ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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New Targets for Small Molecules in Inflammatory Bowel Disease

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G&H What small molecules are already in routine use for the treatment of inflammatory bowel disease?

WS Historically, we have treated inflammatory bowel disease (IBD) using small molecules such as prednisone, budesonide, and mesalamine, along with immunosuppressive drugs such as azathioprine, 6-mercaptopurine, and methotrexate. Until infliximab (Remicade, Janssen) was approved in 1998, the treatment of IBD was entirely based on small molecules. Since that time, virtually all new medications approved for IBD have been biologics.

G&H What is a small molecule?

WS A small molecule is an organic compound that has a low molecular weight (<900 daltons). Biologic drugs are made by living cells and usually are larger than small-molecule inhibitors.

G&H What small-molecule targets are currently under clinical investigation?

WS There has been a resurgence of interest in small molecules in recent years. The broad classes for which new agents are currently in clinical development include Janus kinase (JAK) inhibitors, such as tofacitinib (used to treat rheumatoid arthritis); S1P receptor modulators, such as RPC1063 (ozanimod); and SMAD7 antisense inhibitors, such as mongersen.

These new agents are still in various phases of clinical development. Tofacitinib is currently in a phase 3 study for the treatment of ulcerative colitis and a phase 2 study for Crohn's disease; 2 of the S1P modulators are in phase 2 studies for ulcerative colitis, with a phase 3 study for ulcerative colitis and a phase 2 study for Crohn's disease now getting underway; and mongersen is currently being investigated in a phase 2 clinical trial of Crohn's disease.

G&H How do S1P modulators work?

WS S1P is an abbreviation for sphingosine-1-phosphate. Some effector lymphocytes express chemokine receptor 7 on their surface. This receptor guides the lymphocytes into lymph nodes throughout the body. The vessels going out of lymph nodes are lymphatic vessels lined with lymphatic endothelium, which has a gradient of S1P. In order for lymphocytes to leave the lymph nodes, the S1P receptors on the surface of the lymphocyte must bind to S1P.

S1P modulators cause these S1P receptors on the surface of lymphocytes to be internalized and degraded. This change makes it impossible for the lymphocytes to leave the lymph nodes because the lymphocytes cannot bind to the S1P gradient on the lymphatic endothelium. As a result, the lymphocytes are trapped in the lymph nodes. This trapping reduces the peripheral lymphocyte count, thereby reducing circulating effector T cells. This leads to a selective suppression or modulation of the immune system.

This strategy has been applied in the treatment of multiple sclerosis with fingolimod. For IBD, a drug known as RPC1063, or ozanimod, has been shown in phase 2 studies to be effective for the treatment of both multiple sclerosis and ulcerative colitis. Another such agent, APD334, will also be entering clinical trials for ulcerative colitis and Crohn's disease.

G&H How do the JAK inhibitors work?

WS The 3 Janus kinases—JAK1, JAK2, and JAK3—bind small molecules targeted to these kinases to varying degrees. A JAK inhibitor may be relatively more potent for JAK1, JAK2, or JAK3. The JAK inhibitor tofacitinib is particularly potent against JAK1 and JAK3, with some inhibition of JAK2. This class of drugs can also block what is known as the JAK-STAT pathway, which leads to immunosuppression.

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

WS My colleagues and I conducted a phase 2 study of tofacitinib as induction therapy for Crohn's disease that was published in *Clinical Gastroenterology and Hepatology* in 2014. In this study, 139 patients with moderate to severe Crohn's disease were randomly assigned to treatment with a range of tofacitinib doses or placebo, given twice daily for 4 weeks at 48 centers in 12 countries. We did not see a significant difference in clinical response between patients receiving the experimental drug vs patients receiving placebo. We did observe a reduction in C-reactive protein and fecal calprotectin levels among patients taking the 15-mg dose of tofacitinib, indicating biologic activity of this agent. Subsequently, a larger phase 2b trial in Crohn's disease has been completed, and the results are expected later this year.

G&H Could you describe the clinical trial findings of this agent in the treatment of ulcerative colitis?

WS We studied this drug in a double-blind, phase 2 study for moderately to severely active ulcerative colitis that was published in the *New England Journal of Medicine* in 2012. A total of 194 patients were randomly assigned to 1 of 4 dose levels of tofacitinib or placebo, given twice daily for 8 weeks. The clinical response rate was statistically significantly higher among the experimental groups vs the placebo group. Clinical remission rates ranged from 13% (for the lowest dose) to 41% (for the highest dose) among the experimental arms, vs 10% for the placebo arm. We observed a dose-dependent increase in low-density and high-density lipoprotein cholesterol, and an absolute neutrophil count of less than 1500 among 3 patients treated with tofacitinib.

Based on these findings, there are currently 2 large induction trials aimed at putting patients into remission and a longer-term study focused on the maintenance of remission. All of these studies have completed patient enrollment and will finish next year.

G&H Would you expect more side effects in a longer study of tofacitinib?

WS The completed studies for patients with ulcerative colitis were only 8 weeks long. Usually, any side effects resulting from the use of immunosuppression arise later and, therefore, would not be observed during the span of a short study. In studies of rheumatoid arthritis, some patients experienced infections, and a low but seemingly real increase in lymphoma was reported. These side effects are similar to those expected with azathioprine, another immunosuppressant used to treat IBD.

G&H What other JAK inhibitors are being investigated for the treatment of IBD?

WS An inhibitor known as GLPG0634 is being studied for use in Crohn's disease. Another inhibitor, ASP015K, which has been studied for rheumatoid arthritis, may also be tested for ulcerative colitis.

G&H Is there any rationale for concentrating on inhibiting JAK1, JAK2, or JAK3?

WS Some work has shown that blocking JAK2 results in more anemia and other hematologic side effects. Interestingly, there are JAK2 inhibitors approved for the treatment of myelofibrosis, a hematologic disorder, lending support to this notion. Researchers have also been trying to explore whether a drug that was selective for JAK1 or JAK3 could achieve the desired anti-inflammatory effect without severe infection or immunosuppression. There are several ongoing studies looking at selectively targeting JAK1 or JAK3.

G&H What is currently known about the efficacy of mongersen, an antisense oligonucleotide targeting SMAD7?

WS Mongersen has been investigated in a phase 2 study for use in Crohn's disease. This drug is administered orally and uses a delayed-release delivery system to carry the active ingredient to the ileum and right colon.

A recent report by Monteleone and colleagues that was published in the *New England Journal of Medicine* showed a large clinical effect in this double-blind, phase 2 study. In the study, patients were randomly assigned to treatment with 1 of 3 doses of mongersen or placebo, with treatment taken once per day for 2 weeks. Patients at the 2 highest dose levels achieved statistically significantly higher rates of remission compared with patients taking placebo. The side effects appeared to be mostly related to the underlying Crohn's disease and not the

drug itself. Based on these results, a phase 3 study is now being planned.

G&H Ultimately, might these drugs be used in the treatment of all patients, or would specific subtypes be more likely to benefit?

WS Based on the trial data, we know that not every patient responds to a particular drug. Ultimately, we would like to understand why some patients respond and some do not, so that we could treat the patients who would benefit and avoid prescribing a drug to patients who would not respond. The research to investigate such subgroups, however, is still in its very early days.

G&H Can different small-molecule inhibitors be combined in order to improve outcomes?

WS In theory, different small-molecule inhibitors could be combined. The crucial factor is knowing how immunosuppressive the drug is. Combining multiple drugs that suppress the immune system can be dangerous. Aside from this concern, these drugs could be safely combined. The other issue is cost. Individually, the cost of each proprietary drug is high, so combining drugs may not be practical.

G&H Would these drugs be given as a first-line treatment?

WS Of the agents we have discussed here, mongersen could be a candidate for first-line therapy. We need more data regarding the safety and tolerability of S1P modulation to assess its suitability for first-line therapy. JAK inhibitors are not likely to be acceptable as first-line therapy due to concerns about immunosuppression.

Dr Sandborn is a consultant for Receptos, Arena Pharmaceuticals, Pfizer, and Celgene.

Suggested Reading

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