ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Inhibition of Interleukin-12 and/or -23 for the Treatment of Inflammatory Bowel Disease

Bruce E. Sands, MD
Dr Burrill B. Crohn Professor of Medicine
The Dr Henry D. Janowitz Division of Gastroenterology
Icahn School of Medicine at Mount Sinai
New York, New York

G&H Which agents have been evaluated for inhibiting interleukin-12 and/or -23 for the treatment of inflammatory bowel disease?

BS A handful of agents have been, or are currently being, looked at as inhibitors of either interleukin (IL)-12 and -23 or just IL-23. Ustekinumab (Stelara, Janssen), which was recently approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe Crohn's disease, is an antibody directed against the p40 subunit shared by IL-12 and -23. Thus, ustekinumab inhibits both of these cytokines. In addition, some clinical data have been presented on risankizumab (Boehringer Ingelheim) and MEDI2070 (MedImmune in conjunction with Amgen and AstraZeneca). These 2 agents bind the p19 subunit, which is found only in IL-23. Therefore, these agents are more specific for blocking IL-23 itself. Finally, LY3074828 (Lilly) is an anti-p19 antibody currently in clinical trials for the treatment of Crohn's disease (ClinicalTrials.gov identifier NCT02891226) and ulcerative colitis (NCT02589665).

G&H What are the mechanisms of action of these agents?

BS IL-12 and -23 are important cytokines that are involved in adaptive immune responses. IL-23 is important for the development of T helper 17 cells, which are thought to be effector cells in inflammatory bowel disease (IBD). In addition, findings from genetic studies have implicated IL-12 and -23 in susceptibility to IBD. More importantly, there is also a polymorphism of the IL-23 receptor that is highly protective for IBD, suggesting that by blocking IL-23 signaling it is possible to decrease the risk of developing Crohn's disease or ulcerative colitis. Thus, blocking IL-23 downregulates aspects of the immune system that are thought to be important in causing these diseases.

G&H What is the rationale for inhibiting only IL-12 or -23 instead of both?

BS Interestingly, before it was known that p40 was a subunit in both IL-12 and -23, drug studies were targeting what was thought to be only IL-12 by blocking p40 with an antibody. In theory, both are important in IBD, but mechanistically, preclinical or animal models of IBD suggest that IL-23 may be more important. It may be beneficial to block IL-12 as well, but there may be some theoretical safety benefits to blocking only IL-23. For example, animal models suggest that blocking IL-23, in contrast to IL-12, may be helpful in terms of colon cancer prevention, which is important in patients with IBD, as the risk of colon cancer is increased when IBD affects the large bowel. Thus, there is at least a theoretical rationale for wanting to block only IL-23. That being said, the safety experience of blocking both IL-12 and -23 via an anti-p40 antibody has been good.

This information is important to know because some gastroenterologists have not yet learned much about IL-12 and -23 and what these cytokines do in the immune system. Just as gastroenterologists learned about the importance of tumor necrosis factor (TNF) blockade and the ability to block the $\alpha_4ß_7$ integrin as a treatment for IBD, so too will the community learn more about this mode of therapy, what it is capable of doing, and its advantages and disadvantages.

In particular, inhibiting IL-12 and/or -23 seems to be beneficial even for patients with Crohn's disease who may have been previously treated with TNF inhibitors, including some patients who have had primary failure with these agents. Additionally, the safety profile of this approach appears to be favorable in comparison to TNF inhibition.

G&H What have clinical trials revealed thus far regarding the efficacy of ustekinumab for the treatment of Crohn's disease?

BS There have been 2 parallel induction studies on ustekinumab. One study, UNITI-1, focused on patients who had previously been on and, in some way, failed treatment with anti-TNF agents, whereas the other study, UNITI-2, looked at patients who had failed either corticosteroids or immune modulators. A relatively small number of patients in UNITI-2 may have been on an anti-TNF agent as well, but they stopped it for reasons other than failure or loss of response. In both of these patient populations, there was a powerful induction effect, although the drug seemed to be more efficacious in the patients who had no prior treatment with anti-TNF agents. This is the case for nearly all agents that have been looked at in IBD; patients who have previously been treated with a TNF blocker are somewhat more resistant to treatment.

The highest dose of ustekinumab that was studied in the UNITI program was approximately 6 mg/kg, which was given as an intravenous (IV) loading dose. By week 8, 34% of patients refractory to TNF inhibitors experienced clinical response compared with 22% of patients who received a placebo infusion. In contrast, patients who were naive to anti-TNF agents had response rates of approximately 56% with ustekinumab compared with 29% for placebo.

With the more rigorous outcome of clinical remission in TNF-inhibitor–refractory patients in UNITI-1, at week 8 the response rate was approximately 21% in patients receiving ustekinumab vs only 7% in those receiving placebo infusion. In UNITI-2, which consisted of anti-TNF–naive patients, the response rate was even higher: approximately 40% with ustekinumab vs 20% with placebo. Thus, regardless of whether a patient had prior exposure to an anti-TNF agent, the rates of remission and response were higher with the drug than with placebo treatment, and the drug was effective in all groups.

In a maintenance trial, patients who had responded to induction therapy were given either 90 mg subcutaneous injection of ustekinumab every 8 or 12 weeks or placebo. Clinical remission was maintained in 53% of patients treated every 8 weeks and 49% of patients treated every 12 weeks vs 36% of patients treated with placebo after 52 weeks. Thus, there was a treatment advantage of approximately 17% with 90 mg of ustekinumab every 8 weeks vs placebo. Because the drug has a long half-life, many of the patients who initially entered the maintenance phase were already responding from the induction phase and likely carried their response forward over time.

G&H What studies have been conducted on MEDI2070 and risankizumab?

BS Both of these agents have undergone phase 2 studies in Crohn's disease. For the anti-p19 antibody MEDI2070, patients who had experienced primary nonresponse, loss of response, or intolerance to a TNF blocker were randomized to receive 700 mg IV of drug or placebo at days 1 and 29, and were followed for 12 weeks. At week 8, which was the primary analysis, 49% of patients in the MEDI2070 arm had a clinical response compared with 27% in the placebo arm, which was a statistically significant difference. Thus, it appears that the blockade of p19 (or specifically of IL-23) can produce roughly equivalent efficacy to that seen with ustekinumab.

As for risankizumab, which is also a p19-directed antibody, 2 different doses were explored in a placebo-controlled, double-blinded study. By week 12, researchers found that the 600-mg dose was more effective, with clinical remission rates of approximately one-third of the treated patients compared with 15% of patients receiving placebo. In addition, approximately 20% of patients receiving risankizumab achieved endoscopic remission at week 12 compared with only 2.6% receiving placebo, signaling that p19 blockade can be effective in patients with Crohn's disease.

G&H Have clinical trials been conducted on any of these agents for the treatment of ulcerative colitis?

BS At this point, no studies have been completed in ulcerative colitis with any of these agents. However, 2 studies are underway, one with ustekinumab (NCT02407236) and one with the anti-p19 antibody LY3074828 (NCT02589665).

G&H Thus far, what are the most common adverse events associated with inhibitors of IL-12 and/or -23?

BS Ustekinumab has a long safety record from its use in psoriasis. Although the dosing and patient population are different than in IBD, the drug seems to be safe, which is important given the role of IL-12 and -23 in maintaining immune homeostasis. In the UNITI maintenance study, adverse event rates with the drug were very similar to those seen with placebo. There did not appear to be an appreciable increase in infections, including serious ones,

nor an apparent increase in cancers or cardiovascular toxicity. Similar safety is expected for the p19 blockers.

G&H Are there any potential drug-drug interactions with these agents?

BS I am not aware of any drug-drug interactions. Many of the patients who entered the UNITI studies were already on combinations of corticosteroids and immune modulators, and these drugs did not seem to increase the risk of the studied drug. Thus, in the usual drug combinations that patients with IBD might have, no real safety concerns have emerged.

G&H If approved, where would these agents fit in the IBD treatment algorithm?

BS So far, the research on these agents has been in the setting of Crohn's disease, so at least until phase 3 studies are conducted in patients with ulcerative colitis, the use of these agents will be restricted to patients with Crohn's disease. The question of where these agents fit in the algorithm of Crohn's disease treatment is interesting because ustekinumab, and perhaps the entire class of IL-12 and -23 inhibitors, appears to have approximately the efficacy of TNF inhibitors but perhaps an even better safety profile. Therefore, it is conceivable that these agents might be used before TNF inhibitors. It is also conceivable that these agents could be used in conjunction with or before immune modulators, after the failure of corticosteroids, or perhaps even before the use of corticosteroids, if one wished to avoid that class of agents altogether.

It should be noted that use before corticosteroids has not yet been studied, but there is a growing interest in treating early IBD more aggressively, in general, to improve long-term outcomes. Additionally, there have not been any head-to-head comparisons to date of ustekinumab or any of the other agents with a TNF blocker or with vedolizumab (Entyvio, Takeda), which is an anti-$\alpha_4ß_7$ integrin antibody.

G&H Do you think that any of the IL-12 and/or -23 inhibitors could be a candidate for first-line therapy of Crohn's disease?

BS Ustekinumab, which has undergone the most research of these agents, shows excellent efficacy and safety, and, the cost notwithstanding, I could conceive of using this agent as a first-line biologic agent. As far as first-line therapy altogether, I think the cost of biologic agents will generally be prohibitive and will probably be a barrier.

G&H Is it possible to combine these agents with other treatments to improve outcomes?

BS So far, there have not been any studies combining biologic agents, so it is not possible to say at this time whether that would be beneficial. Before the approval of ustekinumab for Crohn's disease, the drug was used in some patients who developed psoriasis in the setting of TNF blockade. In that sense, the drug has already been used in sequence and at least partially overlapping combination with TNF blockers. However, it is too soon to say whether there are specific patients who would benefit from combinations of biologic therapies. Furthermore, it does not appear that there is additional benefit to concurrent treatment of, say, an immune modulator and ustekinumab, although there is concern of immunogenicity of a biologic therapy such as ustekinumab and, therefore, loss of response over time.

G&H What are the next steps in the research of these agents?

BS It should be determined whether this class of agents is effective in ulcerative colitis; in my opinion, it is very plausible that this class would be as effective in ulcerative colitis as it appears to be in Crohn's disease. More information is also needed in the use of these agents in Crohn's disease. For example, there is little information regarding the efficacy of ustekinumab in patients with fistulizing Crohn's disease, which is a patient population with large unmet need. It would also be interesting to understand whether this class of agents could be used as postoperative prophylaxis and whether it could be used in patients with early-onset Crohn's disease (ie, within 2 years of the onset of disease).

In addition, MEDI2070 and risankizumab are currently only in phase 2 study, so further research is needed to evaluate their efficacy and safety before they can be considered by the FDA.

Dr Sands has received consulting fees from Janssen, Boehringer Ingelheim, Lilly, MedImmune, AstraZeneca, Amgen, AbbVie, and UCB. His institution has received research grants from Janssen, Amgen, and AbbVie.

Suggested Reading

Sandborn W, Gasink C, Blank M, et al. A multicenter, double-blind, placebo-controlled phase 3 study of ustekinumab, a human IL-12/23 P40 mAB, in moderate-severe Crohn's disease refractory to anti-TFNα: UNITI-1. *Inflamm Bowel Dis.* 2016;22(suppl 1):S1.

Sandborn WJ, Gasink C, Gao LL, et al; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med.* 2012;367(16):1519-1528.

Sands BE. New drugs on the horizon for IBD. *Dig Dis.* 2014;32(suppl 1):74-81.

Sands BE, Chen JJ, Penney M, et al. Initial evaluation of MEDI2070 (specific anti-IL-23 antibody) in patients with active Crohn's disease who have failed anti-TNF antibody therapy: a randomized, double-blind placebo-controlled phase 2A induction study. *Gastroenterology.* 2015;148(4 suppl 1):S163-S164.