ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Use of Interleukin-23 Inhibitors for the Treatment of Inflammatory Bowel Disease

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G&H Why did interleukin-23 inhibition become a treatment approach for inflammatory bowel disease?

EL There are several reasons. One is that overexpression of interleukin (IL)-23 has been noticed in inflammatory areas of the gut, and IL-23 can trigger effector cells that can generate and maintain the inflammatory response. Second, several genetic variants impacting the IL-23 pathway, mainly involving the IL-23 receptor, have been described as being associated with Crohn's disease, ulcerative colitis, and other immune-mediated inflammatory disorders. Thus, it appears that IL-23 not only is expressed in inflammation, but seems to have a pathogenic role, as the variants on this pathway, including the IL-23 receptor, may be associated with inflammatory bowel disease (IBD) itself. Finally, several animal models have shown that inhibition of IL-23, through different mechanisms, was associated with improvement of colitis. All these reasons suggest that interfering with IL-23 in patients with IBD is a good therapeutic strategy.

G&H How do the IL-23 inhibitors currently available for IBD treatment differ in terms of pharmacology?

EL There are currently 2 categories of IL-23 inhibitors. First-generation IL-23 inhibition consists of nonspecific, dual cytokine inhibition of IL-12 in addition to IL-23, namely with ustekinumab (Stelara, Janssen), meaning that this drug can interfere with both pathways. Newer, or second-generation, IL-23 inhibitors on the market include risankizumab (Skyrizi, AbbVie), mirikizumab (Omvoh, Lilly), and guselkumab (Tremfya, Janssen), along with others in development, such as brazikumab.

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These antibodies are directed toward the p19 subunit of IL-23, which is specific for that cytokine, meaning that those agents only inhibit IL-23.

Preclinical studies have shown that inhibition of IL-23 appears to be more important in IBD, whereas inhibition of IL-12 may not be useful in IBD. However, the latter still has not been specifically studied because there is currently no specific inhibitor of only IL-12, which would be needed to confirm whether such inhibition has an impact. Another aspect is that inhibiting only IL-23 and not IL-12 eliminates potential side effects that would be linked to the inhibition of the latter cytokine. IL-12 is involved in anti-infection defense against

different types of microbes. Therefore, only inhibiting IL-23 may result in less difficulty with infection and associated issues, although this has not been clearly demonstrated in clinical trials thus far.

G&H Do these agents differ in terms of efficacy in Crohn's disease or ulcerative colitis?

EL At this stage, it appears that IL-23 inhibitors are as effective in Crohn's disease as in ulcerative colitis. Studies have shown that these drugs were superior to placebo and met a majority of secondary endpoints, in addition to primary endpoints, in both Crohn's disease and ulcerative colitis, both in bio-naive and bio-refractory patients. As with many available advanced therapies, not only was the proportion of patients reaching primary and secondary endpoints superior to placebo in first-line treatment, but also in second-line treatment, particularly after anti–tumor necrosis factor (TNF) therapy, where efficacy was well preserved.

As for the individual drugs, the second-generation IL-23 inhibitors, which selectively inhibit only IL-23 and not IL-12 at the same time, appear to be more effective than dual inhibition of IL-12 and IL-23 in the first generation. This potential superiority is not currently understood perfectly but has been clearly shown in several trials. Both risankizumab as well as guselkumab have been demonstrated to be superior to ustekinumab in the treatment of patients with plaque psoriasis. In IBD, mainly in Crohn's disease, several trials have suggested the superiority of risankizumab, guselkumab, and probably also mirikizumab over ustekinumab for some endpoints such as endoscopic remission, which is considered to be quite a stringent outcome and endpoint. For example, the recent SEQUENCE trial was a head-to-head, open-label trial of risankizumab vs ustekinumab in moderate to severe Crohn's disease patients who had experienced inadequate response or unacceptable side effects with anti-TNF therapy. The study found that risankizumab was superior in terms of endoscopic remission at week 48 and was noninferior to ustekinumab in terms of clinical remission at week 24. Additionally, in the phase 3 GALAXI-2 and -3 trials, guselkumab showed superiority over ustekinumab on endoscopic endpoints at week 48 of maintenance therapy.

G&H How safe are the drugs in this class, and are there any differences in safety?

EL Currently, both ustekinumab as well as the newer agents all have very reassuring safety profiles. The rates of side effects and serious adverse events were lower with the active drugs as compared with placebo. No worrying side effects were disclosed by the clinical trials. The most frequent side effects were upper gastrointestinal and respiratory tract symptoms as well as infection (mainly viral and of mild intensity). Even so, all of these drugs appear to be very safe thus far.

> Data have shown that patients typically prefer subcutaneous over intravenous administration and also prefer more time between doses (eg, injection every 8 weeks over injection every 2 or 4 weeks).

G&H Do there appear to be any significant differences among the second-generation IL-23 inhibitors?

EL It is currently unknown whether there are significant differences among the newer IL-23 inhibitors such as risankizumab, guselkumab, and mirikizumab. These drugs are very similar, but their affinity for IL-23, their immunogenicity, the way they interact with other receptors in the immune system, and their tissue distribution may differ. However, thus far, it is very difficult to know whether these potential differences may have any impact on important clinical outcomes. There are no head-to-head trials comparing the various second-generation agents, and the study results that are available thus far comparing these drugs with placebo appear to be very similar.

G&H How should providers and patients choose among the different IL-23 inhibitors?

EL So far, there appears to be a small advantage with the second-generation IL-23 inhibitors over ustekinumab in the treatment of psoriasis, and probably also Crohn's disease, so the newer agents may be preferred. However, superiority has not yet been demonstrated in other settings such as ulcerative colitis. Within the various second-generation IL-23 inhibitors, I would say that it is very difficult to choose so far, provided that they have indeed

demonstrated their efficacy and safety, as some of these agents are still undergoing study for some indications. As mentioned, the efficacy and safety of the second-generation drugs appear to be quite similar. However, there are some differences in terms of administration—intravenous vs subcutaneous—as well as in frequency of dosing. Subcutaneous induction has been shown to be effective with guselkumab in Crohn's disease, whereas only intravenous induction has been tested with risankizumab and mirikizumab. Mirikizumab needs to be injected every 4 weeks for maintenance, whereas risankizumab can be injected every 8 weeks and guselkumab every 4 or 8 weeks (depending on the dose). Data have shown that patients typically prefer subcutaneous over intravenous administration and also prefer more time between doses (eg, injection every 8 weeks over injection every 2 or 4 weeks). These issues have to be considered when providers discuss treatment choices with their patients.

G&H Which IL-23 inhibitors are in development for IBD treatment?

EL A number of IL-23 inhibitors are currently being developed for different indications. There are also oral drugs targeting the IL-23 pathway that would probably be interesting candidates for future therapies in IBD. Patients may prefer oral drugs over injectable drugs. These drugs are still being developed, so we will have to see whether they will prove to be efficacious.

G&H What other research is still needed in this area?

EL Our understanding of the pharmacodynamics of these drugs is incomplete. In particular, we need to know what are the optimal doses of these drugs in individual patients. It is not certain whether there is a linear dose-effect curve, and the drug exposure associated with the best outcomes has not been clearly established. It is also important to know that IL-23 also stimulates other cytokines such as IL-17 and IL-22, which may have deleterious effects on inflammation as well as protective effects for the mucosal and epithelial barrier. This might mean that in some situations too much inhibition of IL-23 would not be optimal.

Another aspect that requires important study is the combination of advanced therapies, such as IL-23 inhibitors with other antibodies or small molecules. We have to better understand the biologic impact on inflammation of the IL-23 inhibitors and the intestinal barrier integrity of these treatments to determine what would be the best combinations. Currently, a series of clinical trials are combining IL-23 inhibitors such as guselkumab with anti-TNF agents such as golimumab, for example. Combining these classes is certainly very interesting, and such research is important for the future.

The community is well aware that the second-generation IL-23 inhibitors are more specific for IL-23 than ustekinumab and is also aware that the differences among the second-generation drugs are currently not so well established. These drugs are well-positioned in IBD, but we still have to better understand their effects, and we should not consider that everything is known about this pathway and about the mechanisms of these drugs. I think we still have a lot to learn about them before they can be used in the best way possible.

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Suggested Reading

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