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Targeting the IL-12/23 Pathway for Inflammatory Bowel Disease: Current Concepts and Future Directions

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Medical therapy for inflammatory bowel disease (IBD), which includes both Crohn's disease (CD) and ulcerative colitis (UC), has rapidly evolved in the last twenty years. Anti-tumor necrosis factor (TNF) therapy was the first of the biologic agents on the market. Up to one-half of patients either will fail to respond to anti-TNF agents or will eventually lose response. Newer biologic agents targeting the IL-12/23 pathway are effective in treating IBD, even among patients who have previously failed other mechanisms including anti-TNF therapy and steroids. Ustekinumab is first in class for IBD. With a favorable safety profile and excellent efficacy, first line use of this agent in patients with IBD is appropriate. Nevertheless, as the newest category of biologic on the IBD market, this class remains somewhat unfamiliar to many clinicians and patients. This review aims to answer common questions regarding IL-12/23 drug mechanism, safety, efficacy, clinical application, and therapeutic pipeline.

INTRODUCTION

Interleukins 12 and 23 (IL-12 and IL-23) play a crucial role in the pathogenesis of Crohn's disease and ulcerative colitis, and serve as a target for new biologic therapies. IL-12 and IL-23 induce inflammation in the gastrointestinal tract by promoting the differentiation of T lymphocytes, which are critical in regulating the inflammatory cytokine cascade.[1] Monoclonal antibody therapy to the p40 subunit of IL-12 and IL-23 in the form of ustekinumab, a fully human IgG1 antibody, is one of the newest treatment options for CD and UC, as either first line therapy or for those with lost response to existing biologic therapy.[2] This therapeutic pathway has proven effective and attractive due to a favorable side effect profile and ease of use. Novel agents that specifically antagonize IL-23 alone are also in various stages of development (risankizumab, brazikumab, mirikizumab, and guselkumab) and may further improve safety profile and efficacy.

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Mechanism, Efficacy, and Safety

Ustekinumab was the first biologic on the market with the target of IL-23. The drug blocks both IL-12 and IL-23 through binding the common subunit p40. The binding of p40 prevents interaction with cell surface receptors inhibiting downstream signaling and cytokine production.[2] Ustekinumab has been

approved by the Food and Drug Administration (FDA) for the treatment of psoriasis and psoriatic arthritis in 2009, Crohn's disease in 2016, and ulcerative colitis in 2019.

UNITI-1 and UNITI-2 trials explored response rate to ustekinumab among patients with moderately to severely active Crohn's disease, in those who had failed anti-TNFs and those not previously exposed to anti-TNFs, respectively. Response rate at week 6 was greater than 30% in TNF-exposed and greater than 50% in TNF non-exposed, both significant in comparison to placebo. Those receiving maintenance therapy every 8 weeks had a statistically significant high rate of remission at week 44 (53% versus 35% for placebo).[3] Likewise, in the UNIFI trial, ustekinumab was more efficacious than placebo for inducing and maintaining remission in patients with moderate to severe ulcerative colitis. Fifteen percent of patients had clinical remission at week 8, which was significantly higher than that among patients who received placebo (5.3%) ($p<0.001$). Endoscopic healing at week 8 was observed in 26%. Week 44 clinical remission was observed in 43% of those receiving every 8 week maintenance dosing as compared to 24% receiving placebo ($p=0.002$).[4]

Although there are no expert consensus guidelines for therapeutic drug monitoring, particularly with newer agents, achieving optimal ustekinumab drug levels has been tied to improved clinical outcome. Post-hoc analysis of the UNITI trials suggests that at week 26 or beyond, the mean trough concentration of ustekinumab was at least 4.5 in patients with a favorable response. Endoscopic response was seen in 76% and endoscopic remission in 28% of those achieving similar drug levels.[5] Antibody formation has been observed to be low with ustekinumab with low immunogenicity in comparison to the anti-TNF class. Antibody formation is seen in 2% of exposed patients.[6] Based on this data, combination therapy with immunomodulator is less likely to be necessary with this drug. Use of azathioprine, 6-mercaptopurine, or methotrexate did not result in observed statistically significant increase in serum drug levels of ustekinumab as compared to those without immunomodulator use at week 10 and 26 of therapy.[5]

Monotherapy is generally effective in the absence of patient history of anti-drug antibody formation or coexisting indications, such as arthralgias, that may benefit from methotrexate. When loss of response occurs, it is then reasonable to check a drug level and anti-drug antibody. Escalation of ustekinumab dosing is associated with recapture of response in greater than 30% of patients. Dose escalation can be achieved either through repeat single intravenous (IV) induction dosing or escalating to every four week dosing.[7]

The safety profile of ustekinumab is excellent and has been studied in a large patient cohort with psoriasis (n>12,000) – the Psoriasis Longitudinal Assessment and Registry (PSOLAR) registry. Malignancy was observed at a rate of 0.68/100 patient years, major adverse cardiovascular events (MACE) was observed at a rate of 0.33/100 patient years, serious infection was observed at a rate of 1.60/100 patient years, and mortality was observed at a rate of 0.46/100 patient years. The study concluded that there was no increased risk of malignancy, MACE, serious infection, or mortality with ustekinumab use as compared to placebo.[8] In the ustekinumab drug trials in patients with CD, two cases of non-melanoma skin cancer were observed in those on therapy.[1,9] Although there are no head-to-head trials comparing safety amongst the various biologic categories, overall safety data is favorable for serious adverse events with ustekinumab as compared to anti-TNF agents in network meta-analysis studies,[10] and a lower rate of serious infections and tuberculosis has been observed with ustekinumab.

Use in Specific IBD Populations

The anti-TNF class, in particular infliximab, has the only randomized controlled trial for fistula closure. Based on subgroup analysis, ustekinumab appears to be efficacious in managing fistulas and therefore is an option for patients with fistulizing Crohn's disease. Secondary analysis in the UNITI and IMUNITI trials suggested a reduction by 50% in number of draining fistulas and fistula resolution in 25%. This is comparable to published data on fistula closure rates with anti-TNF agents.[11]

The efficacy of anti-TNF agents and vedolizumab has previously been established for both Crohn's disease of the pouch and antibiotic resistant chronic pouchitis. Ustekinumab is also being examined for Crohn's of the pouch and refractory pouchitis. Case series suggest that ustekinumab has some efficacy in the management of antibiotic refractory pouchitis in patients with UC after ileal pouch-anal anastomosis

(IPAA). Observed was both a decrease in number of bowel movements per day as well as endoscopic improvement.[12,13] One study of 47 patients with CD of the pouch and 9 patients with chronic pouchitis, the majority of whom had previously been treated with either anti-TNF therapy or vedolizumab after pouch creation, found 83% demonstrated clinical response 6 months after induction with ustekinumab.[12]

Poorly controlled bowel inflammation has been well established as the primary driver of adverse pregnancy outcomes for both mother and child. Priority should always be given to treating active disease; and, ustekinumab appears to be a reasonable drug option in pregnancy. Based on limited available data, ustekinumab is not associated with increased rates of congenital abnormalities or spontaneous abortion.[14] Ustekinumab has been shown to cross the placenta to the infant and does pass into breast milk in minute detectable amounts; however, rates of infection and developmental milestones are similar in those exposed to biologics and those not exposed.[15] Ustekinumab use is compatible with breastfeeding.

When choosing to use ustekinumab extra-intestinal manifestations should be considered. As the drug is approved for psoriasis and psoriatic arthritis, it is a good drug choice for IBD patients with comorbid psoriasis as well as those with psoriaform eruptions from anti-TNF therapy. Those with anti-TNF induced alopecia may also benefit from switch to ustekinumab.[1] Ustekinumab did not show efficacy in ankylosing spondylitis (AS) unlike anti-TNF therapies. Controlling IBD associated arthopathy symptoms has not been directly compared between ustekinumab and anti-TNF agents. A patient's history of antibody formation should also be considered. With low immunogenicity, it is a good choice for patients with secondary loss of response to anti-TNFs in the setting of antibody formation. In addition, safety profile should be considered. Ustekinumab may be a particularly good therapeutic choice for older patients, those at higher risk of infections, and those with prior treated malignancies.

Novel IL-23 Antibody Drugs

More targeted, IL-23 specific biologics (rizankizumab, brazikumab, mirikizumab, guselkumab) are in development for IBD. Specific targeting of IL-23 has already been shown in head-to-head trials to have superior efficacy to ustekinumab for immune-mediated conditions like psoriasis.[16] IL-23 specific agents act through binding the p19 subunit specifically inhibiting the IL-23 pathway and not the IL-12 pathway. Risakizumab is FDA approved for severe plaque psoriasis, and is being tested in Crohn's disease and ulcerative colitis, currently in phase 2/3 trials. In Crohn's disease, the phase 2 study demonstrated 30% clinical remission at week 12, which was statistically greater than those receiving placebo (p=0.048). Many of these patients were previously exposed to anti-TNF agents.[17] At week 52, clinical remission was maintained in 71% patients on risankizumab.[18] Brazikumab has also been studied in moderate to severe Crohn's disease patients having previously failed anti-TNF therapy (phase 2) and shows early efficacy. Clinical response occurred in 49% of patients receiving brazikumab at week 8 as compared with 26% receiving placebo (p=0.010) and clinical response was observed in 53% of patients at week 24.[19] Mirikizumab has been studied in UC and is in trials in CD. In patients with UC week 12 clinical remission was observed in 22% which was significant compared to placebo and clinical response occurred in 59% of patients. At week 52, 46% of patients were in clinical remission.[20] Guselkumab, another IL-23 antibody is FDA approved for severe plaque psoriasis and is in phase 2/3 trials in CD.

De Novo IBD with IL-17A Antibody Drugs

IL-17A is a cytokine, which acts further downstream from IL-12 and IL-23. The blockade of IL-17A with biologic agents has shown promising results in immune mediated disease processes such as psoriasis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis. Sekukinumab and ixekinumab are examples of FDA approved drugs for such indications. Interestingly, secukinumab and brodalumab have not been efficacious for CD or UC, and were actually associated with increased disease activity in early phase trials. There are multiple case reports of fulminant new onset IBD in patients who received IL-17A antagonists such as secukinumab and ixekinumab for alternate indications.[21,22] Providers should be aware when prescribing these therapies that they are not appropriate for patients with comorbid IBD and new gastrointestinal symptoms precipitated by these drugs require endoscopic evaluation.

CONCLUSION

Drugs that target IL-23 (alone or IL-12/23) have shown excellent efficacy in both CD and UC and are appropriate for both biologic naïve patients and those with loss of response to the anti-TNF class. Ustekinumab is now FDA approved for both UC and CD. Ustekinumab has excellent efficacy, a favorable safety profile, and less immunogenicity than older biologics. As a subcutaneous injection that can be given every 8 weeks it is a medication of convenience with ease of administration that is an attractive option for patients with IBD. As prescribers become more familiar and comfortable with ustekinumab it may be prescribed first line with greater frequency.

There are multiple IL-23 specific drugs in the pipeline, which will likely also be approved for UC and CD in the near future and will compete with ustekinumab as first line options. These drugs have further specificity and have the potential to provide greater efficacy (as in psoriasis) and may have an equal or more favorable side effect profile. These medications will be excellent choices for patients with a similar profile to those on ustekinumab. We look forward to head-to-head comparisons between IL-12/23 and IL-23 agents for efficacy and safety in IBD as well to trials of combination therapy with other biologics for enhanced efficacy in the most challenging patients. ■

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