ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Positioning Sphingosine-1 Phosphate Receptor Modulators in Inflammatory Bowel Disease

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G&H What was the rationale for first considering sphingosine-1 phosphate receptor modulators as a treatment approach for inflammatory bowel disease?

BS Biologic therapies have revolutionized the treatment of inflammatory bowel disease (IBD) since the introduction of infliximab in 1998 to the US market. This first biologic agent was very effective but could only be delivered as an intravenous infusion. Subsequent biologic therapies, including vedolizumab (Entyvio, Takeda), ustekinumab (Stelara, Janssen), and, more recently, anti–interleukin (IL)-23 antibodies such as mirikizumab (Omvoh, Lilly) and risankizumab (Skyrizi, AbbVie), are administered intravenously, subcutaneously, or via a combination of both routes. Patients by and large prefer to take medications orally for convenience, but there has been a lack of those types of agents except for more conventional, older therapies such as 5-aminosalicylates, corticosteroids, or classic immunomodulators such as azathioprine and mercaptopurine, which have limitations in safety or efficacy. Thus, there was a need for advanced IBD therapies that were orally delivered.

The rationale for looking at sphingosine-1 phosphate (S1P) receptor modulators is that they had a long history of effective use in multiple sclerosis. The grandparent compound fingolimod, which is a nonselective S1P receptor modulator, has proven to be an effective therapy for patients with relapsing and remitting multiple sclerosis. Building upon that, it was thought that more selective agents may have an improved safety profile and tolerability and may be more effective, leading to their investigation for the treatment of IBD, especially for ulcerative colitis.

G&H How do the S1P receptor modulators currently approved in IBD work?

BS There are currently 2 approved S1P receptor modulators: ozanimod (Zeposia, Bristol Myers Squibb), which is an S1P1 and S1P5 receptor modulator, and, more recently, etrasimod (Velsipity, Pfizer), which is selective for S1P1, S1P4, and S1P5. These agents are more selective than, say, fingolimod, which does not have selectivity for any of the 5 known receptors of S1P. Selectivity is potentially an important concept in terms of safety because S1P receptors are found in many different organs and systems in the body. Most relevant to IBD is the effect on immune cells, which mainly occurs through S1P1 receptor 1. The other receptors also have physiologic effects on renal physiology, the lungs, and brain vasculature. The S1P1 receptor, which is most important for immune trafficking, also has a role in cardiac conduction, making this an on-target effect of these agents, in a sense, although not desirable. Fortunately, the effect of S1P receptor modulators on cardiac conduction is subject to rapid tachyphylaxis, so

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it is only an issue at the start of treatment. Overall, the hope is that the more selective the agent, the better the safety profile. Nevertheless, these agents have a long and excellent safety record in multiple sclerosis and a growing record of safety in ulcerative colitis.

G&H Could you discuss the study designs and key efficacy data involving ozanimod and etrasimod?

BS Ozanimod was the first of these agents to be studied in ulcerative colitis. The phase 3 TRUE NORTH program was designed with a blinded randomized induction cohort, looking at 1 of the doses shown to be effective in phase 2. Week 10 responders were then re-randomized to drug or placebo for approximately 1 year in the maintenance phase. A second cohort received open-label ozanimod, and responders at week 10 were randomized to the maintenance phase to achieve sufficient power. This design was a variation of the classic re-randomization of responders.

In contrast, the etrasimod phase 3 ELEVATE program used a treat-through design in ELEVATE UC 52 in which patients were randomized to a single dose of drug or placebo and followed all the way to week 52, with outcomes reported at week 12 for induction and at week 52 for maintenance. In many ways, this design more closely replicates what providers do in real life when treating patients. We do not have an artificial stop for treatment and label a patient as a nonresponder if they have not responded by a specific, fixed time point, as, in the real world, many factors weigh on the timing of decision-making. For many treatments, more responders can be accumulated by giving the drug more time, particularly if patients have failed 1 or more prior advanced therapies. In addition, ELEVATE UC 12, a 12-week induction study, was performed separately without maintenance because the US Food and Drug Administration requires at least 2 pivotal trials to corroborate results to approve a drug, whereas the ozanimod development program relied on the earlier phase 2 TOUCHSTONE study for corroboration.

Despite the differences in study design, both ozanimod and etrasimod proved to be effective for induction and maintenance in ulcerative colitis patients. Essentially, the primary endpoints were met in both programs, as were a variety of secondary endpoints. The primary endpoints were uniformly clinical remission, which, in ulcerative colitis, incorporates both patient-reported outcomes (stool frequency and rectal bleeding) and an endoscopic outcome in a composite of the modified Mayo Clinic score. Additionally, a number of secondary outcomes such as clinical response, endoscopic improvement, endoscopic remission, histologic response or remission, endoscopic and histologic response or remission, and quality-of-life parameters were all aligned with the efficacy of both of these drugs.

G&H In which patient subgroups did these agents appear to be most effective?

BS It should be first pointed out that approximately 25% to 30% of patients in both development programs experienced prior failure of an advanced therapy, meaning beyond failure of corticosteroids or immunomodulators, such as an anti–tumor necrosis factor agent or vedolizumab. In the case of the ELEVATE program, some of the patients had failed the Janus kinase (JAK) inhibitor tofacitinib (Xeljanz, Pfizer), but these were not the majority of patients in the program. The studies looked at patients who had failed 1 or 2 advanced therapies, but not more. In general, the patients who did best were those who had more moderate disease activity and who had not failed multiple therapies. In post hoc analyses with ozanimod, patients who had failed more than 1 advanced therapy were less likely to achieve clinical remission at week 10 than patients who had failed just 1 advanced therapy. Still, some of the patients who had prior failure of more than 1 advanced therapy did achieve clinical response by week 10, and these patients were randomized into the maintenance phase. In maintenance therapy, these more refractory patients did about as well as the other patients in terms of remission at the end of the year. Thus, the general theme is that patients on the moderate side of disease who had less prior failure of advanced therapies were the patients who responded best to this class of medications and that patients with more severe disease activity or who had failed multiple advanced therapies could still respond, albeit at lower rates overall, and over a longer period of time to reach maximal efficacy.

Interestingly, the ELEVATE program included a subset of patients who had isolated proctitis and were treated with etrasimod. These patients have historically been excluded from large development programs. In the analysis, those patients did as well as, if not better than, the patients who had more extensive colitis. Therefore, that is another subgroup of patients for whom this class of agents appears to be quite good.

G&H Thus far, how do real-world experiences with ozanimod and etrasimod appear to be playing out?

BS In my practice, these medications appear to be living up to what has been reported in clinical trials. However, the uptake of these agents has been relatively slow. This

is a new class of medications unfamiliar to gastroenterologists, even if neurologists have been using this class for many years. For this reason, we have only a small number of recent reports of real-world experience. So far, these reports have substantiated the efficacy of these agents to the same degree as that seen in the pivotal trials.

G&H Could you discuss the key safety data and any potential safety concerns involving these agents?

BS It is interesting to note that these drugs work by sequestering lymphocytes and a variety of immune cells in the lymph nodes and keeping them out of circulation. Therefore, one of the direct effects of treatment with either of these agents is a drop in the lymphocyte count, somewhere between 40% and perhaps as high as 60% from baseline. This is an expected effect of this class of medications. Despite this, the class is not associated with an increased risk of various cancers or opportunistic infections except possibly for herpes infections such as herpes zoster. Accordingly, it is recommended that patients be vaccinated for herpes zoster simultaneously to, or hopefully preceding, initiation of therapy.

However, an effect on cardiac conduction has been seen early in treatment. On average, studies demonstrate a decrease in mean heart rate of perhaps 5 or 6 beats per minute from baseline, so the vast majority of patients are not going to experience symptomatic bradycardia. Nevertheless, this class of medications should not be used in patients who have class 2B or class 3 heart block. All patients should undergo a cardiogram before initiating therapy.

The two development programs took different approaches to the bradycardia effect. Ozanimod, for example, has an initiation dose pack in which there is ramping up of the medication, which leads to tachyphylaxis of the effect on heart rate over the first week. Etrasimod, on the other hand, does not have a ramping up of dose, and all patients start with the full dose of 2 mg once daily. Very few patients in either program had symptomatic bradycardia. The provider is not required to observe patients after the first dose of either medication but needs to tell patients about the potential bradycardia effect, which might manifest as dizziness or lightheadedness. Importantly, major adverse cardiovascular events such as myocardial infarction, thrombosis, and pulmonary embolus have not been seen. Those have been seen with JAK inhibitors, which have a very different and much more significant cardiac risk than do S1P receptor modulators.

Additionally, there is a rare risk of macular edema. This appears to be greatest among patients who have predisposing factors, such as a history of uveitis or diabetes mellitus. The prescribing information for both drugs now indicates that a fundoscopic examination should be performed prior to initiation of therapy. There have been some reports of increased risk of skin cancer with fingolimod. This risk has been extended to the labels of etrasimod and ozanimod as well, so baseline and annual skin checks are suggested. Elevations of liver enzymes (3%-5%) can be seen, so it is recommended that providers check baseline and quarterly liver function tests. Patients in the clinical trials did not meet Hy's Law, so this does not appear to be a significant effect. For some patients, liver enzyme elevations disappeared despite continued treatment. Safety in pregnancy is not known at this point, so it is recommended that women who are planning to become pregnant soon not initiate treatment with these agents and that women of childbearing age be on effective contraception.

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G&H Based on all of this information, what appears to be the optimal positioning of these S1P receptor modulators among the multitude of ulcerative colitis therapies currently available?

BS Right now, the best positioning of the S1P receptor modulators would be for patients who need their first advanced therapy, such as patients who have failed 5-aminosalicylates and/or corticosteroids or immunomodulators, and who want a therapy that is orally dosed and safe. These are the most optimum candidates, along with patients more on the moderate side of moderate to severe disease, although many patients with more severe ulcerative colitis, as signified by the disease activity indices used in clinical trials, still do respond. This is not a therapeutic approach for patients who have acute severe

ulcerative colitis. These agents do not work nearly as quickly as JAK inhibitors, another class of oral agents used in ulcerative colitis, but they can be very effective as a first-line advanced therapy.

G&H Should any other factors be taken into account when trying to decide on a therapy?

BS Choosing therapies in IBD in general has become less algorithmic as more classes of agents have been added. Providers are looking at patient preference much more, as well as risk profiles and extraintestinal manifestations. Through discussion with the patient and shared decision-making, the best choice of therapy can be determined for a specific individual. There may also be constraints imposed by third-party payers in terms of the sequence of therapies. All things being equal, providers want to weigh the patient's preferences against the risks and benefits of the medications and choose the most optimal therapy. Flowcharts and algorithms can no longer easily direct the choice of IBD treatments given the abundance of mechanisms, each with unique attributes, and the specific characteristics and preferences of each patient.

Although gastroenterologists need to learn about the safety issues involving S1P receptor modulators, they are not daunting, and the tradeoff is the convenience of oral dosing of these medications. I think these agents will be used more and more as patients learn about the availability of oral medication to treat their moderately to severely active ulcerative colitis.

G&H What research needs remain regarding these S1P receptor modulators?

BS We would love to see much more real-world evidence than we have so far. It is still early with this new class of agents. Over the next year or two, I think we will see abundant evidence of the efficacy of these agents and that data from the clinical trials translate well to the real world. More investigation is also needed to better predict who is more likely to respond to this class of agents. There have been some suggestions from analyses of subsets of patients included in the trials, but it would be better to be more precise. It would also be helpful to be able to predict more precisely who should not receive these medications because of risks of adverse events, although these medications have excellent safety profiles.

It also needs to be determined whether this class of medications might be effective in Crohn's disease. A recent press release about the YELLOWSTONE phase 3 program for ozanimod in Crohn's disease reported that the study did not meet its primary endpoint of clinical remission at week 12. More information is needed to understand why that might have been the case and whether etrasimod or other agents in this class might be effective in Crohn's disease.

At this past year's Digestive Disease Week, data were presented on 2 other agents in this class. Amiselimod was investigated in a phase 2 study for mild to moderate ulcerative colitis and had positive results. I presented data on tamuzimod, which was effective in a phase 2 study of ulcerative colitis patients. Further research is awaited.

Finally, because S1P receptor modulators are safe oral agents, there is also a desire to think of them as a platform for combination therapy. One could consider, for example, combining these agents with anti–IL-23 antibodies, which are also quite safe, or an anti-p40 antibody such as ustekinumab. Those might be rational combinations to consider, but there may be many others as well.

Disclosures

Dr Sands reports honoraria for consulting and speaking from AbbVie, Bristol Myers Squibb, Celltrion, Janssen, Lilly, Takeda, and Pfizer, and honoraria for consulting and stock/stock options from Ventyx Biosciences.

Suggested Reading

Peyrin-Biroulet L, Dubinsky MC, Sands BE, et al. Efficacy and safety of etrasimod in patients with moderately to severely active isolated proctitis: results from the phase 3 ELEVATE UC clinical programme [published online April 13, 2024]. *J Crohns Colitis.* doi:10.1093/ecco-jcc/jjae038.

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