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Is IL-23 the Winner? Lessons from Inflammatory Bowel Disease (IBD) and Psoriasis (PsO)

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Key Takeaways
Interleukin-23 (IL-23), and the IL-23/Th-17 interaction, plays a pivotal role in the pathogenesis of immune-mediated diseases, such as psoriasis (PsO) and inflammatory bowel disease (IBD). This has led to the development and commercialization of several anti-IL-23 therapies, all demonstrating high efficacy and safety in the management of these conditions.
Anti-IL-23 therapies, have been shown to be amongst the most highly effective treatments in PsO, achieving meaningful and durable treatment response (PASI-90) in over 80 percent of participants in registrational clinical trials, while in IBD the meaningful one-year efficacy, based on the varied definitions of the studies' primary endpoints, is achieved (at most) in just over 50 percent of participants, though rates of achieving remission in Crohn's disease are much lower.
Several ongoing studies examining the role of IL-23 inhibition in specific IBD populations (e.g., perianal Crohn's disease), and studies examining the combination of IL-23 inhibitors with other targeted therapies, capitalizes on the excellent safety and efficacy profile of anti-IL-23, reflecting the long-term importance of these therapies in the IBD treatment landscape.

Introduction

Psoriasis (PsO) and inflammatory bowel disease (IBD) are two immune-medicated inflammatory disorders (IMIDs) that have overlapping pathogenic mechanisms and thus share many advanced treatments for patients with moderate-to-severe disease. Historically, both conditions have faced limitations in the degree to which conventional therapies could promote safe and effective disease control. This landscape has shifted with the introduction and widespread adoption of advanced therapies for IMID management. The first class of advanced therapies, anti-tumour necrosis factor alpha (anti-TNF) agents, nearly doubled the meaningful response to treatment in PsO over that of conventional corticosteroid-sparing therapies (e.g., methotrexate), with comparable results in pivotal studies of anti-TNF therapies over conventional immunosuppressants (e.g., azathioprine) in IBD.[1] Despite these advances, most IBD patients in both clinical studies and real-world settings treated with anti-TNF agents (e.g., adalimumab, infliximab) still fail to achieve long-lasting, durable remission.[1,2]

Interleukin-23 (IL-23), first identified in 2000 as a mediator of inflammation in IMIDs, has since been shown to be a key cytokine in the inflammatory disease process. Overproduction of IL-23 by antigen-presenting cells and other myeloid cells promotes the proliferation of pathogenic T-helper 17 (Th17) cells that produce and secrete other inflammatory mediators, such as IL-17A, IL-17F, TNF-a, and IL-22, while suppressing regulatory T-cell differentiation (an important mediator of immune homeostasis).[1,2] This process, in turn, leads to an amplification of IL-23 production from stromal cells and local myeloid cells, which further drives the inflammatory process. The IL-23/Th17 immune pathway also plays an important role in maintaining gut homeostasis through the production of IL-17A, though overproduction of IL-23 can impair gut barrier function by other mechanisms.[1,2] Both IL-17A and IL-17F mediate inflammatory activity, representing the primary pathogenic mechanism contributing to PsO. IL-23 shares homology with IL-12, another proinflammatory cytokine initially identified in 1989 and implicated in PsO and IBD pathogenesis due to its influence on interferon gamma (IFNg) production and in promoting Th1 activity.[3] These insights led to the development and commercial use of ustekinumab, a monoclonal antibody (MAb) targeting the p40 subunit, shown to be effective in the management of PsO and IBD.

IL-12 and IL-23 are heterodimeric cytokines composed of two distinct subunits. Both share the p40 subunit, while the p19 subunit is specific to IL-23. Although both IL-12 and IL-23 cytokines were initially thought to be involved in the IMID process, preclinical and clinical data has subsequently determined IL-23 overactivity as the primary driver of inflammatory disease activity in PsO, psoriatic arthritis (PsA), and IBD.[1,2] In IBD, for example, genome-wide association studies have identified several single nucleotide polymorphisms in the IL-23 receptor that increase the risk of ulcerative colitis (UC) and Crohn's disease (CD), whereas studies on IL-12 deficiency alone have shown no impact on IBD.[4] These findings have allowed the development and commercialization of several anti-p19-specific MAbs, first approved for PsO and more recently for IBD. Given the central role of IL-23 in mediating these disease conditions, this review examines the efficacy and safety data supporting p19 inhibitor use in PsO and IBD, and their overall impact on disease management.

Impact of p19 Inhibitors in PsO and IBD

Review of Phase 3 Clinical Trials of p19 Inhibitors in Psoriasis: an IL-23-dominant Disease

Consistent with preclinical studies establishing the importance of IL-23/Th17 in PsO, p19 inhibitor therapy has dominated the PsO treatment landscape, outperforming the preceding advanced therapies, such as ustekinumab. PsO disease activity is graded according to the Psoriasis Area and Severity Index (PASI) score, which assesses disease extent and severity on a scale with a maximum score of 72. Clinical trials typically define standard primary outcome measures in PsO as achieving a 75% or 90% reduction in the PASI score (PASI 75 and PASI 90, respectively), allowing for reasonable comparisons of outcomes. Across phase 3 clinical trials, long-term extension studies, and head-to-head comparison studies, p19 inhibitors have consistently demonstrated the highest rates of efficacy. Notably, guselkumab and risankizumab in particular have achieved PASI 75 response rates of 88–91% at week 24, with sustained results through week 48.[1] Guselkumab has further demonstrated superiority over active comparator adalimumab in the pivotal VOYAGE 1 and VOYAGE

2 trials.[5] Similarly, the phase 3 risankizumab studies (UltIMMA-1 and 2) employed ustekinumab as an active comparator, with superiority demonstrated in PASI 90 (75% vs 42% at week 16, respectively, and sustained through week 52 (82% vs 44%, respectively).[6] The subsequent phase 3 ECLIPSE trial has shown that guselkumab was superior to secukinumab (an IL-17 inhibitor) in achieving PASI 90 at week 48 (84% vs 70%, respectively).[7] A recent systematic review and network meta-analysis of phase 3 therapeutic trials further demonstrated numerical superiority of p19 inhibitors over other available advanced therapies, namely IL-17 inhibitors ixekizumab and secukinumab, when adjusted for placebo group response, across PASI 75, 90 and 100 at week 28.[8] Throughout these trials, systematic reviews and network meta-analyses, no new safety signals have been reported, consistent with the targeted nature of IL-23 inhibition and its role in promoting regulatory T-cell function.

These p19 inhibitors have also been shown to provide a durable and long-lasting response over other classes of treatment for PsO. A systematic review and meta-analysis of electronic health records, registries, and pharmacy/claims data assessing drug survival of IL-17 and IL-23 inhibitors for PsO demonstrated high persistence rates for all agents assessed, with guselkumab and risankizumab consistently outperforming secukinumab and ixekizumab, at each annual checkpoint over 5 years of assessment.[9]

In addition, prospective and retrospective data also suggests that p19 inhibition may be more effective in the prevention of PsA compared with IL-17 inhibitors and ustekinumab.[10] Indeed, this potential alteration in the natural history of PsO, combined with the superior efficacy of p19 inhibitors, their dominance in head-to-head studies, their impressive durability of response, and their excellent safety profile, reflect the high impact of targeting IL-23 in PsO. Collectively, these features present a compelling argument to consider using IL-23 therapies as a first-line option in the management of this condition.

Review of Pivotal Clinical Trials of p19 Inhibitors in Inflammatory Bowel Disease

The importance of IL-23 inhibition in CD was first highlighted by the success of ustekinumab, which achieved statistically significant efficacy in its pivotal phase 3 CD registrational studies (UNITI 1, UNITI 2, IM-UNITI) (**Table 1**).[11] Additionally, ustekinumab exhibited an impressive safety profile, with no increase in adverse events, serious adverse events, malignancies, or infections above that of placebo therapy. More recently, the importance of IL-23 inhibition in CD was demonstrated in a head-to-head non-inferiority study of ustekinumab compared to adalimumab in an advanced therapy-naïve CD population (SEAVUE trial).[12] After 52 weeks of open-label therapy, 65% of participants on ustekinumab achieved the primary endpoint of clinical remission (CDAI <150), while 42% achieved an endoscopic response (defined as a reduction in the simple endoscopic score [SES-CD] by at least 50% from baseline, SES-CD ≤3, or SES-CD 0 for those starting with an SES-CD of 3). While these outcomes were statistically non-inferior to those in the adalimumab cohort, ustekinumab showed slightly higher numerical results. Similarly, ustekinumab has demonstrated both efficacy and safety in the phase 3 UC program (UNIFI), resulting in its approval for UC in 2019 (**Table 1**).[13]

Since the UNITI and UNIFI trials, clinical endpoints in IBD studies have evolved to incorporate more objective parameters to assess treatment efficacy. The recent approvals of three p19 inhibitors (guselkumab, risankizumab, and mirikizumab) for the management of CD, UC, or both, are based on strong and objective results from phase 3 registrational trials. Yet, targeting of the p19 subunit in IBD has not produced treatment responses as robust as those observed in PsO. While no clear explanation can account for such a difference, it is likely that PsO is primarily driven by the IL-23/Th17 axis, while the pathogenesis of IBD may be more heterogeneous, involving additional immune pathways beyond IL-23. Results of the phase 3 CD trials and their primary endpoints are summarized in **Table 1**.

Crohn's Disease

Risankizumab was the first p19 inhibitor approved for use in CD in 2023, on the basis of its phase 3 intravenous (IV) induction trials (ADVANCE, MOTIVATE) and subcutaneous (SC) maintenance trial (FORTIFY). In ADVANCE, endoscopic response at week 12 was achieved in 40% of patients receiving 600 mg IV risankizumab versus 12% with placebo.[14] Responders to induction were re-randomized for maintenance to placebo, risankizumab 180 mg, or 360 mg every 8 weeks. At week 52 of maintenance, 46.8% of those receiving 360 mg risankizumab

Study Therapy (*ST*)	Intervention Period	Dosing vs Placebo	Study Dur (*wk*)	Primary Endpoint Definition	% Achieving Primary Endpoint			% Achieving Primary Endpoint by Prior ADT-Failure		Clinical Trial
					ST (*N*)	PBO (*N*)	Δ (%)	No Prior ADT (*N*)	Prior ADT (*N*)	
Crohn's disease										
Ustekinumab	Induction	6 mg/kg IV, wk 0	6	Clinical Remission (CDAI <150)	18.5 (249)	9 (247)	9	N/A	18.5 (249) (TNF IR only)	UNITI-1[11]
	Induction	6 mg/kg IV wk 0	6	Clinical Remission (CDAI <150)	34.9 (209)	17.7 (209)	17.2	34.9 (209)	N/A	UNITI-2[11]
	Maintenance (responder re-randomization)	90 mg sc, q 8 wk	44	Clinical remission (CDAI <150) in ustekinumab induction responders	53.1 (132)	35.9 (131)	17.2	62.5 (74)	41.1 (58)	IM-UNITI[11]
Risankizumab	Induction	600 mg IV, wk 0,4,8	12	**1.** Clinical remission (SF/APS) **2.** Endoscopic response (SES-CD decrease by >50%)	43.5 (336) 40.3 (336)	21.7 (175) 12 (175)	21.9 28.3	48 (141) 50 (141)	41 (195) 33 (195)	ADVANCE[14]
	Induction	600 mg IV, at wk 0,4,8	12	**1.** Clinical remission (SF/APS) **2.** Endoscopic response (SES-CD decrease by >50%)	34.6 (191) 28.8 (191)	19.3 (187) 11.2 (187)	15.2 17.6	N/A	All Bio-IR	MOTIVATE[14]
	Maintenance (responder re-randomization)	360 mg sc, q 8 wk	52	**1.** Clinical remission (SF/APS) & **2.** Endoscopic response (SES-CD decrease by >50%)	51.8 (141) 46.5 (141)	39.6 (164) 22 (164)	12.2 24.5	62 (34) 54 (34)	48 (183) 44 (183)	FORTIFY[15]

Study Therapy (*ST*)	Intervention Period	Dosing vs Placebo	Study Dur (*wk*)	Primary Endpoint Definition	% Achieving Primary Endpoint			% Achieving Primary Endpoint by Prior ADT-Failure		Clinical Trial
					ST (*N*)	PBO (*N*)	Δ (*%*)	No Prior ADT (*N*)	Prior ADT (*N*)	
Guselkumab	Induction & Maintenance (Treat-through)	200 mg IV at wk 0,4,8, then 100 mg sc, q 8 wk	48	**1.** Clinical response (CR100) at wk 12 + clinical remission (CDAI<150) at wk 48	49.0 (143) 46.9 (143)	11.8 (76) 12.5 (72)	38.1 34.2	51.7 (116) (pooled results – GALAXI 2+3)		GALAXI 2[17] GALAXI 3[17]
				2. Clinical response at wk 12 + endoscopic response (SES-CD decrease by >50%) at wk 48	39.2 (143) 33.6 (143)	5.3 (76) 5.6 (72)	33.7 27.9	40.5 (116) (pooled results – GALAXI 2+3)		GALAXI 2[17] GALAXI 3[17]
	Induction & Maintenance (Treat-through)	200 mg IV at wk 0,4,8, then 200 mg sc q 4 wk	48	**1.** Clinical response (CR100) at wk 12 + clinical remission (CDAI<150) at wk 48	54.8 (146) 48.0 (150)	11.8 (76) 12.5 (72)	42.8 35.0	54.7 (128) (pooled results – GALAXI 2+3)		GALAXI 2[17] GALAXI 3[17]
				2. Clinical response at wk 12 + endoscopic response (SES-CD decrease by >50%) at wk 48	38.4 (146) 36.0 (150)	5.3 (76) 5.6 (72)	32.9 30.8	43.8 (128) (pooled results – GALAXI 2+3)		GALAXI 2[17] GALAXI 3[17]
Mirikizumab	Induction & Maintenance (Treat-through)	900 mg IV at wk 0,4,8, then 300 mg sc, q 4 wk	52	**1.** Clinical response (SF/APS) at wk 12 + clinical remission (CDAI <150) at wk 52	45.4 (579)	19.6 (199)	25.8	47.3 (298)	43.4 (281)	VIVID-1[18]
				2. Clinical response at wk 12 + endoscopic response (SES-CD decrease by >50%) at wk 52	38.0 (579)	9.0 (199)	28.9	39.3 (298)	36.7 (281)	

Study Therapy (*ST*)	Intervention Period	Dosing vs Placebo	Study Dur (*wk*)	Primary Endpoint Definition	% Achieving Primary Endpoint			% Achieving Primary Endpoint by Prior ADT-Failure		Clinical Trial
					ST (*N*)	PBO (*N*)	Δ (%)	No Prior ADT (*N*)	Prior ADT (*N*)	
Ulcerative colitis										
Ustekinumab	Induction	6 mg/kg IV, wk 0	8	Clinical remission (Mayo score ≤2, no subscore >1)	15.5 (322)	5.3 (319)	10.2	19 (156)	13 (166)	UNIFI[13]
	Maintenance (responder re-randomization)	90 mg sc, q 8 wk	44	Clinical remission (Mayo score ≤2, no subscore >1)	43.8 (176)	24.0 (175)	19.8	48.2 (85)	39.6 (91)	UNIFI[13]
Mirikizumab	Induction	300 mg IV wk 0,4,8	12	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	24.2 (868)	13.3 (294)	10.9	30.6 (507)	15.2 (361)	LUCENT-1[20]
	Maintenance (responder re-randomization)	200 mg sc, q 4 wk	44	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	49.9 (365)	25.1 (179)	24.8	51.9 (237)	46.1 (128)	LUCENT-2[20]
Risankizumab	Induction	1200 mg IV, at wk 0,4,8	12	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	20.3 (650)	6.2 (325)	14.1	29.7 (317)	11.4 (333)	INSPIRE[22]
	Maintenance (responder re-randomization)	360 mg sc q 8 wk	52	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	37.6 (186)	25.1 (183)	12.6	61.7 (47)	29.5 (139)	COMMAND[22]
Guselkumab	Induction	200 mg IV, at wk 0,4,8	12	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	22.6 (421)	7.9 (280)	14.7	31.7 (202)	12.5 (208)	QUASAR[21]
	Maintenance (responder re-randomization)	100 mg sc, q 8 wk	44	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	49.4 (188)	18.9 (190)	30.5	50.4 (105)	40.3 (77)	QUASAR[21]
	Maintenance (responder re-randomization)	200 mg sc, q 4 wk	44	Clinical remission (aMayo ≤2, no subscore >1, RB 0)	51.6 (190)	18.9 (190)	32.7	58.3 (96)	39.8 (88)	QUASAR[21]

Table 1. Efficacy of IL-23 inhibition in Phase 3 registrational trial programs for approved doses in Crohn's disease and ulcerative colitis; *courtesy of Jesse Siffledeen, MD*

Abbreviations: ADT: Advanced Therapy; **aMayo:** adapted Mayo score; **APS:** abdominal pain score; **Bio-IR:** biologic inadequate responder; **CDAI:** (Crohn's Disease Activity Index; **CR100:** clinical response – CDAI reduction by 100 points; **IV:** intravenous; **N:** total number of subjects in the treatment cohort; **PBO:** placebo; **q:** every; **RB:** rectal bleeding score; **sc:** subcutaneous; **SES-CD:** simple endoscopic score for Crohn's disease; **SF:** stool frequency; **Stud Dur:** Study Duration & Endpoint; **wk:** week

demonstrated an endoscopic response (defined as a reduction in the SES-CD of ≥50%) compared to 13% in the placebo withdrawal group.[15] Endoscopic remission (defined as an SES-CD ≤4, a ≥2 point reduction from baseline, and no individual score >1) at week 48 was 39% versus 13%, respectively. The study population was considered a difficult to treat group, with a high mean SES-CD score of 14–14.8. In the ADVANCE trial, 58% of patients had previously demonstrated an inadequate response to at least one advanced therapy, including 22% who had failed ustekinumab; all participants in MOTIVATE were required to have failed at least one biologic agent. Subsequently, the SEQUENCE trial, a head-to-head study of risankizumab versus ustekinumab in CD patients with prior anti-TNF therapy failure showed that the primary endpoint of endoscopic remission at week 48 was significantly superior for risankizumab (32% vs 16%, respectively).[16]

The efficacy of guselkumab in the management of moderate-to-severe CD was assessed in two identical phase 3 trials (GALAXI 2 and GALAXI 3). These treat-through trials included IV induction with guselkumab (200 mg every 4 weeks for three doses) followed by SC maintenance (either 100 mg every 8 weeks or 200 mg every 4 weeks). Comparator arms included ustekinumab (6 mg/kg IV induction, then 90 mg SC every 8 weeks) and placebo. The co-primary endpoints were clinical response at week 12 and clinical remission/endoscopic response at week 48 versus placebo.[17] Endoscopic response at weeks 12 and 48, along with endoscopic remission at week 48, were among several prespecified secondary endpoints, all of which, along with the primary and secondary endpoints, were statistically superior for guselkumab versus placebo. Importantly, guselkumab also demonstrated statistical superiority over ustekinumab for endoscopic response at week 48 (48% and 53% in the 100 mg every 8 weeks and 200 mg every 4 weeks treatment cohorts, respectively, vs 37% in the ustekinumab cohort) and for endoscopic remission (33.2% and 37.2% vs 24.7%).[17] These results are numerically comparable to those observed in the risankizumab phase 3 trials.

The efficacy of mirikizumab in CD was assessed in the VIVID-1 phase 3 clinical trial, which used a treat-through design similar to the GALAXI 2 and GALAXI 3 studies. Participants received mirikizumab 900 mg IV at weeks 0, 4, and 8, followed by 300 mg SC every 4 weeks from week 12 through week 52, or were assigned to comparator arms of ustekinumab (6 mg/kg IV induction, then 90 mg SC every 8 weeks), or placebo.[18] The co-primary endpoints were clinical response at week 12 and clinical remission/endoscopic response at week 48 versus placebo, with endoscopic response and remission at week 52 as prespecified secondary outcome measures. As with guselkumab, mirikizumab demonstrated statistically significant and clinically meaningful improvements versus placebo for both co-primary endpoints and all key secondary endpoints. At week 52, endoscopic response was 48.4% in the mirikizumab cohort versus 9% in the placebo cohort, while endoscopic remission rates were 28.5% versus 4%, respectively.[18] In contrast to the GALAXI studies, however, mirikizumab did not demonstrate statistical superiority over ustekinumab in VIVID-1, reflected in a relatively higher ustekinumab response in VIVID 1, compared with the ustekinumab response in the GALAXI studies (endoscopic response 46.3% at week 52 vs 37.1% at week 48, respectively).[17,18]

Overall, p19 inhibition in CD yields comparable outcomes and demonstrates highly statistically significant improvements over the comparator placebo cohort. However, several shortcomings in these results are evident when they are compared to its dominance of p19 inhibition in PsO. Notably, only half of trial participants achieved a meaningful endoscopic response after one year of treatment, and even fewer achieved remission, highlighting a significant unmet need for more efficacious therapies. Response and remission rates are significantly lower in patients with prior exposure to advanced therapies, and robust data remains lacking for patients with complex phenotypes of CD, such as complex perianal fistulizing CD, which confer significant health and quality of life burden.

Ulcerative Colitis

Mirikizumab was the first p19 inhibitor to be approved for UC, based on results from the phase 3 induction (LUCENT 1) and maintenance (Lucent 2) trials.[19] In LUCENT 1, participants were randomized to receive mirikizumab 300 mg IV, or placebo, at weeks 0, 4, and 8. Treatment responders were then re-randomized in LUCENT 2 to receive mirikizumab 200 mg SC, or placebo, every 4 weeks from week 12 to week 52. The primary endpoint was clinical remission

assessed at week 12 for LUCENT 1 and at week 52 for LUCENT 2, defined by the adapted Mayo score ≤2 (stool-frequency subscore of 0, or a stool-frequency subscore of 1 with a decrease of ≥1 point from baseline, a rectal-bleeding subscore of 0, and an endoscopic subscore of 0 or 1, excluding friability). Clinical remission rates for mirikizumab were 24.2% at week 12 and 49.9% at week 52, compared with 13.3% and 25.1% for placebo, respectively. Several prespecified secondary endpoints were also achieved, including patient-reported outcomes, such as early improvement in bowel urgency. Long-term durability has been demonstrated as well: in the LUCENT-3 extension study, 70% of those in remission at one year remained in remission at 3 years, based on non-responder imputation.[20]

The efficacy of guselkumab in moderate-to-severe UC was demonstrated in the phase 3 QUASAR induction and maintenance trial.[21] During induction, participants received guselkumab 200 mg IV, 400 mg IV, or placebo at weeks 0, 4, and 8. At week 12, responders to guselkumab were re-randomized to receive maintenance therapy with guselkumab 100 mg every 8 weeks, 200 mg every 4 weeks, or placebo, for 44 weeks. The primary outcome was clinical remission, assessed by the adapted Mayo score at week 12 (for induction) and at the end of the 44-week maintenance period. All primary and secondary endpoints were met for both induction and maintenance outcomes. At week 12, 54% of participants receiving guselkumab 200 mg achieved clinical remission, compared with 25% in the placebo cohort. During maintenance, 45% of participants receiving 100 mg every 8 weeks and 50% of participants receiving 200 mg every 4 weeks achieved clinical remission, compared with 18% among those re-randomized to placebo therapy.

The efficacy of risankizumab in UC was demonstrated in the phase 3 induction (INSPIRE) and maintenance (COMMAND) trials.[22] During induction, participants received risankizumab 1200 mg IV or placebo at weeks 0, 4, and 8. At week 12, responders to risankizumab were re-randomized to maintenance therapy with risankizumab 180 mg or 360 mg every 8 weeks, or placebo, for 52 weeks. The primary endpoint was clinical remission, assessed by the adapted Mayo score at week 12 (induction) and after 52 weeks of maintenance. All primary and prespecified secondary endpoints were met in both the induction and maintenance studies. These included novel patient-reported outcomes such as bowel urgency, fecal incontinence, fatigue scores, and reduced hospitalization at week 12. During induction, clinical remission was achieved in 20% of participants receiving risankizumab, compared with 6% of the placebo cohort. After 52 weeks of maintenance, remission rates were 40% and 38% for participants receiving risankizumab 180 mg and 360 mg every 8 weeks, respectively, compared with 31% of those in the placebo withdrawal cohort.[22]

The p19 inhibitor class exhibits exceptional safety, with no associated severe adverse events such as increased risk of serious infections, hospitalization, cardiovascular events, malignancies, death, or other adverse events of interest (i.e., opportunistic infections) identified. With this safety profile in mind, several ongoing clinical trials are investigating combinations of p19 inhibitors with other targeted therapies. In support of this approach, the phase 2 VEGA study examined the combination guselkumab plus golimumab (an anti-TNF agent) versus either agent alone for induction of remission in UC. Combination therapy showed a statistically significant advantage over guselkumab monotherapy in achieving clinical remission at week 12 (by adapted Mayo Score), and this benefit was maintained after switching to guselkumab monotherapy for an additional 24 weeks (48% vs 31% at week 38).[23] Importantly, tissue transcriptomic profiles revealed a synergistic effect of combination therapy with regards to downregulation of proinflammatory cytokine gene expression and upregulation of genes promoting epithelial normalization.[24] Guselkumab and golimumab are currently under investigation for induction and maintenance of remission in phase 2 trials for CD (DUET-CD) and UC (DUET-UC). These studies use primary endpoints aligned with those of the GALAXI and QUASAR studies, respectively, at 48 weeks of treatment. Both studies have completed enrolment.

Is IL-23 the Clear Winner in IBD?

Collectively, these phase 3 registrational studies of IL-23 inhibitors in UC and CD highlight a strong class effect in achieving both response and remission, along with superiority in head-to-head evaluations. Coupled with their established safety profile, reduced hospitalizations, and improvements in quality-of-life measures, p19 inhibitors clearly stand out amongst the currently

available advanced therapeutic options for patients. This has further been reinforced in network meta-analyses of phase 3 registrational studies, which place risankizumab, for example, as among the most effective agents for inducing UC remission and potentially superior in patients naïve to advanced therapies. However, any conclusions regarding comparative efficacy from network meta-analyses are limited by the heterogeneity in trial designs and endpoint definitions across phase 3 trials in CD and UC.[25] Looking ahead, the future is bright for these therapies, with several active and pending pivotal trials targeting IL-23 inhibition, either as monotherapy, or in combination with other targeted therapies.

Despite these positive features, questions do remain amongst clinicians on how to choose between the three anti-IL-23 therapies currently available for CD and UC, while other limitations to IL-23 inhibition in IBD prevent it from achieving broad dominance in the field. These therapies have not been able to surpass the therapeutic ceiling for objective endoscopic disease remission, which remains below 40% in registrational trials for both UC and CD. Additionally, evidence supporting IL-23 therapy in special IBD populations is limited, such as patients with concomitant IMID not driven by the IL-23/Th17 pathway, patients with severe hospitalized UC, and those with complex perianal fistulizing CD. Ongoing clinical studies aim to address these limitations. For example, the efficacy and safety of guselkumab in fistulizing, perianal CD is currently being evaluated in the phase 3 placebo-controlled FUZION trial, with the primary outcome of fistula remission (closure) at week 24.[26] In addition, an ambitious head-to-head trial of risankizumab vs guselkumab is being planned, to identify differences in the efficacy of these therapies in CD. Moreover, excitement continues to grow regarding combination advanced therapy strategies that include p19 inhibition, which may achieve much higher rates of objective resolution of inflammation in IBD than is currently observed with monotherapies or immune targeting approaches. This broad research activity, taken together with robust safety data and a wide therapeutic index, IL-23 inhibitors are poised to increase their impact in the management of IBD.

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