composed of the a p19 and p40 subunits, playing a pivotal role in the differentiation, expansion, and maintenance of Th17 cells, which are key drivers of inflammation in conditions like CD and ulcerative colitis (UC).[13] By selectively binding to the p19 subunit, anti-IL-23 agents inhibit the IL-23 pathway without affecting IL-12, which shares the p40 subunit.[14] Targeted inhibition of IL-23 demonstrates superior efficacy compared to dual inhibition of IL-12 and IL-23 but the underlying reason remains unclear.[15] However, this enhanced efficacy could be explained by a higher binding affinity for IL-23 providing greater potency in IL-23 inhibition, or the potential protective role of IL-12 in maintaining the gut microenvironment against inflammation.[16,17] This specificity reduces the activation of Th17 and other IL-23-dependent inflammatory cells, ultimately decreasing the production of pro-inflammatory cytokines such as IL-17 and IL-22.[13] Furthermore, the rationale behind selectively targeting the p19 subunit of IL-23 is to improve safety by preserving the normal IL-12-mediated Th1 immune response, which is essential for protection against intracellular pathogens that trigger interferon-gamma release from T and NK cells.[18] This strategy maintains the therapeutic benefits of p40 antibodies while minimizing potential interference with immune function.[19] Of note, the IL-12-driven Th1 response plays a critical role in susceptibility to infections such as mycobacterial diseases, pneumocystis jiroveci, Cryptococcus neoformans, and toxoplasma gondii.[20] By selectively targeting the IL-23p19 subunit while preserving IL-12 activity, it may be possible to retain host immunity against a broad range of pathogens.[19] To date, several IL-23 inhibitors are available or are being tested in the field of IBD including risankizumab, mirikizumab, and guselkumab.[7,21] However, despite belonging to the same class of biologic agents, these molecules have distinct molecular characteristics. Preclinical studies showed that CD64+ myeloid cells were elevated in the inflamed colon of patients with IBD correlating with disease severity on endoscopy.[22] Interestingly, guselkumab demonstrated dual functionality by engaging CD64+ myeloid cells via its Fc region while simultaneously neutralizing IL-23 with high affinity and potency.[12,23] However, the clinical relevance of those findings still need to be established.

Efficacy and Safety of Guselkumab

The role of guselkumab in moderate-to-severe CD was assessed in a Phase 2 trial (GALAXI-1)[10] and in Phase 3 trials (GALAXI-2, GALAXI-3 and GRAVITI).[24–27]

In GALAXI-1, a double-blind, placebo-controlled Phase 2 trial, patients were randomized into five groups to receive either intravenous (IV) guselkumab at doses of 200 mg, 600 mg, or 1200 mg at weeks 0, 4, and 8; IV ustekinumab at

approximately 6 mg/kg at week 0 followed by 90 mg subcutaneously at week 8; or placebo. The primary endpoint was the change in CD Activity Index (CDAI) from baseline. Of the 309 participants, nearly 50% had prior biologic failure. By week 12, each guselkumab dose group showed a significantly greater reduction in CDAI from baseline compared to placebo (least squares mean: 200 mg: −160.4, 600 mg: −138.9, 1200 mg: −144.9 versus placebo: −36.2; all P<0.05). Additionally, a significantly higher proportion of patients receiving guselkumab achieved clinical remission (CDAI <150) compared to placebo (57.4%, 55.6%, and 45.9% vs 16.4%; all P<0.05) (Table 1). Safety profiles were similar across groups, with comparable adverse event (AE) rates by week 12 (placebo: 60.0%; combined guselkumab: 45.7%; ustekinumab: 50.7%) (Table 2).

Following the promising induction results, guselkumab was further evaluated for the maintenance phase in a randomized, multicenter, double-blind Phase 2 trial in adult CD patients.[11] In total, 309 participants (112 biologic-naïve and 197 biologic-experienced) were randomly assigned to one of five regimens, including three arms with guselkumab IV induction followed by subcutaneous (SC) maintenance (guselkumab 200 mg IV at weeks 0, 4, and 8, then 100 mg SC every 8 weeks; guselkumab 600 mg IV at weeks 0, 4, and 8, then 200 mg SC every 4 weeks; guselkumab 1200 mg IV at weeks 0, 4, and 8, then 200 mg SC every 4 weeks), an ustekinumab group, used as a reference arm; (approximately 6 mg/kg IV at week 0, then 90 mg SC every 8 weeks) and a placebo group with a crossover to ustekinumab at week 12 for non-responders. At week 48, clinical remission (CDAI <150) rates were 64% (200→100 mg guselkumab), 73% (600→200 mg), and 57% (1200→200 mg), with 59% in the ustekinumab group. Similarly, endoscopic response (≥50% SES-CD improvement or SES-CD ≤2) rates were 44%, 46%, and 44% for the guselkumab groups and 30% for ustekinumab. Endoscopic remission (SES-CD ≤2) was achieved in 18%, 17%, and 33% of the guselkumab groups and 6% of the ustekinumab group. Regarding immunogenity, antibodies to guselkumab were detected in three (1%) of 215 patients up to week 48; none were positive for neutralising antibodies. Safety findings up to week 48 indicated comparable AE rates among groups, with infection rates, primarily nasopharyngitis and upper respiratory infections, similar between guselkumab and ustekinumab. No active tuberculosis, opportunistic infections, or deaths were reported.

GALAXI 2 (508 participants) and GALAXI 3 (513 participants) are two identical 48-week phase 3 double blinded, treat-through confirmatory studies, with ongoing long-term extension, in which efficacy and safety of guselkumab in moderate-to-severe CD were evaluated and presented as combined (pooled) analysis for both trials.[27] Patients were randomized 2:2:2:1 to guselkumab 200 mg IV at week 0, 4, and 8, then 100 mg SC every 8 weeks (q8w), guselkumab 200 mg IV at week 0, 4, and 8, then 200 mg SC every 4 weeks (q4w), ustekinumab IV at 6 mg/kg at week 0 followed by 90 mg SC at week 8, or placebo. Approximately two-thirds of patients treated with guselkumab (overall population) achieved clinical response at week 12. At week 48, guselkumab demonstrated superior efficacy compared to ustekinumab across several key endpoints. In terms of endoscopic response, guselkumab achieved significantly higher rates than ustekinumab. Specifically, 47.9% of participants receiving guselkumab 200 mg IV every 4 weeks (q4w) followed by 100 mg SC q8w and 52.7% of those transitioning to 200 mg SC q4w achieved an endoscopic response, compared to 37.1% in the ustekinumab group. This resulted in differences of +15.6% ($p < 0.001$) and +10.6% ($p = 0.009$) for the two guselkumab regimens, respectively, when compared to UST. For endoscopic remission, 33.2% of patients in the guselkumab 100 mg SC group and 37.2% in the guselkumab 200 mg SC group achieved remission, compared to only 24.7% in the ustekinumab group. There were differences in achieving endoscopic remission of +12.3% ($p = 0.001$) and +8.5% ($p = 0.024$) for the respective guselkumab regimens compared to ustekinumab. When considering clinical remission combined with endoscopic response, guselkumab again outperformed ustekinumab. A total of 41.6% of patients in the guselkumab 100 mg SC group and 47.3% in the guselkumab 200 mg SC group achieved this combined outcome, compared to 33.7% in the ustekinumab group, with differences of +13.6% ($p < 0.001$) and +7.8% ($p = 0.049$), respectively. Deep remission, defined as both clinical and endoscopic remission, was also more frequently achieved with guselkumab. Rates were 29.7% for guselkumab 100 mg SC and 33.8% for guselkumab 200 mg SC, compared to 22.3% with ustekinumab. These differences were statistically significant at +11.3% ($p = 0.002$) and +7.4% ($p = 0.040$), respectively. Finally, for clinical remission, guselkumab demonstrated rates of 65.4% and 70.3% for the 100 mg SC and 200 mg SC groups, respectively, compared to 62.9% in the ustekinumab group. While the differences were smaller (+7.3% [$p = 0.058$] and +2.6% [$p = 0.512$]), the results still suggest a trend favoring guselkumab for this outcome.

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Table 1 Efficacy of Guselkumab in Moderate-to-Severe Crohn's Disease

Author	Patients	Dose (Number of Patient)	Efficacy					
GALAXI-1 Induction phase (week 12)	**309**		***Primary Endpoints***	***Secondary Endpoints***				
			Change from baseline in CDAI (least squares mean)	**Clinical remission (%)**	**Clinical response (%)**	**PRO-2 remission (%)**	**Clinical-biomarker response (%)**	**Endoscopic response (%)**
		GUS 200 mg IV q4w	−160.4	57.4	70.5	44.3	54.1	37.7
		GUS 600 mg IV q4w	−138.9	55.6	66.7	50.8	49.2	36.5
		GUS 1200 mg IV q4w	−144.9	45.9	60.7	32.8	37.7	32.8
		GUS combined	−148	53.0	65.9	42.7	47.0	35.7
		UST 6mg/kg IV→90 mg sc	−135.9	46.0	66.7	39.7	46.0	28.6
		PBO	−36.2	16.4	24.6	16.4	6.6	11.5
GALAXI-1 Maintenance phase (week 48)	**309**		***Primary and major secondary endpoints***					
			Clinical remission (%)	**Clinical response (%)**	**PRO-2 remission (%)**	**Endoscopic remission (%)**	**Endoscopic response (%)**	**Endoscopic remission (alternative definition) (%)**
		GUS 200→100 mg SC q8w	64	74	57	18	44	26
		GUS 600→200 mg SC q4w	73	84	70	17	46	30
		GUS 1200→200 mg SC q4w	57	67	51	33	44	39
		90 mg SC q8w	59	68	46	6	30	14

Notes: Clinical remission, CDAI score <150; clinical response: ≥ 100-point reduction from baseline in CDAI score or CDAI score <150); PRO-2 remission: the unweighted CDAI component of daily abdominal pain (AP) score 1, and the unweighted CDAI component of daily average stool frequencies (SF) score 3 (ie, AP 1 and SF 3 and no worsening from baseline); endoscopic response: at least 50% improvement from baseline in Simple Endoscopic Score for CD (SES-CD) or SES-CD score 2; clinical-biomarker response: clinical response and ≥ 50% reduction from baseline in C-reactive protein (CRP) or fecal calprotectin; endoscopic remission: SES-CD ≤ 2. Endoscopic remission (alternative definition): SES-CD ≤ 4, at least a 2-point reduction versus baseline, and no subscore greater than 1 in any individual variable.

Abbreviations: GUS, Guselkumab; UST, Ustekinumab; IV, intravenous; SC, subcutaneous; qW4, every 4 weeks; qW8, every 8 weeks; PBO, placebo; CDAI, Clinical Disease Activity Index; PRO-2, Patient Reported Outcomes-2.

Table 2 Safety of Guselkumab in Moderate-to-Severe Crohn's Disease

Author	Patients	Dose (Number of Patient)	Safety		
GALAXI-1 Induction phase (week 12)	**309**		***AEs (%)***	***SAEs (%)***	***Infections (%)***
		GUS 200 mg IV q4w	43.8	4.1	12.3
		GUS 600 mg IV q4w	50.7	5.5	17.8
		GUS 1200 mg IV q4w	42.5	1.4	15.1
		GUS combined	45.7	3.7	15.1
		UST 6mg/kg IV→90 mg sc	50.7	5.6	12.7
		PBO	60	5.7	21.4
GALAXI-1 Maintenance phase (week 48)	**309**		***AEs (%)***	***SAEs (%)***	***Infections (%)***
		GUS 200→100 mg SC q8w	71	8	34
		GUS 600→200 mg SC q4w	81	7	41
		GUS 1200→200 mg SC q4w	70	7	34
		PBO only	66	9	24
		Ustekinumab crossover*	63	0	35
		Ustekinumab only	85	13	37

Notes: *Patients who did not respond to placebo and crossed over to ustekinumab at week 12.
Abbreviations: AE, adverse event; SAE, serious adverse event; GUS, Guselkumab; UST, Ustekinumab; IV, intravenous; SC, subcutaneous; qW4, every 4 weeks; qW8, every 8 weeks; PBO, placebo.

Interestingly, the majority of guselkumab-treated patients who achieved clinical response after induction achieved clinical remission (77% and 83.5% with guselkumab 200mg IV→100mg SC q8w and guselkumab 200mg IV→200mg SC q4w respectively) and endoscopic response (58.4% and 60.4% with guselkumab 200mg IV→100mg SC q8w and guselkumab 200mg IV→200mg SC q4w respectively) at week 48. Similarly, PRO-2 remission (defined as an average daily abdominal pain score ≤1 and stool frequency score ≤3, with no worsening from baseline in either measure) was reached by 71.3% of patients on 100 mg and 75.8% on 200 mg.[24] Importantly, among the guselkumab-treated participants who achieved the clinical endpoints, 93–97% were corticosteroid-free for at least 90 days before week 48. This highlights the potential of guselkumab to not only achieve sustained clinical remission but also reduce dependency on corticosteroids, a critical goal in managing CD. Among participants with elevated baseline concentrations of C-reactive protein (>3 mg/L) or faecal calprotectin (>250 mg/kg), guselkumab was associated with clinically meaningful reductions of both through week 12 and out to week 48. Furthermore, efficacy at week 48 was also observed in patients who had not achieved a clinical response at week 12, with clinical response, endoscopic response, and PRO-2 remission rates of 55.6%, 36.7%, and 46.7% for the 100 mg SC q8w group, and 58.3%, 47.9%, and 49.0% for the 200 mg SC q4w group, respectively.[24] These findings suggest that continued treatment with guselkumab may offer benefit even for those who do not experience an early clinical response.[24]

GRAVITI was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study with a treat-through design that evaluated the efficacy and safety of 12 weeks of guselkumab SC induction therapy followed by SC maintenance therapy. In total, 347 participants were randomized 1:1:1 to guselkumab 400 mg SC q4w→100 mg SC q8w (n=115); guselkumab 400 mg SC q4w→200 mg SC q4w (n=115); or placebo SC (n=117).[25] Particularly in this trial, the efficacy and safety of SC guselkumab were specifically evaluated for both the induction phase and the maintenance phase, highlighting its use as a SC formulation from the onset of treatment. Guselkumab 400mg SC induction demonstrated superiority to placebo at week 12 (56.1% vs 21.4% for clinical remission and 41.3% vs 21.4% for endoscopic response, $p<0.001$). These results were comparable to the effect observed in GALAXI 2 and 3 trials at

week 12 following the 200mg iv induction. Moreover, both SC maintenance dose regimens were also superior to placebo at week 24 (clinical remission of 60.9% and 58.3% compared to 21.4%, p<0.001) and 48 (for clinical remission 60% and 66.1% compared to 17.1%, p<0.001; for endoscopic response 44.3% and 51.3% compared to 6.8%). Interestingly, guselkumab achieved higher rates of clinical endpoints compared to those observed with ustekinumab. However, it stands out in its ability to deliver a significant advantage in endoscopy-driven outcomes, an essential marker of mucosal healing and long-term disease control in CD. This balance of robust clinical efficacy and strong endoscopic performance highlights its potential as a valuable option for addressing both symptomatic relief and underlying inflammation in this patient population. Median CRP concentrations decreased through week 48 with guselkumab compared with placebo. Among participants with an elevated CRP (>5 mg/L) at baseline, 40.7% and 44.3% of patients receiving guselkumab 400 mg SC q4w→100 mg SC q8w group and guselkumab 400 mg SC q4w→200 mg SC q4w respectively achieved CRP normalization (≤5 mg/L) at week 48 versus placebo (2.9%). Median fecal calprotectin concentrations decreased with guselkumab treatment through week 48 compared with placebo. Among participants with fecal calprotectin levels (>250 µg/g) at baseline, 37.3% and 39.2% of patients receiving guselkumab 400 mg SC q4w→100 mg SC q8w group and guselkumab 400 mg SC q4w→200 mg SC q4w respectively achieved levels that were below ≤250 µg/g at week 48 versus placebo (3.5%). Improvements with guselkumab treatment were observed as early as week 4 (the timepoint at which the first assessment was performed) and were maintained through 48 weeks. Greater proportions of patients treated with guselkumab achieved clinical response through week 12 versus placebo, with greater responses observed as early as week 4.

Safety findings were consistent with the known safety profile of guselkumab in approved indications. The numbers of guselkumab-treated patients with serious infections were low compared to placebo (1.5% vs 0%). AEs were similar between guselkumab-treated patients and placebo (80.3% vs 65.8%). In conclusion the rates of clinical and endoscopic endpoints achieved at the end of induction were consistent with those observed in the GALAXI program. Longer-term data at week 24 and week 48 further confirm that the SC formulation is both safe and effective, making it a suitable option for use based on patient characteristics and physician preference.

Two ongoing studies, FUZION CD (NC T05347095)[28] and REASON (NCT06408935),[29] are currently investigating guselkumab in CD. The FUZION CD trial focuses on evaluating its efficacy in managing fistulizing perianal CD, while the REASON study evaluates the efficacy of guselkumab in healing of all layers of the digestive tract (transmural healing).

Efficacy of Guselkumab in Bio-Naïve and Bioexposed Patients

A pooled analysis showed that in biologic-naïve patients, 49.6% achieved clinical remission at week 12 with guselkumab 200 mg IV q4w compared to 16.4% with placebo (Δ 32.1%P<0.001).[30] Among those with previous biologic exposure, remission rates were 46% for guselkumab versus 19.2% for placebo (Δ 26.9% P<0.001).[30] By week 12, an endoscopic response (≥50% improvement from baseline in SES-CD or SES-CD ≤ 2) was achieved in 46.3% of biologic-naïve patients receiving guselkumab compared to 18% with placebo (Δ 27.7%, P<0.001), highlighting a significant improvement.[30] For biologic-experienced patients, endoscopic response rates were 29% with guselkumab versus 6.4% with placebo (Δ 22.6%, P<0.001), underscoring a substantial benefit.[30] Additionally, long-term composite outcomes were assessed, including clinical response (≥100-point reduction from baseline in CDAI or CDAI < 150) at week 12 followed by clinical remission at week 48, as well as clinical response at week 12 combined with endoscopic response at week 48.[30] For biologic-naïve patients, the composite endpoint of clinical response at week 12 followed by clinical remission at week 48 was achieved by 51.7% of those receiving 100 mg SC guselkumab and 54.7% of those on 200 mg SC guselkumab, compared to just 11.5% in the placebo group (all p<0.001).[30] Among biologic-experienced patients, the outcome was reached by 45.8% in the 100 mg group and 49.7% in the 200 mg group, compared to 12.8% with placebo (all p<0.001).[30] For the composite endpoint of clinical response at week 12 plus endoscopic response at week 48, similar results were detected.[30] In biologic-naïve patients, this outcome was observed in 40.5% of those in the 100 mg SC guselkumab group and 43.8% in the 200 mg group, compared to 6.6% in the placebo group (all p<0.001). In biologic-experienced patients, 35.9% in the 100 mg group and 31.3% in the 200 mg group achieved the endpoint, compared to only 5.1% in placebo (all P<0.001).[30] These results indicate that guselkumab, at both 100 mg and 200 mg dosages,

provides robust efficacy in achieving both clinical and endoscopic outcomes across CD population, regardless of prior biologic exposure.[30]

In addition, at week 48, both guselkumab dose groups (100mg and 200mg) showed superior rates of endoscopic response, endoscopic remission (SES-CD ≤ 4 and a ≥2-point reduction from baseline and no subscore greater than 1 in any individual component), and composite outcomes of clinical remission plus endoscopic response, as well as clinical remission plus endoscopic remission (deep remission), in both the biological-experienced patients and biological-naïve subgroups, compared to the ustekinumab group.[31] In the biological-experienced patients, both guselkumab doses also demonstrated higher rates of clinical remission at week 48 compared to ustekinumab (60.8% and 63.9% vs 52.6%, p=0.132 and p=0.043, respectively) while clinical remission rates in the biological-naïve subgroup were similar between the two treatments (73.3% 76.6% vs 75.2%, p=0.755 and p=0.784, respectively).[31] Over 90% of patients successfully reached their endpoints without relying on steroids.

Additionally, a post-hoc analysis of the GALAXI 2 and GALAXI 3 studies was performed to specifically assess the efficacy of guselkumab in biologic-naïve patients with a disease duration of ≤2 years.[32] Among the 426 biologic-naïve patients included in the pooled analysis, 180 were identified as having a disease duration of ≤2 years. Among these patients, those treated with guselkumab 200 mg IV demonstrated significantly better outcomes compared to placebo at week 12. Clinical response rates and clinical remission rates were higher in the guselkumab group (67.3% vs 25.0%, Δ=42.3%, p<0.001, and 51.0% vs 16.7%, Δ=30.8%, p=0.002 respectively). Additionally, endoscopic response rates at week 12 favored guselkumab (49.0% vs 29.2%; Δ=19.9%; p=0.058). Patients receiving either guselkumab 100 mg SC or 200 mg SC showed greater proportions achieving combined clinical response at week 12 and clinical remission at week 48 compared to placebo. Specifically, 57.1% of patients on the guselkumab 200 mg IV qw4 → 100 mg SC q8w regimen and 58.2% on the guselkumab 200 mg IV q4w→ 200 mg SC q4w regimen reached these endpoints, while only 8.3% of placebo-treated patients did (p<0.001). Similarly, clinical response at week 12 combined with endoscopic response at week 48 showed improved outcomes, with 49.0% of patients achieving these endpoints on guselkumab 200 mg IV qw4 → 100 mg SC q8w and 38.2% on guselkumab 200 mg IV q4w→ 200 mg SC q4w, compared to none in the placebo group (p<0.001).

At week 48, when compared to ustekinumab, guselkumab 100 mg SC and 200 mg SC demonstrated higher proportions of patients achieving endoscopic response (61.2% and 58.2% vs 40.4%), endoscopic remission (46.9% and 50.9% vs 30.8%), combined clinical remission and endoscopic response (57.1% and 52.7% vs 40.4%), and deep remission (44.9% and 49.1% vs 28.8%). Furthermore, guselkumab-treated patients achieved notably high levels of clinical remission by week 48 (73.5% and 83.6% for guselkumab 100 mg SC and 200 mg SC respectively).

Guselkumab demonstrated comparable efficacy in both biologic-naïve and biologic-experienced patients, underscoring its versatility across different treatment histories. Notably, the data suggest an apparent advantage of early intervention, where initiating guselkumab treatment within the early stages of CD may enhance outcomes by addressing inflammation before irreversible structural damage occurs. This highlights the potential value of timing in maximizing therapeutic benefit.

Guselkumab in Other Immunomediated Inflammatory Diseases

Guselkumab is emerging as a therapeutic option for several immune-mediated inflammatory diseases. It is already approved by the European Medicines Agency (EMA) for the treatment of moderate to severe plaque psoriasis in adults, particularly when topical treatments are insufficient. It is also authorized for use in psoriatic arthritis, either alone or in combination with methotrexate, for patients who have not responded adequately to disease-modifying antirheumatic drugs.[33]

Moreover, the role of guselkumab has been investigated in moderate-to-severe UC. Particularly, the efficacy and safety of guselkumab as induction therapy in moderate to severe UC were evaluated in the QUASAR trial, a randomized, double-blind phase IIb/III study. A total of 701 patients, who had previously received conventional or advanced therapies, were enrolled. Participants were assigned to receive either placebo or guselkumab at doses of 200 mg or 400 mg every 4 weeks. At week 12 of the induction phase, clinical response rates were significantly higher in the guselkumab groups compared to placebo: 61.4% in the 200 mg group and 60.7% in the 400 mg group, versus 27.6% in

the placebo group (p<0.001). Safety outcomes were generally consistent with prior studies for approved indications. Serious AEs occurred at a rate of 1% in both guselkumab groups, compared to 5.7% in the placebo group. The rate of AEs leading to discontinuation was also lower in the guselkumab groups (0.5%) compared to placebo (1.9%). Infection rates were similar between guselkumab (10.6% and 11.4%) and placebo (11.4%), with no serious infections in the guselkumab groups compared to 1.9% in the placebo group. Importantly, no deaths occurred throughout the study.[34]

Guselkumab proved its efficacy also as maintenance therapy for UC.[35] Patients who achieved a clinical response 12 weeks after receiving intravenous guselkumab during the induction phase (QUASAR trial) were randomly assigned in a 1:1:1 ratio at the start of the maintenance phase. In total, 568 patients who had responded to guselkumab during induction were randomized to receive either guselkumab 200 mg SC q4w (33%, 190 patients), guselkumab 100 mg SC q8w (33%, 188 patients), or placebo (guselkumab withdrawal, 33%, 190 patients). The primary endpoints of the study were clinical remission at week 12 of induction and at week 44 of maintenance. At week 12, clinical remission was observed in a significantly greater proportion of patients treated with guselkumab IV (23%, 95 of 421 patients) compared to those receiving placebo (8%, 22 of 280 patients), with an adjusted treatment difference of 15% (95% CI, 10–20; p<0.0001). During the maintenance phase at week 44, clinical remission was achieved by a significantly higher proportion of patients receiving guselkumab SC 200 mg q4w (50%, 95 of 190 patients; adjusted treatment difference of 30%, 95% CI, 21–38; p<0.0001) or 100 mg q8w (45%, 85 of 188 patients; adjusted treatment difference of 25%, 95% CI, 16–34; p<0.0001) compared to those on placebo (19%, 36 of 190 patients). The safety profile of guselkumab was favorable and aligned with its established use in approved indications. In the induction study, adverse events occurred in 49% of patients in both groups (208 of 421 guselkumab-treated patients and 138 of 280 placebo-treated patients). Serious adverse events were reported in 3% (12 of 421) of guselkumab-treated patients and 7% (20 of 280) of placebo-treated patients, while adverse events leading to treatment discontinuation occurred in 2% (7 of 421) of guselkumab-treated patients and 4% (11 of 280) of placebo-treated patients.

In the maintenance study, the rates of adverse events were similar across all groups (placebo, guselkumab 100 mg SC q8w and guselkumab 200 mg SC q4w), with the most commonly reported events being ulcerative colitis (30%, 9% and 13%, respectively), COVID-19 (14%, 13% and 9%, respectively), and arthralgia (7%, 4% and 8%, respectively). Notably, no cases of active tuberculosis, anaphylaxis, serum sickness, or clinically significant hepatic disorders were reported in either study.

Moreover, a phase 2 randomized study evaluated guselkumab in patients with moderate-to-severe hidradenitis suppurativa.[36] At Week 16, hidradenitis suppurativa clinical response was achieved by 50.8% SC and 45.0% IV of patients vs 38.7% with placebo, without statistical significance. Patient-reported outcomes also showed modest improvements. Guselkumab was well tolerated but did not meet the primary efficacy endpoint.

Guselkumab has also been evaluated in pregnancy in other IMIDs, providing preliminary insights into its safety profile during gestation.[37] Lin et al[38] reported pregnancy outcomes following maternal exposure to guselkumab using data from the Janssen Global Safety Database through July 12, 2023. A total of 586 patients were exposed to guselkumab, and 590 pregnancy outcomes were reported, including outcomes of known or unknown status, two twin pregnancies, and one triplet pregnancy. Among the 178 cases with known pregnancy outcomes, 63.5% resulted in live births (113 cases). Spontaneous abortions accounted for 22.5% (40 cases), while elective terminations without known fetal defects or with unknown fetal status represented 6.7% (12 cases). Other outcomes included ectopic pregnancies (3.4%, 6 cases), induced abortions (1.1%, 2 cases), fetal deaths (1.1%, 2 cases), elective terminations due to fetal defects (0.6%, 1 case), missed abortion (0.6%, 1 case), and unspecified abortion (0.6%, 1 case). No cases of live birth with congenital anomalies, unspecified abortion (with no fetal defects or unknown), or stillbirth were reported.

Discussion

Guselkumab, a monoclonal antibody that selectively inhibits IL-23, has been shown to be effective and safe in patients with moderate-to-severe CD and has been recently approved by regulatory authorities. Several factors make it an attractive drug. First of all, its effectiveness both in naive patients and in patients already exposed to advanced therapies. In line with literature data on other drugs,[10,11,30,31] guselkumab has greater efficacy in naïve patients but excellent results are also reported in patients already treated with other advanced drugs, supporting its use in both settings.

Importantly, both IV and SC administrations are effective in inducing disease remission and there are two different dosages of SC drug for maintenance. This certainly represents a strength of guselkumab. Clinicians could be flexible preferring the IV or SC administration route based on patient preferences and adapting the drug dose based on clinical needs or the risk of side effects. Furthermore, the easy handling of guselkumab could differentiate it from other selective IL-23 inhibitors that do not include an induction phase with SC drugs. Additionally, guselkumab showed to be safe and well-tolerated.[11] No safety issues were found in the CD Phase II and phase III trials with low rates of serious AEs and no reports of active tuberculosis or opportunistic infections.[11] No increased risk of thrombotic, cardiovascular, or neoplastic events has been reported, thus differentiating it from other drugs such as JAK inhibitors.[39] However, as with other biologics, caution is advised in patients with active infections, latent tuberculosis, or a history of hypersensitivity reactions to monoclonal antibodies.[33] In patients with liver comorbidities, in the absence of comparative studies and further specific data, it is reasonable to hypothesize that guselkumab may be preferred over other IL-23 inhibitors to avoid any complications. Unlike other biologics, guselkumab does not induce significant immunogenic responses, a key factor in maintaining long-term efficacy and avoiding complications associated with immune system dysregulation.[40] This could allow it to be distinguished from TNFα inhibitors, which often require monitoring of drug levels to adapt the dosage and combination with immunosuppressants to reduce the risk of developing autoantibodies.[41]

The crucial point remains the positioning of guselkumab in the therapeutic algorithm and the definition of the drivers for choosing this drug. For decades, TNFα inhibitors have been the first line therapy in CD as they have a confirmed efficacy, long-term safety, and low economic impact given the availability of biosimilars.[42] TNF antagonists remain a cornerstone in the treatment of CD patients presenting with high-risk disease features, such as perianal disease, penetrating complications,[43] or stricturing involvement.[44] However, the recent development of biosimilars of ustekinumab and the confirmed non-inferiority compared to anti-TNF agents could change the therapeutic scenario.[9,45]

In non-responders to TNF inhibitors, there is a significant increase in the expression of genes related to the IL-23R-dependent signaling pathway compared to those who respond positively to TNF therapy.[46] These findings suggest that patients who are refractory to TNF inhibitors might benefit from targeted therapies that focus on IL-23. This strategy allows for the escalation to more targeted therapies when first-line treatments fail to achieve the desired clinical response, potentially improving long-term outcomes.

Unfortunately, there is limited data comparing mirikizumab, guselkumab, and risankizumab directly in clinical studies. For this reason, research clarifying pharmacokinetic differences and head-to-head studies to compare their efficacy and safety will be essential to differentiate them and understand which drug to prefer.

It should also be underlined that there are still unmet needs inherent to guselkumab. Indeed, long-term efficacy data are limited, with data available for up to 48 weeks of treatment preventing a thorough understanding of the drug's sustained benefits. However, experience with guselkumab in plaque psoriasis and psoriatic arthritis demonstrated an excellent long-term safety profile up to 5 years with no increased risk of infections, malignancies, or cardiovascular events.[47] For this reason, guselkumab could be beneficial for the management of special populations such as elderly patients or those with a history of cancer, where the use of other drugs may raise concerns.[48–50]

Additionally, there is no real world data. While clinical trials often provide optimistic outcomes, they may not fully reflect the diverse range of patient experiences outside controlled settings. Given the growing availability of new drugs, data regarding the efficacy of guselkumab in so-called difficult-to-treat patients (eg complex disease manifestations, failure to multiple biologics, or post operative recurrence) is lacking.[51] Dual therapy might be a potential strategy to break the therapeutic ceiling and maximize therapeutic outcomes.[52] In the VEGA trial,[53] a fixed dose combination of guselkumab and golimumab demonstrated superior efficacy in UC compared to monotherapy, providing a rationale for similar strategies in CD. DUET CD trial (NCT05242471) is currently ongoing, which aims to explore the potential of combining guselkumab with golimumab for patients with CD.[54] This study could inform how such a new compound might enhance efficacy, especially in patients with more refractory disease.

Since few comparative studies are available between advanced therapies in order to define the best positioning in the therapeutic algorithm, based on the available data, guselkumab could be considered both as the first line for the

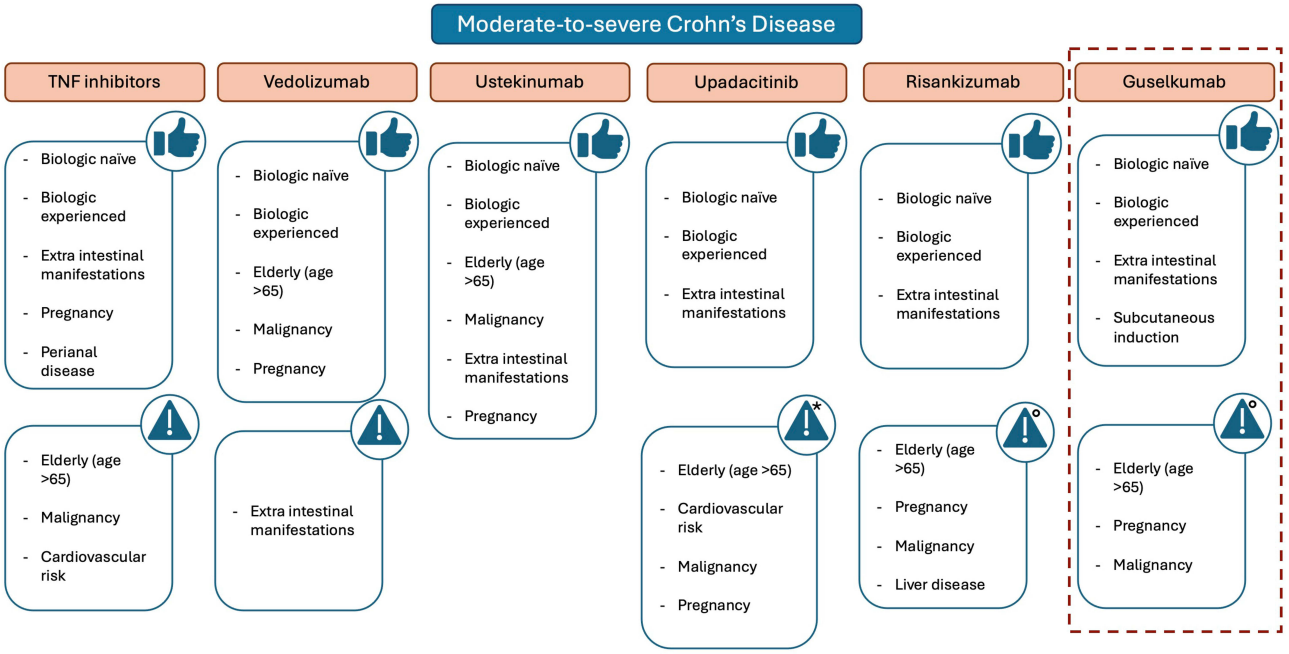

Figure 1 Pros and cons of available advanced therapies in Crohn's disease. *Data extrapolated from studies on other immune-mediated inflammatory diseases o Missing data.

management of patients with moderate-severe CD (in case of contraindications to the TNF inhibitor), either as a second or subsequent line of therapy. Several factors will influence clinicians choice including the severity of the disease, the rapidity of action, the route and interval of administration, as well as the cost, the safety profile, and the possibility of combination with another advanced therapy (Figure 1).

Conclusion

Guselkumab is a promising new option for the management of moderate-to-severe CD with several advantages including efficacy in bio-naïve and bio-exposed patients, convenient SC administration, reassuring safety profile, and potential use in special populations. In relation to the current efficacy and safety data, it is reasonable to hypothesize that guselkumab may even be better than other IL-23 inhibitors especially in particular sub settings. However, long-term data, real-world evidence, and direct comparisons with other molecules are necessary for optimizing its role in the treatment landscape of CD and for advancing personalized treatment strategies. Future research should also explore its positioning in specific disease phenotypes—such as refractory or postoperative CD—as well as the potential benefits of combination strategies, including dual biologic or small molecule therapies. Additionally, a better understanding of predictors of response and patient stratification tools will be essential to fully integrate guselkumab into a precision medicine framework.

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