ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Choosing Among Small Molecule and Biologic Therapies for Patients With Ulcerative Colitis

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G&H How do the small molecule and biologic therapies currently approved for ulcerative colitis differ in terms of mechanism of action and mode of administration?

DH The US Food and Drug Administration (FDA) has approved 3 small molecule therapies for adult patients with moderate to severe ulcerative colitis: the sphingosine-1 phosphate (S1P) receptor modulator ozanimod (Zeposia, Bristol Myers Squibb), the nonselective Janus kinase (JAK) inhibitor tofacitinib (Xeljanz, Pfizer), and the selective JAK1 inhibitor upadacitinib (Rinvoq, AbbVie). Biologic treatments that have been approved by the FDA for moderate to severe ulcerative colitis are the anti–tumor necrosis factor (TNF) agents infliximab and adalimumab (for which biosimilars are available), as well as the anti-TNF agent golimumab (Simponi, Janssen), the α4β7 antagonist vedolizumab (Entyvio, Takeda), and the interleukin (IL)-12/23 inhibitor ustekinumab (Stelara, Janssen).

One of the major differences among these agents is the mode of administration. All of the small molecules are orally administered. As for the anti-TNF biologics, infliximab is administered by intravenous (IV) infusion, adalimumab by subcutaneous injection every other week, and golimumab by subcutaneous injection every 4 weeks. For the other biologics, vedolizumab is administered by IV infusion and ustekinumab by a onetime IV infusion and then subcutaneous injection every 8 weeks.

G&H What types of research are currently available comparing these small molecule and biologic treatments?

DH The ideal evidence consists of head-to-head trials. In all of ulcerative colitis, there has been only 1 head-to-head trial, the VARSITY trial, which was conducted between the biologics vedolizumab and adalimumab. A treat-through study design was used, meaning that the dosages or frequencies of vedolizumab and adalimumab could not be adjusted. At the end of 1 year, both therapies worked in patients with moderate to severe ulcerative colitis, but vedolizumab outperformed adalimumab in both clinical and endoscopic endpoints.

The next level of evidence consists of comparative-effectiveness studies from real-world data, whether collected prospectively or retrospectively, and network meta-analyses. However, although it is important to consider such data, providers should take them with a grain of salt and reflect on whether the findings match what they are seeing in their clinical practice. For network meta-analyses on the remission of ulcerative colitis, we have the most and oldest data with infliximab, which tends to move the drug toward the top. I do not think that necessarily means infliximab works better than all of the other agents for moderate to severe ulcerative colitis; I think it is just a matter of the data that are put into the meta-analyses and the fact that most involve that drug. Based on data on bio-naive patients, all of these treatments work well.

Looking at comparative-effectiveness data on second-line agents (ie, treatment after failing an anti-TNF agent such as infliximab or adalimumab) is where some separation starts to be seen. What we have been seeing is that both the oral nonselective small molecule JAK inhibitor tofacitinib and the biologic IL-12/23 inhibitor ustekinumab outperform the anti-integrin vedolizumab.

It should also be noted that we do not have much data on ozanimod and upadacitinib yet because these agents are so new that they have not been incorporated into much comparative research so far.

Societal guidelines reflect these data. For first-line treatment, all of these agents are good options, so the guidelines do not recommend choosing one over another. Despite the VARSITY study, in which vedolizumab outperformed adalimumab, adalimumab is still a reasonable option for first-line ulcerative colitis treatment. However, for second-line treatment, the aforementioned comparative-effectiveness data lean toward using a JAK inhibitor or ustekinumab. Nevertheless, these data do not mean that vedolizumab does not work in the second line; it is important to take into account the specific characteristics of a particular patient.

G&H How do you choose which of these agents to use in clinical practice?

DH In my mind, treatment selection should start with the efficacy of the drug; everything else, including safety or mode of administration, does not matter if the drug is not going to be efficacious for an individual patient. Thus, the provider should first consider the possible therapies that are appropriate and that would likely work well for an individual patient, and then narrow down the choices with safety considerations, including age and comorbidities, and patient concerns or preferences.

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The first and most important step is to define the extent and severity of the patient's disease, looking at the entire history of their disease course and what their disease activity is at the time of treatment, to determine whether the patient is on the more moderate end of the disease spectrum or the more severe end. In moderate to severe ulcerative colitis, if a patient is on the more moderate end, all of these agents have a good likelihood of working. If a patient has more moderate disease and does not have any extraintestinal manifestations, such as joint pain or skin rash, I usually start with a more targeted therapy such as the anti-integrin vedolizumab, the IL-12/23 inhibitor ustekinumab, or the S1P receptor modulator ozanimod. However, if a patient has extraintestinal manifestations, I lean more toward anti-TNF agents or JAK inhibitors.

The patient population in which a drug was evaluated should also be considered. For example, the majority of patients in the registration trial for ozanimod were bio-naive, and post hoc analyses of the trial showed efficacy in both bio-naive patients and patients failing 1 biologic. Thus, when using ozanimod in clinical practice, I want to use it as a first-line agent or after failure of 1 agent, not as much after failing multiple agents.

If a patient with moderate disease has comorbidities and is older, a more targeted therapy would be best, such as vedolizumab, ustekinumab, or ozanimod, which have better safety profiles. Nevertheless, it is important to keep in mind that all of these agents are safe and that safety is directly tied to the efficacy of a therapy. If a therapy is not going to work, the patient may need to go on corticosteroids or may develop disease complications, so that therapy will not be as safe to use.

The more severe end of the disease spectrum is where anti-TNF agents and JAK inhibitors particularly come into play. Specifically, I use infliximab as my main anti-TNF agent for moderate to severe ulcerative colitis. Based on FDA guidance, JAK inhibitors cannot be used until the patient fails an anti-TNF agent. If a patient has more severe disease and has failed an anti-TNF agent, I would use either of the JAK inhibitors tofacitinib or upadacitinib.

Pregnancy is also an important consideration for treatment selection. As of yet, good data are not available on the safety of the oral small molecules in pregnant patients. There have been some theoretical concerns in animal models about the use of small molecules at high doses. Therefore, oral small molecules are not currently recommended in patients who are thinking about becoming pregnant soon.

G&H How should patients be involved in the decision-making process?

DH As important as anything else is having shared decision-making with the patient and understanding their concerns. Many times, providers assume that the largest patient concern is safety, but that is not always the case. For example, patients may be most concerned about

durability because they have lost treatment response in the past and do not want to feel better for 6 months or a year and then have to switch therapies. The patient's lifestyle should also be discussed. If the patient is traveling often or has a job where it would be difficult to come in frequently for infusions, the patient may prefer to just take a pill or inject themself. Thus, shared decision-making is key and should be intertwined in every step of the discussion that providers have with their patients.

G&H Is cost frequently a large factor in the decision-making process?

DH Cost also tends to be important for patients, but there is no specific drug that has a higher cost per patient across the board. Cost is very variable across different parts of the country, and there are a number of factors that influence the cost that the patient ends up paying and what insurance companies will approve for first- and second-line treatment. With a number of adalimumab biosimilars coming to the market, it will be interesting to see whether there will be a push toward using them for first-line treatment more frequently because of their lower cost to insurance companies.

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G&H After failure of first-line therapy, when should patients stay within the drug class and when should they try a different mechanism of action?

DH After failure of first-line therapy, I think an anti-TNF agent, ustekinumab, or JAK inhibitor has the best evidence for second-line treatment overall. However, when determining second-line therapy, it is important to consider why the first treatment failed. If the patient initially did well with a specific agent and then lost response over time, I think it makes sense to consider staying with that class or type of therapy because it has been shown to work in that patient. On the other hand, if a patient never responded initially to the first agent, I would switch classes. For example, if a patient started on the anti-TNF agent infliximab and never had a good response (ie, the patient was a true primary nonresponder despite the dose being increased and the provider monitoring the drug level), I would not try adalimumab or golimumab; I would switch out of the drug class. In contrast, if the patient has moderate to severe ulcerative colitis and was doing well for years with infliximab but then developed antibodies and lost response, I think staying in that class makes sense since that type of therapy is known to work in the patient; nevertheless, switching classes is also an option.

G&H What are the most important next steps in research?

DH Head-to-head trials are needed for both first-line and second-line ulcerative colitis treatment, in addition to sequencing studies. Some trials are underway, but such research is difficult to design and enroll. Our current data also need to be analyzed further, which is starting to be done with some comparative-effectiveness research, to help providers better understand how to sequence these therapies. There is now a large number of biologic and small molecule options for ulcerative colitis treatment, and the coming introduction of biosimilars will make treatment selection even more complex. Some providers, especially those who do not see many patients with ulcerative colitis, may experience confusion or uncertainty about how to choose among the different options; these providers may be tempted to just stay with the therapies that they are most comfortable with or have the most experience with, even though there may be better options available depending on the clinical situation. Staying up-to-date is important, whether through education or conferences, to understand how to best position treatment.

Disclosures

Dr Hudesman has received research support from Janssen and Pfizer and has served as a consultant for AbbVie, BMS, Fresenius Kabi, Janssen, Pfizer, Takeda, and UCB.

Suggested Reading

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