ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

The Role of Small Molecule Inhibition of Leukocyte Trafficking in Inflammatory Bowel Disease

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G&H What is the role of leukocyte trafficking in the pathogenesis of inflammatory bowel disease?

HR It is well known that inflammatory bowel disease (IBD) is an autoimmune disease. We are not certain which antigens or autoantigens drive the process, but we know that the process depends upon the movement of lymphocytes. Lymphocytes recirculate through blood, secondary lymphoid organs, and lymph nodes, and return to the circulation through lymphatics. Antigen presented by dendritic cells causes clonal expansion of autoreactive T cells. To damage tissue in an autoimmune response and recruit neutrophils and macrophages to enhance collateral tissue damage, lymphocytes need to enter tissue and encounter the antigen that they recognize and then orchestrate an inflammatory response. Thus, a key part of the pathogenesis of IBD is the movement of lymphocytes through the bloodstream into the tissue, and then the activation of those lymphocytes and the secretion of a variety of cytokines that then amplifies the autoimmune damage to the tissue.

G&H Which small molecule inhibitors of leukocyte trafficking are currently being studied for the treatment of IBD?

HR The drug in the most advanced stage is ozanimod (Zeposia, Bristol Myers Squibb), of which I am an inventor. The drug recently completed a phase 3 study for ulcerative colitis (True North) and is under priority review by the US Food and Drug Administration (FDA), with a decision likely by the end of May 2021. Ozanimod is also undergoing phase 3 investigation for Crohn's disease that is expected to continue through 2022. In addition, a variety of other small molecule inhibitors of leukocyte trafficking, including amiselimod and etrasimod, are in earlier phases of development.

G&H How does this mechanism work in ozanimod?

HR Altering lymphocyte trafficking is generally a useful method to treat certain autoimmune diseases. Ozanimod is a sphingosine-1 phosphate (S1P) receptor agonist that modulates the movement of lymphocytes and has a variety of additional effects, resulting in multistep interdiction of the pathogenesis of the autoimmune disease. The term multistep interdiction is used because the same receptor that modulates lymphocyte trafficking also modulates a variety of other functions. The receptor is found on lymphocytes as well as on plasmacytoid dendritic cells and endothelial cells. In endothelial cells, it tightens the endothelial barrier, diminishing leakage into the lamina propria of the gastrointestinal tract. In lymphocytes, the receptor modulates trafficking. It sequesters activated lymphocytes, which then fail to migrate into the lamina propria, where they can cause damage. In addition, modulation of the S1P receptor inhibits autoamplification of the inflammatory response by suppressing production

of key cytokine feedback loops, most particularly the interferon alpha autoamplification loop. Data show that modulating the S1P receptor suppresses cytokine production in both multiple sclerosis and IBD and provides protection from cytokine response syndrome in viral infections, including H1N1 influenza. There is suppression of interferon alpha, interleukin 17, and a range of downstream cytokines that represent the interferon signature, which is frequently associated with significant subsets of patients with autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, and IBD.

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Thus, there is not only an impact directly on lymphocyte trafficking, but there are additional effects involving endothelial integrity, leakage of fluid and inflammatory materials into the lamina propria of the gut, prevention of lymphocytes from directly damaging the gut mucosa (ie, mucosal protection), and suppression of cytokine amplification that also limits the recruitment of other leukocytes (ie, protection of gut integrity). Over time, these multiple effects lead to protection of the mucosa and suppression of the inflammatory response. These are seen in patients clinically as an improvement in their clinical signs and symptoms, endoscopically as the protection and healing of the mucosal surface, and histologically as the inhibition of the inflammatory response in biopsies of the gastrointestinal tract.

G&H What are the advantages of using a small molecule for the inhibition of leukocyte trafficking?

HR Small molecules are small organic synthetic chemicals that are selected for their activity on specific targets. Through their activity on these targets, they mediate useful clinical effect. This is classic pharmacology. A ligand is made for a receptor. It binds to the receptor and drives certain functions. The advantages of small molecules are that they are small (<500 atomic mass units in molecular weight) and are orally bioavailable. In the case of ozanimod, the induction and maintenance doses are 0.92 mg per day in a small oral capsule. Thus, the drug has the advantages of being orally administered and not requiring parenteral treatment or admission to a hospital or infusion center to initiate treatment.

G&H What are the most recent clinical trial data on ozanimod?

HR Results of the True North study for ulcerative colitis were presented at gastroenterology meetings last year. The *P* values for the primary endpoints in the 12-week induction phase as well as the 52-week maintenance phase in moderate to severe ulcerative colitis compared with placebo were less than .0001. There was a distinct advantage over placebo, and the scale of the advantage appeared to be in the range that would be expected from the biologics that are currently the standard of care for moderate to severe ulcerative colitis. Although ozanimod has not been directly compared with biologics, a high proportion (>40%) of the patients enrolled in the phase 3 studies already had experience on biologics and had, in fact, failed biologic therapy. In addition, there was a cohort of patients between 12 and 18 years of age enrolled in the ulcerative colitis study, whereas the inclusion criteria are 12 to 75 years of age in the ongoing Crohn's disease phase 3 study, suggesting that this mechanism is well tolerated regardless of age in the setting of moderate to severe disease.

The drug appears to be promising for the patients who respond to it, keeping in mind that IBD has always been a disease of patient subsets, and there does not appear to be a single agent that induces fully efficacious and well-maintained responses in 100% of patients. Therefore, the best outcome for patients is when they have options with different mechanisms and treatment modalities, and physicians have the opportunity to personalize treatment so that the mechanism and tolerability can be tailored to the needs of an individual patient.

G&H What is the rate of response with this treatment approach?

HR The rate of response may vary. One of the features of this mechanism is that it sequesters lymphocytes and inhibits the migration of disease-causing T lymphocytes to tissue, causing efficacy to improve over time.

Therefore, it is important to look at response in 2 phases. Some patients may respond very quickly in the induction phase and then are well maintained, whereas other patients may respond slowly in the induction phase but are well maintained over time. It is important that over time physicians generate the data and experience to know how best to use agents with this new mechanism.

G&H Thus far, do there seem to be any safety or toxicity issues associated with this approach?

HR This mechanism has been proven to be highly safe and efficacious in multiyear phase 3 studies in multiple sclerosis, for which the agent is already on the market. Thus, there is a large multiyear, clinical safety database that informs the tolerability of the mechanism. The phase 3 safety data set for the True North study was comparable to that seen for multiple sclerosis. There are no black box warnings associated with ozanimod under the multiple sclerosis label, and the drug has not been associated with significant or severe infectious consequences. The most common infectious complication is herpes zoster, and a full course of varicella zoster virus vaccination is recommended for antibody-negative patients. The most common side effects include elevations of aminotransferases. Ozanimod is currently approved for relapsing forms of multiple sclerosis in the United States, Europe, and other countries.

G&H Should ozanimod be avoided in any patients with IBD?

HR Labeling for ulcerative colitis is not yet available. In multiple sclerosis, the drug is contraindicated in patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, or decompensated heart failure, and in patients who have certain cardiac conduction abnormalities without a functioning pacemaker.

In addition, it is important to ensure that patients have been vaccinated against shingles before initiating therapy because a small shingles signal has been seen with ozanimod. A drug interaction has been reported with tyramine, so it may be worth counseling patients to avoid certain foods while taking the drug. The full list of precautions can be found in the FDA label.

G&H If approved, where does ozanimod fit in the treatment algorithm for IBD?

HR Given its tolerability, oral bioavailability, and the absence of black box warnings, I would hope that, if priced correctly, it could be used in both naive, as well as biologically experienced, patients with IBD. It has potential utility both before and after the use of biologics in moderate to severe ulcerative colitis. However, as previously mentioned, it is important to match individual patients with mechanisms and treatment modalities that are well tolerated and suited to their particular needs.

G&H What are the next steps in research in this area?

HR The next step is to obtain a more complete understanding of the role of this mechanism in Crohn's disease, where it is expected to have advantageous efficacy and tolerability as well. In my opinion, the key is to begin to understand which groups of patients are particularly helped by this mechanism and then to determine how they can be identified and treated early to ensure the fewest consequences in terms of the development of the disease and its associated pathologies. As a general approach, understanding patient subsets and their responses is helpful to efficiently target the appropriate therapies for patients, and thus improve their quality of life and protection from pathology.

Disclosures

Dr Rosen is an inventor of ozanimod (Zeposia), and, as such, his institution, his laboratory, and the inventors all share in the royalty proceeds.

Suggested Reading

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