ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Update on Tofacitinib for Inflammatory Bowel Disease

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G&H How does tofacitinib differ from the current therapeutic options for inflammatory bowel disease?

BF Unlike the monoclonal antibodies that comprise many of the newer agents for the treatment of inflammatory bowel disease (IBD), tofacitinib (Pfizer) is a conventional small-molecule drug that can be orally administered. This property is an inherent advantage over the parentally administered monoclonal antibodies. Furthermore, monoclonal antibodies are large–molecular-weight foreign proteins that can induce sensitization with the formation of antidrug antibodies that lead to loss of response or allergic reactions. Because tofacitinib is a small molecule, hypersensitivity reactions are uncommon.

At the same time, it is important not to assume that tofacitinib is necessarily safer than monoclonal antibodies just because it is an oral drug. Small-molecule drugs frequently cause dose-dependent toxicities as a result of off-target side effects. In contrast, monoclonal antibodies are highly selective and are generally not associated with dose-dependent toxicity. It is important to recognize that tofacitinib is a potent immunosuppressive agent.

G&H What is the mechanism of action of tofacitinib?

BF Tofacitinib inhibits the Janus kinase (JAK) family of proteins, which consists of JAK 1, 2, and 3 and the related kinase tyrosine kinase 2 (TYK2). When cell surface receptors for various cytokines interact with the JAKs, signal transduction pathways are activated that result in chemical messages being sent to the cell nucleus. This process results in the selective production of messenger RNA and the subsequent synthesis of inflammatory proteins, primarily members of the interleukin (IL) family, including IL-2, -4, -6, -7, -9, -12, -15, -21, -23, and -27. However, these pathways also regulate synthesis of other proteins, such as erythropoietin, which is important for generating new red blood cells, growth hormone, prolactin, and some members of the interferon family. In summary, JAKs are intracellular proteins that participate in the cell signal transduction process for a wide range of important proteins.

Essentially, tofacitinib inhibits these signal transduction pathways, resulting in downregulation of a variety of inflammatory mediators. Several JAK inhibitors have been developed for the treatment of rheumatoid arthritis, IBD, and psoriasis. Each of these agents has variable selectivity for the different JAK isotypes (JAK 1, 2, 3, and TYK2). In this respect, tofacitinib broadly inhibits JAK 1, 2, and 3. In ulcerative colitis, the dominant benefit is likely via JAK 1 inhibition with downregulation of IL-6 and interferon-gamma. However, additional data from translational medicine studies are needed to confirm this hypothesis. Importantly, the optimal specificity for the various JAK isotypes is unknown, and whether inhibition of multiple isotypes is a desirable or an unfavorable attribute remains uncertain.

Although clinical experience with JAK inhibitors is at an early stage, an evolving understanding of these agents is available for the treatment of rheumatoid arthritis, and phase 2/3 trials in ulcerative colitis and Crohn's disease have been completed.

G&H What is the rationale for using tofacitinib in patients with IBD?

BF An overexpression of proinflammatory cytokines exists in IBD, including IL-6 and interferon-gamma, which are potent mediators of the TH1 response. Some of the best therapies in IBD, such as tumor necrosis factor (TNF) antagonists, target cytokines.

G&H What clinical trials have been conducted thus far on the use of tofacitinib in patients with ulcerative colitis?

BF Findings from a phase 2 clinical trial were published several years ago in the *New England Journal of Medicine*, with Dr William Sandborn as the first author. This trial gave a very strong signal that tofacitinib was effective for induction of remission in ulcerative colitis and explored 3 different doses of the drug vs placebo: 5 mg, 10 mg, and 15 mg. Patients had an excellent response, with the highest dose group having almost a 70% response rate.

However, there were safety concerns such as hyperlipidemia and viral infections for the highest dose group, and the US Food and Drug Administration subsequently mandated that only the 10-mg dose should proceed with clinical development. Therefore, the most recent data only involve the 10-mg dose, given twice daily, vs placebo in phase 3 trials.

The results of the tofacitinib induction studies, OCTAVE-1 and -2 (Oral Clinical Trials for Tofacitinib in Ulcerative Colitis), have been presented at international meetings but have not yet been published. These 2 studies were large, consisting of more than 500 patients in each, and conventional in design. Patients with active ulcerative colitis were randomized to drug or placebo for 8 weeks. The primary endpoint was remission at the end of the study, defined as a Mayo score of less than 2, with no individual clinical subscore greater than 1 and the rectal bleeding subscore less than 0.

Importantly, the endoscopic results were all read centrally by a blinded observer, which is a methodologic advance that has occurred in more recent ulcerative colitis studies. At the end of 8 weeks, the 2 trials had similar results—there was a therapeutic gain of roughly 10% to 13% over placebo in remission rates at week 8. The results of the secondary endpoints of these induction trials, such as mucosal healing, were consistent with the primary outcome comparisons.

Although at first these numbers may not look impressive, it is important to recognize that the study participants were highly treatment-refractory; many of the patients had failed TNF-blocker therapy, which is a poor prognostic sign, and all had failed conventional therapies for ulcerative colitis. In addition, at baseline, approximately half of the patients were receiving corticosteroids, further demonstrating that these patients were exceedingly difficult to treat.

G&H What adverse events have been reported with tofacitinib?

BF In the OCTAVE studies, adverse events, including serious side effects, did not differ between the treatment and placebo groups. Having said this, safety differences are not often detected in short (8-week) ulcerative colitis studies. Tofacitinib is an immunosuppressive drug, and its safety profile is fairly well established in rheumatoid arthritis. As expected with immunosuppressive drugs, there is an increased risk of infection with tofacitinib, particularly viral (herpetic) infections.

Several other adverse events are specific to tofacitinib. These include elevations in both low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, which are caused by the effects of JAKs on pathways that affect intermediate metabolism. In addition, some patients will develop anemia because production of erythropoietin, one of the proteins driving bone marrow production of red blood cells, is also decreased by JAK inhibition. Notably, these unique side effects of tofacitinib are not seen with monoclonal antibodies.

G&H Due to these adverse events, should tofacitinib be avoided in any patients?

BF The presence of severe anemia or previous infectious complications would probably be a relative contraindication. Although it would seem sensible to avoid use of the drug in patients with multiple cardiac risk factors, both HDL ("good" cholesterol) and LDL ("bad" cholesterol) are increased in a minority of patients. Therefore, the net effect on cardiac risk is currently unknown. Tofacitinib has been on the market for rheumatoid arthritis for several years now, so a large number of patients have been exposed.

G&H Has there been any research on the use of this drug for maintenance?

BF The 2 induction studies also had maintenance components, which were recently completed. A press release by the manufacturer indicated that the primary endpoints of the trials had been met. The maintenance findings will likely be published or presented soon.

G&H Has tofacitinib been studied in Crohn's disease as well?

BF In Crohn's disease, only one phase 2 study has been completed. This trial was a disappointment, in that it was a multiple-arm dose-finding study that did not show significance against placebo, and had a very high placebo rate. Therefore, limited information is available regarding the use of tofacitinib in Crohn's disease.

G&H Where is tofacitinib in terms of the approval process by the US Food and Drug Administration?

BF The US Food and Drug Administration is currently reviewing tofacitinib for use in ulcerative colitis. A decision is expected within the next 6 months.

G&H If approved, where would this agent fit in the IBD treatment algorithm?

BF Gastroenterologists, like most doctors, are conservative by nature, so tofacitinib would likely be used initially as a salvage drug in patients who have failed TNF antagonists or vedolizumab (Entyvio, Takeda). However, this drug likely has a role earlier in the treatment paradigm for select patients. Research investigating this area is greatly needed.

Another possibility that has not yet been explored is the use of tofacitinib in combination with other drugs. Although this strategy might lead to a higher incidence of side effects because of additional immunosuppression in many diseases, including IBD, combination therapy is more effective than monotherapy with an acceptable safety profile. For example, tofacitinib might be a good partner for vedolizumab, an alpha-4 beta-7 antagonist that is highly effective in ulcerative colitis.

G&H Could tofacitinib eventually be used even as a first-line IBD therapy?

BF First-line therapy in ulcerative colitis is 5-aminosalicylic acid, which is completely safe and fairly effective for mild to moderate disease. However, tofacitinib could perhaps be used in lieu of corticosteroids.

G&H Might it be possible to use tofacitinib in all IBD patients as salvage therapy?

BF Additional Crohn's disease studies would have to be conducted. I do not believe that the previously described negative phase 2 study really showed that the drug does not work in Crohn's disease. Filgotinib, another JAK inhibitor that is more specific for JAK-1, will be entering phase 3 studies in Crohn's disease. The results of one study do not show that JAKs are ineffective in Crohn's disease.

G&H Are there any other JAK inhibitors in clinical development?

BF There are approximately half a dozen agents currently under development. However, not much data are currently available apart from positive findings from filgotinib in the Crohn's disease phase 2 study presented at this year's Digestive Disease Week.

G&H What are the next steps in research for tofacitinib?

BF It is important to understand which patients could be optimally treated with this agent and whether there are biomarkers that can predict response. In addition, I am still intrigued by the 15-mg dose and whether a higher dose could be used safely, as well as whether tofacitinib could be used in combination with other agents.

Dr Feagan has been a consultant to both Pfizer (tofacitinib) and Galapagos (filgotinib).

Suggested Reading

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