ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Dose Optimization of Interleukin-23 Inhibitor Therapies in Inflammatory Bowel Disease

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G&H How are the pharmacokinetics and pharmacodynamics of interleukin-23 inhibitors similar to or different from other biologics in inflammatory bowel disease?

GL Interleukin (IL)-23 inhibitors differ significantly from other biologics in inflammatory bowel disease (IBD) because of their linear clearance and low immunogenicity as well as their highly targeted, tissue-specific pharmacodynamics. Although IL-23 inhibitors function as monoclonal antibodies similarly to anti–tumor necrosis factor (TNF) agents and anti-integrins, their pharmacokinetic and pharmacodynamic profiles offer unique therapeutic advantages.

Selective IL-23 inhibitors such as risankizumab (Skyrizi, AbbVie), mirikizumab (Omvoh, Lilly), and guselkumab (Tremfya, Johnson & Johnson) typically use an initial weight-based or fixed intravenous (IV) induction followed by regular subcutaneous maintenance dosing. This mirrors older biologics such as infliximab or vedolizumab (Entyvio, Takeda), which also require IV induction. However, some IL-23 inhibitor regimens permit longer maintenance intervals (eg, dosing is every 8 weeks for risankizumab, but conventional maintenance dosing of guselkumab is every 4 weeks and every 4 weeks for mirikizumab). Also, IL-23 inhibitors exhibit highly predictable, stable linear clearance profiles. Conversely, anti-TNF agents are known for nonlinear, rapid clearance driven by severe, active intestinal inflammation. This often creates a sink effect in which these agents are rapidly lost through the stool. IL-23 inhibitors also have exceptionally low immunogenicity. The rate of antidrug antibodies (ADAs) forming against IL-23 inhibitors is significantly lower than that of anti-TNF therapies. Patients using anti-TNF agents frequently require concomitant immunomodulators to suppress ADA formation and prevent secondary loss of response. IL-23 inhibitors typically do not require such combination therapies because they maintain stable serum drug concentrations as monotherapy.

In terms of pharmacodynamics, IL-23 inhibitors selectively bind the p19 subunit of the IL-23 cytokine, blocking its binding to the IL-23 receptor. This is more precise than ustekinumab, a dual IL-12/23 inhibitor that targets the shared p40 subunit. It is also fundamentally distinct from anti-TNF agents, which bind systemic TNF-α, blocking a broad array of inflammatory cascades. IL-23 inhibitors also have intestinal tissue specificity. The IL-23 pathway is heavily localized to mucosal and gut-associated lymphoid tissue rather than circulating systemically. In contrast, anti-TNF agents cause broad systemic immunosuppression, and anti-integrins are entirely gut-selective because they physically block leukocyte trafficking into the gut tissue. IL-23 inhibitors occupy a middle ground, as they are systemically available but block a pathway heavily skewed toward active intestinal lesions. Additionally, when an IL-23 inhibitor binds the p19 subunit, it stops the activation of Janus kinase (JAK) 2 and tyrosine kinase 2, which prevents the phosphorylation of the transcription factor STAT3. Consequently, it halts the differentiation and survival of pathogenic T helper 17 (Th17) cells, suppressing the production of further downstream destructive cytokines such as IL-17, IL-22, and localized TNF-α.

G&H What is the rationale for dose optimization of IL-23 inhibitors in IBD?

GL There are several scientific and clinical arguments that support dose optimization. Although IL-23 inhibitors have

revolutionized management of immune-mediated diseases, a large proportion of patients still do not achieve complete disease control. In moderate-to-severe Crohn's disease and ulcerative colitis, standard-dose maintenance clinical remission rates are generally between 40% and 50%. Another argument is that pharmacokinetic data reveal a definitive exposure-response relationship for IL-23 inhibitors, especially during induction. Patients with higher systemic drug concentrations consistently achieve higher rates of clinical, endoscopic, and histologic remission. Conversely, patients with low serum drug levels—often driven by high body weight, severe baseline inflammation, or rapid drug clearance—frequently face primary or secondary treatment failure. Also, standard, fixed-dose regimens assume the patient has a moderate inflammatory burden. In highly active disease, massive tissue expression of IL-23 binds standard doses of the drug before it can achieve therapeutic saturation. Dose optimization via shortening the interval or increasing the dose ensures complete tissue receptor blockade, allowing the drug to access and diminish the pathogenic Th17 axis effectively. In addition, unlike anti-TNF therapies or JAK inhibitors, selective IL-23p19 inhibitors carry a very clean safety profile. They preserve the IL-12 pathway, which keeps systemic immune surveillance against intracellular infections intact. It is perceived that the IL-12 pathway drives intestinal inflammation in IBD. IL-12 is secreted by immune cells to promote Th1 cell responses, stimulate interferon-γ production, and trigger the early tissue damage and immune cascade characteristic of chronic gut disorders. Because clinical trials and real-world registries show no significant increase in serious infections or adverse events at higher doses, clinicians have a wide therapeutic window to escalate doses without compromising patient safety.

G&H How is loss of response different in patients who stop responding vs those who just need intensified dosing?

GL The primary difference lies in whether the loss of response is caused by a pharmacokinetic failure (insufficient drug levels) or a pharmacodynamic/mechanistic failure (the drug works, but the disease has bypassed its mechanism). Clinicians use therapeutic drug monitoring (TDM) to measure trough drug concentrations and ADAs to differentiate between these mechanisms. Patients who need intensified dosing include those who experience nonimmune pharmacokinetic failure. The biologic mechanism of the drug is still effective, but the patient's body is clearing the medication too quickly. Rapid clearance can be driven by a high inflammatory burden, low serum albumin, high body mass, or severe mucosal leakage. In this scenario, trough drug levels are low, but ADAs are completely absent. Increasing the dose or shortening the interval between doses successfully recaptures clinical response in 50% to 70% of these patients.

Patients who completely stop responding face permanent therapeutic failure with the current molecule because the underlying disease processes have fundamentally changed or blocked the drug. This occurs either presumably because of mechanistic escape in which the disease mutates or adapts, bypassing the drug's target path and utilizing alternative inflammatory pathways instead, or because the patient's immune system develops high titers of neutralizing ADAs that destroy or block the medication. Patients show either high/therapeutic drug levels with ongoing active inflammation (proving mechanistic failure) or undetectable drug levels alongside high antibody titers. Giving more drug is not beneficial and can increase patient risk of developing adverse events. Patients with high antibodies may switch to another drug within the same class, whereas those with mechanistic escape must switch to an entirely different drug class.

G&H Are therapeutic target levels currently available for any IL-23 inhibitors?

GL Established therapeutic target levels or routine TDM do not currently exist for IL-23 inhibitors in IBD. Although retrospective studies (primarily for risankizumab) explore exposure-response relationships and potential maintenance thresholds, routine TDM remains strictly investigational. Unlike for anti-TNF agents, clear concentration cutoffs tied to clinical or endoscopic remission have not been validated or standardized for the selective IL-23 inhibitors risankizumab, mirikizumab, and guselkumab. As mentioned, these agents feature linear clearance, long half-lives, and low immunogenicity, which historically reduces the immediate clinical urgency for routine drug level monitoring.

However, clinical studies and consensus data suggest specific therapeutic concentration thresholds for ustekinumab in IBD management: an induction threshold of roughly 3.7 μg/mL at week 8 and maintenance trough targets ranging from 1.0 to 4.0 μg/mL. In the induction phase, serum levels at or above 3.7 μg/mL around week 8 are linked to positive clinical response rates, whereas in the maintenance phase, target trough concentrations of 1.0 to 3.0 μg/mL (and up to >4.0 μg/mL in some specialized cohorts) correlate with improved rates of sustained clinical remission and biomarker normalization. Recently presented data have suggested that in cases where patients require dosing interval shortening (eg, from every 8 weeks to every 4 weeks), real-world data demonstrate that achieving median maintenance levels between 6.2 and 9.8 μg/mL optimizes clinical and biological outcomes. Nevertheless, TDM for ustekinumab is still considered developing compared with older anti-TNF therapies, and universal

guidelines are not yet formally standardized. Higher drug levels are generally associated with better endoscopic and biochemical outcomes (such as reduced C-reactive protein or fecal calprotectin), helping clinicians decide whether to maintain or reduce injection intervals or switch therapies.

G&H Could you discuss real-world evidence of dose intensification with IL-23 inhibitors?

GL Real-world evidence confirms that dose intensification is actively used in clinical practice to manage suboptimal responses or secondary loss of response to IL-23 inhibitors. Although IL-23 inhibitors generally demonstrate exceptional drug survival and long-term durability, dose intensification can serve as an effective clinical tool in IBD. The strongest real-world data for IL-23 dose optimization exist for Crohn's disease and ulcerative colitis with risankizumab. Multicenter real-world studies show that shortening the maintenance interval (eg, escalating risankizumab from every 8 weeks to every 4 weeks) successfully recaptures clinical response in roughly 62.5% of patients who experienced a secondary loss of response. In cases of severe clinical degradation, real-world protocols often deploy an IV rescue dose (eg, a 1200 mg IV infusion of risankizumab) prior to shortening the subcutaneous maintenance interval. Additionally, real-world tracking shows that patients with prior exposure to other biologics, specifically the IL-12/23 inhibitor ustekinumab, carry a significantly higher likelihood (up to a 5.6-fold increase) of needing dose intensification to achieve or maintain clinical remission. Real-world registries report that intensifying the dose of IL-23 inhibitors does not increase the risk of serious adverse events or infections, mirroring the favorable safety profile seen in clinical trials.

G&H What side effects have been reported from dose intensification of IL-23 inhibitors?

GL Although older biologics like anti-TNF agents often carry a higher risk of side effects when doses are elevated, selective IL-23p19 inhibitors have a distinctively flat safety profile. It has been shown that higher exposure or elevated dosing of anti-TNF therapy, especially when combined with other immunosuppressants such as corticosteroids or immunomodulators, generally correlates with an increased risk of serious infections in IBD. However, active, uncontrolled IBD itself is associated with a high baseline infection risk, making therapeutic balance vital. It is thus hard to discern if it is the higher dose that is driving the higher infection incidence in this scenario. When patients undergo dose escalation with IL-23 inhibitors, the observed side effects remain consistent with those of standard dosing. The most common mild-to-moderate side effects include upper respiratory tract infections, nasopharyngitis, urinary tract infections, mild-to-moderate headaches, arthralgia, fatigue, and injection site reactions. Transient weight gain has been observed in some clinical cohorts, although this is primarily attributed to the presence of improved disease control and mucosal healing. Unlike other advanced therapies, increasing the dose of an IL-23 inhibitor does not show a linear increase in opportunistic infections or sepsis. Dose escalation rarely triggers secondary immune-mediated hypersensitivity or serum sickness, and long-term and high-dose extension data have shown no associated increase in malignancies or major adverse cardiovascular events. Because targeting the p19 subunit leaves the protective IL-12 immune pathway intact, the body retains much of its natural ability to fight off pathogens even at higher drug concentrations. Consequently, dose optimization is increasingly viewed by practitioners as a safe and effective mechanism to recapture clinical response in refractory IBD.

G&H Are there any data for combinations of IL-23 inhibitors and immunomodulators?

GL Data exist for combining IL-23 inhibitors and immunomodulators in IBD, although the clinical utility of such combinations differs significantly from combining immunomodulators with older biologics like anti-TNF agents. Data regarding ustekinumab combined with traditional immunomodulators such as azathioprine or 6-mercaptopurine show limited added clinical benefit. Large clinical registry analyses and clinical trials (eg, the UNIFI and UNITI long-term extensions) indicate that adding an immunomodulator does not significantly increase clinical response or remission rates compared with ustekinumab monotherapy. Traditional combination therapy is primarily used to prevent ADAs, but ustekinumab naturally has a very low rate of immunogenicity. Consequently, co-administration does not provide the same clear protective effect against loss of response that is observed when combining immunomodulators with anti-TNF therapies.

As for selective IL-23 inhibitors, there are several subgroup analyses from phase 2 and 3 randomized controlled trials. Subgroup data from registration trials consistently show that clinical and endoscopic remission rates remain excellent regardless of whether a patient receives concurrent immunomodulator therapy. Because second-generation selective IL-23 inhibitors display high stability, low immunogenicity, and an optimized safety profile, international consensus guidelines generally support using them as monotherapy rather than adding a traditional immunomodulator.

However, although such combinations do not appear to affect efficacy, they can impact the safety profile of the treatment regimen. Data from retrospective cohort studies and real-world registries note that when serious

or opportunistic infections requiring hospitalization occur in patients taking advanced IBD therapies, they are frequently linked to the concomitant use of systemic corticosteroids or traditional immunomodulators. Because of these findings, research has largely shifted away from combining IL-23 inhibitors with traditional immunomodulators. Instead, investigators are evaluating advanced combination treatment, which pairs an IL-23 inhibitor with a nonoverlapping advanced biologic or small molecule (eg, combining guselkumab with golimumab in the VEGA trial) to treat severe, multi-refractory IBD.

G&H Is there a rationale for using dual biologic therapy before dose optimization with IL-23 inhibitors?

GL The clinical rationale for initiating dual biologic therapy before attempting dose optimization with IL-23 inhibitors rests on overcoming the therapeutic ceiling of monotherapy by targeting different, nonoverlapping inflammatory pathways simultaneously. Although dose optimization pushes a single mechanism to its limit, it cannot address alternate pathways of inflammation if the patient's disease has bypassed or evolved past the IL-23 axis. The selective IL-23 inhibitors are highly effective at neutralizing the p19 subunit to block upstream cytokine signaling but do not directly halt already-activated leukocyte migration or macrophage activation. Combining an IL-23 inhibitor with an anti-integrin or an anti-TNF agent targets separate biologic cascades. For example, vedolizumab blocks lymphocyte trafficking to the gut mucosa while the IL-23 inhibitor suppresses systemic cytokine differentiation. Increasing the dose of the IL-23 inhibitor would still not address leukocyte trafficking.

In patients with severe, medically refractory IBD, it is biochemically sound to assume that multiple pathways are active. Dual biologic therapy can be initiated first because escalating a single drug's dose yields diminishing returns if the underlying disease has successfully established a mechanistic escape route.

Historically, escalating anti-TNF doses carried high risks of systemic immunosuppression and infection, as previously discussed. The newer selective IL-23p19 inhibitors and gut-selective integrin inhibitors have good safety profiles and low immunogenicity. Because these individual agents carry lower baseline toxicity, combining them sequentially or simultaneously provides a wide therapeutic window. Clinicians prefer to leverage this safe multitarget approach early on, rather than delaying it to try an optimized monotherapy dose that may still fail to break the therapeutic ceiling.

Additionally, many IBD patients experience extraintestinal symptoms such as psoriatic arthritis, ankylosing spondylitis, or pyoderma gangrenosum. High-dose IL-23 inhibitor monotherapy may effectively treat the luminal gut inflammation but fail to control specific systemic manifestations driven by TNF-α or other cytokines. Utilizing dual biologic therapy addresses the phenotypic diversity of the disease immediately across both the gut mucosa and peripheral organ systems, which dose optimization of an IL-23 inhibitor alone cannot achieve.

G&H What are the priorities of research?

GL Research priorities involving IL-23 inhibitors in IBD focus on comparative effectiveness, precision medicine through drug monitoring, and combination approaches. Direct comparisons between selective IL-23p19 inhibitors would be helpful to determine optimal selection. Research is also needed to evaluate performance in difficult-to-treat phenotypes such as perianal Crohn's disease, pouchitis, and complex extraintestinal manifestations. There should also be research investigating the clinical benefits of deploying IL-23 inhibitors earlier in the disease course rather than waiting for conventional treatment or anti-TNF failure. There is also a need to establish validated target serum trough concentrations and robust pharmacokinetic-pharmacodynamic thresholds to guide maintenance and dose optimization, as well as to identify multi-omics and molecular biomarkers that accurately predict individual patient response or primary nonresponse to specific p19 inhibitors. Research should also explore the safety and synergistic efficacy of combining IL-23 inhibitors with other advanced mechanisms of action for refractory cases and should develop alternative delivery mechanisms, including oral IL-23 inhibitor formulations.

Disclosures

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Suggested Reading

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