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GUSELKUMAB AS A NEW BIOLOGIC OPTION FOR THE MANAGEMENT OF ULCERATIVE COLITIS: A NARRATIVE REVIEW

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ABSTRACT

Introduction: Ulcerative colitis (UC) is a chronic inflammatory bowel disease associated with substantial morbidity and an increasing global burden, for which durable disease control remains challenging despite advances in biologic and small-molecule therapies. Growing evidence implicates the interleukin-23 (IL-23) signaling axis as a key driver of UC pathogenesis, providing a strong biological rationale for selective IL-23 inhibition. This narrative review aims to synthesize the mechanistic basis, preclinical data, and emerging clinical evidence supporting the use of guselkumab, a fully human monoclonal antibody targeting the IL-23p19 subunit, in the treatment of UC.
Methods: A comprehensive literature search of the PubMed database was conducted to identify relevant preclinical, clinical, and translational studies evaluating guselkumab in UC, with a focus on pharmacology, efficacy, safety, and clinical positioning.
Results: Evidence from the phase 2 and phase 3 QUASAR clinical development program demonstrates that guselkumab provides statistically and clinically meaningful improvements in clinical remission, endoscopic outcomes, and steroid-free disease control in patients with moderately to severely active UC, including both biologic-naive and treatment-experienced populations. Preclinical and mechanistic studies further support its selective and potent inhibition of the IL-23/Th17 pathway, while clinical trials indicate a favorable and predictable safety profile.
Conclusions: In conclusion, current evidence positions guselkumab as an effective and well-tolerated advanced therapy for induction and maintenance of remission in moderate-to-severe UC. Ongoing real-world studies, longer-term follow-up, and comparative effectiveness research will be essential to further define its optimal role within evolving treatment algorithms.

KEYWORDS

Ulcerative Colitis, Guselkumab, IL-23p19 Inhibitor, Biologic Therapy, Clinical Efficacy, Safety

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disorder of the colon and rectum and belongs to the spectrum of inflammatory bowel diseases (IBD) [1]. It is characterized by continuous mucosal inflammation that typically starts in the rectum and extends proximally in a contiguous manner to involve variable lengths of the colon [1]. Ulcerative colitis represents a substantial and increasing global health burden, with marked geographic variability; while the highest incidence and prevalence have historically been reported in Europe and North America, recent population-based studies demonstrate a rising incidence in newly industrialized regions [2]. The clinical presentation of UC typically includes rectal bleeding, diarrhea, urgency, tenesmus, abdominal pain, and systemic manifestations such as fatigue and weight loss, with a relapsing–remitting disease course [1]. Persistent inflammatory activity is associated with an increased risk of intestinal complications, extraintestinal manifestations, and colorectal cancer, particularly with longer disease duration and sustained inflammatory burden [3] [4] [5]. The pathogenesis of UC is multifactorial and reflects a complex interplay between genetic susceptibility, environmental exposures, epithelial barrier dysfunction, alterations in the gut microbiota, and dysregulated mucosal immune responses [1].

Despite substantial advances in ulcerative colitis management, including the introduction of biologic therapies and small-molecule agents, a considerable proportion of patients fail to achieve durable clinical and endoscopic remission. Primary non-response and secondary loss of response remain common challenges, limiting sustained disease control and long-term treatment success. Moreover, prolonged exposure to systemic corticosteroids and conventional immunosuppressants is associated with clinically relevant adverse effects, highlighting the need for effective therapies with favorable long-term safety profiles. Contemporary treatment paradigms emphasize treat-to-target strategies, including mucosal healing, steroid-free remission, and

improvement in health-related quality of life; however, achieving these goals consistently remains challenging for many patients [6].

Selective interleukin-23 (IL-23) inhibition has been incorporated into contemporary clinical practice guidelines for the management of moderately to severely active ulcerative colitis. The American Gastroenterological Association (AGA) living guideline includes guselkumab among recommended advanced therapies for induction and maintenance of remission in adult outpatients with moderate-to-severe ulcerative colitis, based on evidence demonstrating clinical benefit compared with no treatment [6].

Accumulating experimental and translational evidence indicates that the interleukin-23 (IL-23) signaling axis plays a key role in the immunopathogenesis of ulcerative colitis [7]. In ulcerative colitis, IL-23 is produced in the inflamed colonic mucosa predominantly by antigen-presenting myeloid cells, including macrophage and dendritic cell populations, supporting its relevance at the tissue level in active disease [8]. IL-23 promotes and sustains Th17-type immune responses, thereby amplifying downstream pro-inflammatory cytokine pathways implicated in intestinal inflammation [7]. Consistent with this, increased mucosal IL-23 pathway activity has been demonstrated in inflamed colonic tissue from patients with ulcerative colitis compared with non-inflamed control tissue, supporting activation of the IL-23/Th17 axis at sites of disease activity [8]. Because IL-23 functions upstream of multiple effector inflammatory mechanisms, selective inhibition of IL-23 represents a biologically rational therapeutic strategy for interrupting chronic intestinal inflammation in ulcerative colitis [7]. Within this therapeutic framework, guselkumab, a fully human monoclonal antibody targeting the IL-23p19 subunit, enables selective blockade of IL-23–dependent signaling while preserving IL-12–mediated pathways [9]. The clinical development of guselkumab in ulcerative colitis has demonstrated efficacy across clinical remission, endoscopic outcomes, and steroid-free disease control, together with a favorable safety profile [10].

Methodology

This manuscript represents a narrative, non-systematic review of the literature. The review was conducted to synthesize the current literature regarding the use of guselkumab in the treatment of ulcerative colitis (UC). A comprehensive literature search was performed using the PubMed database to identify relevant publications available up to December 2025. The search strategy included the following keywords and their combinations: “guselkumab,” “ulcerative colitis,” “biologic therapy,” “IL-23,” and “IL-23 antagonist.” In addition, the reference lists of selected articles were manually reviewed to identify further relevant studies. Formal meta-analysis was not performed due to heterogeneity of study designs and outcomes.

Results

Mechanism of action

Guselkumab is a fully human IgG1 monoclonal antibody that selectively binds the p19 subunit of interleukin-23 (IL-23), thereby inhibiting IL-23–dependent signaling [11]. Selective targeting of IL-23p19 (as opposed to the shared p40 subunit) is intended to spare IL-12–mediated immune pathways [9] [12]. The IL-23 signaling pathway functions upstream in the inflammatory cascade and plays a central role in sustaining pathogenic Th17-mediated immune responses implicated in chronic intestinal inflammation in ulcerative colitis [7]. In addition to neutralizing soluble IL-23, guselkumab has a native Fc domain that enables Fc-mediated binding to the high-affinity FcγRI (CD64) receptor expressed on inflammatory myeloid cells, which represent a major cellular source of IL-23 in inflamed tissue [13]. In vitro experiments showed that guselkumab binding to CD64 did not induce cytokine production, and live-cell confocal imaging demonstrated internalization of IL-23 to low-pH intracellular compartments following CD64 binding [13]. The clinical relevance of IL-23p19 inhibition with guselkumab has been supported by phase 3 data from the QUASAR program, in which guselkumab demonstrated clinically and endoscopically meaningful efficacy in patients with moderately to severely active ulcerative colitis, with a favourable safety profile [10].

Pharmacokinetics and dosing

In the phase 3 QUASAR clinical development program, guselkumab was administered as intravenous induction therapy at a dose of 200 mg at weeks 0, 4, and 8, followed—among induction responders—by subcutaneous maintenance therapy with either 200 mg every 4 weeks or 100 mg every 8 weeks [10]. Pharmacokinetic analyses indicate that guselkumab exhibits linear pharmacokinetics over the clinically relevant dose range, consistent with typical IgG1 monoclonal antibody behavior [14]. Population pharmacokinetic modeling has estimated a terminal elimination half-life of approximately 18 days, supporting sustained systemic exposure with fixed-interval dosing [14]. In clinical pharmacology analyses, the formation

of anti-drug antibodies to guselkumab has been infrequent and has not been associated with clinically meaningful effects on drug clearance or systemic exposure [15]. Exposure–response analyses from the QUASAR phase 2b induction study demonstrated that intravenous doses of 200 mg and 400 mg achieved comparable clinical efficacy at week 12, indicating a plateau in therapeutic response beyond the 200 mg induction dose [16]. During maintenance therapy, higher systemic exposure achieved with subcutaneous dosing every 4 weeks was associated with numerically higher rates of sustained clinical remission compared with dosing every 8 weeks, supporting dosing flexibility based on clinical response [10]. Body weight has been identified as the primary covariate influencing interindividual variability in guselkumab pharmacokinetics, with higher body weight associated with increased clearance and lower systemic exposure; however, the magnitude of this effect has been modest and does not necessitate weight-based dosing adjustments [14].

Preclinical efficacy

Preclinical comparative analyses indicate that guselkumab inhibits IL-23–driven signaling and inflammation in translational experimental models [17]. In a human whole-blood assay assessing IL-23–induced STAT3 phosphorylation, guselkumab inhibited STAT3 activation with an IC_{50} of 0.01 nM (95% CI, 0.008–0.014). Under the same experimental conditions, risankizumab, tildrakizumab, and ustekinumab demonstrated IC_{50} values of 0.006 nM (95% CI, 0.003–0.013), 0.04 nM (95% CI, 0.033–0.047), and 0.04 nM (95% CI, 0.031–0.057), respectively [17]. In an in vivo IL-23–induced ear inflammation model, guselkumab reduced ear swelling in a dose-dependent manner, as assessed by area under the curve for ear thickness over days 0–4, with statistical significance determined using one-way ANOVA with appropriate multiple-comparison testing [17]. In head-to-head experiments conducted at a dose of 0.1 mg/kg, inhibition of IL-23–induced ear swelling was numerically 10% for guselkumab and 33% for risankizumab, although this difference did not reach statistical significance. In contrast, risankizumab produced greater inhibition of IL-23–induced expression of IL-17A, IL-22, S100A7a, and β-defensin 4 mRNA compared with guselkumab in this model. These findings reflect differences observed in specific preclinical experimental systems and do not directly predict comparative clinical efficacy [17].

Clinical efficacy

The clinical efficacy of guselkumab in ulcerative colitis (UC) has been established through the global phase 3 QUASAR clinical development program, comprising randomized, double-blind, placebo-controlled induction and maintenance studies in patients with moderately to severely active disease [10] [16]. During induction, intravenous guselkumab was associated with statistically and clinically significant improvements in disease control, with clinical remission at week 12 achieved in 23% of patients compared with 8% in the placebo group, corresponding to an adjusted treatment difference of 15% (95% CI 10–20; $p<0.0001$) [10]. Clinical response rates were consistently higher with guselkumab than with placebo across clinically relevant subgroups, including biologic-naïve patients and those with prior biologic exposure, supporting efficacy in both treatment-naïve and treatment-experienced populations [10]. Analyses of symptom trajectories further demonstrated early reductions in rectal bleeding and stool frequency during induction, suggesting a relatively rapid onset of clinical benefit [18]. The durability of response was confirmed in the maintenance phase of QUASAR. Among induction responders, continued guselkumab therapy resulted in significantly higher rates of sustained clinical remission at week 44 compared with placebo withdrawal, with remission maintained in 50% of patients receiving 200 mg subcutaneously every 4 weeks and in 45% receiving 100 mg every 8 weeks, compared with 19% in the placebo group for both regimens [10]. Earlier phase 2b QUASAR data corroborated these findings, demonstrating significantly higher clinical response rates at week 12 with guselkumab compared with placebo and informing dose selection for the phase 3 program [16]. Secondary analyses from the phase 3 program further suggested an increased likelihood of achieving steroid-free disease control during maintenance, consistent with contemporary treat-to-target strategies in UC [19]. Exploratory evidence for pathway complementarity was provided by the VEGA proof-of-concept trial, which evaluated combination therapy with guselkumab and the anti-TNF agent golimumab; although combination therapy achieved higher clinical response rates than golimumab monotherapy at week 12, no statistically significant advantage over guselkumab monotherapy was observed, underscoring the need for further investigation in adequately powered studies [20].

Efficacy in clinically relevant subgroups

Although the pivotal QUASAR program established the overall efficacy of guselkumab in moderately to severely active ulcerative colitis, understanding treatment response across clinically relevant subgroups remains important for individualized therapy. Subgroup analyses from the QUASAR phase 3 program demonstrate that guselkumab improves both clinical and endoscopic outcomes compared with placebo in biologic-naïve patients as well as in those with prior biologic exposure, supporting efficacy in treatment-experienced populations [10]. Extraintestinal manifestations, including musculoskeletal, dermatologic, and ocular involvement, occur in a substantial proportion of patients with ulcerative colitis and contribute significantly to disease burden and disability [4]. However, specific data evaluating the efficacy of guselkumab for extraintestinal manifestations in ulcerative colitis are currently lacking, representing an important gap for future clinical research. Disease extent may also influence therapeutic decision-making. Distal phenotypes, such as ulcerative proctitis and left-sided disease, are underrepresented in large phase 3 trials of advanced therapies, limiting the ability to draw firm conclusions regarding efficacy in these subgroups and underscoring the need for dedicated analyses [21].

Safety overview

The safety profile of guselkumab in ulcerative colitis (UC) has been primarily characterized by data from the phase 3 QUASAR clinical development program and the phase 2 proof-of-concept VEGA study. In the QUASAR induction trial, the overall incidence of treatment-emergent adverse events was comparable between guselkumab and placebo (49% vs 49%). The proportion of patients experiencing serious adverse events was numerically lower in the guselkumab group than in the placebo group (3% vs 7%), and discontinuation of treatment due to adverse events occurred less frequently with guselkumab (2% vs 4%) [10]. During the induction period, no cases of active tuberculosis, anaphylaxis, serum sickness–like reactions, or clinically significant hepatotoxicity were reported, and no new safety signals related to IL-23p19 inhibition were identified within the scope of the trial [10]. Additional safety data were provided by the VEGA study. Through week 50, any adverse event was reported in 65% of patients receiving guselkumab, 76% receiving golimumab, and 63% receiving combination therapy. Serious adverse events occurred in 6% of patients in each treatment arm, and serious infections were reported in 3% of patients, with no numerical increase observed in the guselkumab monotherapy group [20]. Across clinical studies, the most frequently reported adverse events with guselkumab were generally mild to moderate in severity and included nasopharyngitis, upper respiratory tract infections, headache, and disease exacerbation. Available clinical trial data do not suggest a higher incidence of opportunistic or serious infections with guselkumab compared with placebo or active comparators, although longer-term safety data remain limited [22]. Immunogenicity analyses further indicate that anti-drug antibodies to guselkumab occur infrequently and have not been associated with reduced efficacy or increased adverse events [15].

Role of real-world evidence

Real-world evidence (RWE) refers to clinical evidence on the use, benefits, and risks of medical products derived from real-world data sources, including electronic health records, disease registries, and administrative claims databases, collected outside the controlled setting of randomized clinical trials [23]. By complementing randomized evidence, RWE enables the evaluation of treatment effectiveness, safety, and utilization in broader and more heterogeneous patient populations than those typically enrolled in clinical trials, while requiring careful consideration of confounding and other sources of bias inherent to observational research [24] [25]. In inflammatory bowel disease, RWE is particularly valuable for characterizing long-term outcomes such as treatment persistence and for informing comparative effectiveness across biologic therapies in routine clinical practice [26] [27]. For therapies such as guselkumab, future real-world studies may complement data from the QUASAR program by providing additional information on durability of response, treatment persistence, and patient-relevant outcomes in unselected ulcerative colitis populations, particularly in the absence of head-to-head randomized trials. In addition, high-quality RWE plays an important role in health technology assessment and reimbursement decision-making by informing generalizability, healthcare resource utilization, and the economic value of advanced therapies beyond the controlled trial setting [23] [24].

Guselkumab versus other IL-23p19 inhibitors

Among IL-23p19 inhibitors approved or evaluated for ulcerative colitis, including mirikizumab and risankizumab, guselkumab belongs to the same therapeutic class but has been characterized by a proposed dual-acting mechanism based on mechanistic and preclinical investigations. In addition to neutralizing soluble IL-23, preclinical and mechanistic studies suggest that guselkumab retains Fc-mediated binding to the high-affinity FcγRI (CD64) receptor on IL-23–producing myeloid cells, potentially enabling localized cytokine sequestration within

inflamed tissue [22] [13]. By contrast, mirikizumab and risankizumab are conventional anti-IL-23p19 monoclonal antibodies evaluated in the LUCENT-1/LUCENT-2 program and other phase 3 ulcerative colitis trials, for which FcγRI-mediated binding or tissue-level IL-23 sequestration has not been reported [28] [29]. Importantly, the absence of head-to-head randomized clinical trials comparing IL-23p19 inhibitors in ulcerative colitis precludes definitive conclusions regarding relative efficacy or safety, necessitating cautious interpretation of indirect comparisons across separate clinical development programs [30].

Future directions

Future research on guselkumab in inflammatory bowel disease should focus on consolidating long-term efficacy and safety data, refining treatment positioning within evolving therapeutic algorithms, and expanding evidence across patient populations and disease indications. In Crohn's disease, phase 3 data from the GALAXI-2 and GALAXI-3 trials have demonstrated clinically meaningful induction and maintenance efficacy, including improvements in endoscopic outcomes, providing a robust evidence base for broader clinical implementation [31]. In the United States, guselkumab has received regulatory approval for the treatment of moderately to severely active Crohn's disease, underscoring the expansion of its clinical development beyond ulcerative colitis.

A key near-term priority will be to translate pivotal trial efficacy into real-world effectiveness and durability across heterogeneous and treatment-experienced populations, while continuing to define long-term safety with extended exposure. Additional research directions include the development of biomarker-guided strategies to predict treatment response, systematic assessment of patient-reported outcomes and treat-to-target endpoints, and further evaluation of combination strategies in difficult-to-treat disease, building on proof-of-concept data suggesting pathway complementarity with anti-TNF therapy [20]. In clinical practice, guselkumab can be considered an advanced therapy for adult outpatients with moderately to severely active ulcerative colitis requiring induction and maintenance of remission, based on efficacy and safety demonstrated in the phase 3 QUASAR program [10]. This positioning is consistent with the American Gastroenterological Association living guideline for moderate-to-severe ulcerative colitis, which includes guselkumab among recommended advanced therapies and supports its use within evidence-informed sequencing strategies [6]. In the absence of head-to-head randomized trials, treatment selection should remain individualized and guided by comparative evidence syntheses, such as network meta-analyses, alongside patient-specific priorities [30] [32].

Discussion

Despite the robust efficacy and safety signals observed in the QUASAR program, several limitations of the current evidence base for guselkumab in ulcerative colitis warrant consideration. Controlled clinical trial data remain limited in duration, with maintenance follow-up extending to approximately one year, and therefore do not yet fully capture long-term durability of response or the incidence of rare cumulative safety events [10] [22]. As with other randomized controlled trials in ulcerative colitis, patient selection criteria may limit generalizability to real-world populations, particularly older individuals, patients with significant comorbidities, isolated distal disease, or complex extraintestinal manifestations, which tend to be underrepresented in pivotal studies [30]. Moreover, the absence of head-to-head randomized comparisons with other advanced therapies, including within the IL-23 inhibitor class, necessitates reliance on indirect comparisons and network meta-analyses that are inherently constrained by cross-trial heterogeneity [6] [32]. While population-level pharmacokinetic and exposure–response relationships for guselkumab are increasingly well described, validated biomarker-driven strategies to guide individualized treatment selection or optimization in ulcerative colitis have not yet been established, representing an important area for future investigation [22].

The efficacy outcomes reported across the QUASAR program are aligned with contemporary treat-to-target principles as defined by the STRIDE-II consensus, which emphasizes clinical remission and endoscopic healing as primary therapeutic targets, with steroid-free remission as a key adjunctive goal; accordingly, the demonstrated effects of guselkumab on symptomatic control, endoscopic improvement, and maintenance of steroid-free disease control correspond to outcomes considered clinically meaningful and prognostically relevant in modern ulcerative colitis management [10] [33].

From a health-economic perspective, the expanding use of advanced therapies in ulcerative colitis raises important considerations regarding cost-effectiveness and resource allocation, and although ulcerative colitis–specific cost-effectiveness analyses for guselkumab remain limited, broader economic evaluations indicate that biologic and targeted therapies substantially increase direct treatment costs, which may be partially offset by reductions in hospitalizations, corticosteroid exposure, surgery, and productivity loss when durable remission

is achieved [26] [34]. Model-based economic analyses further suggest that therapies associated with higher rates of sustained remission and steroid-free disease control may offer improved long-term value despite higher upfront costs, particularly in patients with moderate-to-severe or treatment-refractory disease; however, such analyses are not specific to individual IL-23p19 inhibitors [34] [35].

Patient-reported outcomes, including measures of health-related quality of life and symptom burden, represent an increasingly important component of treatment evaluation in ulcerative colitis, and improvements observed in the QUASAR program were consistent with objective disease control, supporting the clinical relevance of IL-23p19 inhibition from the patient perspective [10] [22].

Conclusions

In conclusion, evidence from preclinical, translational, and phase 2–3 clinical studies indicates that guselkumab is an effective and generally well-tolerated therapeutic option for the induction and maintenance of remission in adults with moderately to severely active ulcerative colitis, as demonstrated in controlled clinical trial settings [10] [22]. The selective inhibition of the IL-23p19 pathway with guselkumab has been associated with clinically meaningful improvements in disease control together with a favorable and predictable safety profile within the scope of randomized trials.

In clinical practice, guselkumab can be considered within the expanding landscape of advanced therapies for ulcerative colitis, in line with contemporary guideline recommendations and treat-to-target strategies that emphasize sustained remission and mucosal healing [6] [10]. Ongoing real-world studies, longer-term follow-up, and comparative effectiveness research will be essential to further define the optimal positioning and long-term value of guselkumab within evolving treatment algorithms for ulcerative colitis [22] [30].

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