ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Combining Biologic Agents in Inflammatory Bowel Disease

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G&H What is the rationale for combining biologic agents in inflammatory bowel disease?

MA Most of the biologic agents that gastroenterologists are currently using are monoclonal antibodies against a single target. Usually, that target is a very defined cytokine, and although having a focused target is advantageous, it can also be a disadvantage. The immune response in inflammatory bowel disease (IBD) is likely to be multidimensional, analogous to what is seen in the immune response to an infection. Doctors typically use multiple antibiotics, rather than just one, to treat an infection so that bacteria do not become resistant. Likewise, the immune system can become resistant if only one pathway is targeted at a time.

> Combining drugs may produce complementary effects.

This has been seen in spades in the context of anti–tumor necrosis factor (TNF) therapy, which is the most established of the therapies in the biologic arena. In the short run, which could be years, anti-TNF therapy can be extraordinarily effective, but there is an important subset of patients who develop a bypass mechanism to anti-TNF agents. After some period of success on anti-TNF therapy, the immune system of some patients figures out a way to cause inflammation, even in the face of high levels of an anti-TNF agent. We term this occurrence mechanistic escape, although the nature of this immune response is poorly characterized. What we do know is that it becomes very difficult to treat these patients with any other biologic agents, whether vedolizumab (Entyvio, Takeda), an anti–interleukin (IL)-12/-23 agent such as ustekinumab (Stelara, Janssen), or a Janus kinase (JAK) inhibitor such as tofacitinib (Xeljanz, Pfizer), to recapture the response that was initially seen. It is unclear what causes patients to lose response to anti-TNF agents. Although it might be tempting to hypothesize that using a combination approach might mitigate some of the loss of response to one agent, it is unknown if this would happen.

Combining drugs may produce complementary effects. Anti-TNF therapy inhibits only TNF-α, leaving many other inflammatory cytokines or pathways that might be playing a role in the inflammatory process. Gastroenterologists fairly routinely combine thiopurines and methotrexate with anti-TNF therapy, primarily for the purpose of preventing immunogenicity and increasing blood levels of the anti-TNF agent. However, I would argue that, in fact, there are patients who need the complementary mechanistic effects of both agents.

Anti-TNF therapy is also known to be very effective for treating extraintestinal manifestations of IBD such as arthritis, uveitis, and rashes (eg, pyoderma gangrenosum). However, some of the newer biologic agents, such as vedolizumab, are very effective at treating mucosal inflammation but are not as effective at dealing with extraintestinal manifestations of the disease. Thus, it might be appealing to take a patient on such a biologic

agent, which is working well for the luminal disease, and combine it with an anti-TNF agent to treat extraintestinal manifestations of the disease that might develop. Hirten and colleagues recently reviewed various case reports of biologic combinations and noted that when patients have both rheumatoid arthritis and IBD, combining biologic agents can be effective.

G&H What other combinations might be effective?

MA Looking at the inflammation that is left over in patients on anti-TNF agents, there is an IL-12/-23 signal in the inflammatory response, suggesting that combining ustekinumab with an anti-TNF agent might also be an effective strategy. Ustekinumab has a very low immunogenicity. Other agents, such as infliximab (Remicade, Janssen) or adalimumab (Humira, AbbVie), have a higher rate of immunogenicity and should be stopped judiciously because patients might develop antibodies, which would mean that they could never be on the drug again.

Thus, it would be useful if a combination with an agent that inhibits TNF in the short term could be used and then remission could be maintained with a single agent, such as vedolizumab or ustekinumab, especially given the fact that not only are these complementary mechanisms of action but also that there is a difference in the rapidity of response. Anti-TNF agents have a very rapid response. I think that combining anti-TNF agents with anti–IL-12/-23 agents is an effective theoretical strategy and has been used on several occasions. However, although ustekinumab might be effective for treating IBD, it is not effective for treating ankylosing spondylitis or other spondyloarthropathies. Therefore, using an anti-TNF agent to complement what is lacking in ustekinumab may be effective.

> With some of the newer biologic agents ... the risk of infections is very low, so it becomes more actionable to think about combining these agents with anti-TNF agents.

G&H Might JAK inhibitors also have a role in combination therapy?

MA This is an interesting question because JAK inhibitors are oral drugs. When used in naive patients, tofacitinib works very quickly, and some of the other JAK inhibitors also seem to work quickly. However, the verdict is still out, at least for tofacitinib, regarding long-term safety in young patients who have IBD. Tofacitinib has been associated with an increased risk of herpes zoster reactivation because it inhibits viral immunity. Thus, one combination may be short-term use of a JAK inhibitor followed by maintenance with an agent such as vedolizumab.

G&H Is it known if combining biologic agents might cause safety issues, such as an increased risk of infection?

MA When natalizumab (Tysabri, Biogen) was first being developed, before it was known to be associated with progressive multifocal leukoencephalopathy, the US Food and Drug Administration asked researchers to look for any safety signals in patients on an anti-TNF agent who added natalizumab or vice versa. In this study, there did not seem to be an increased risk of infection. However, this was a short-term study, and patients in such studies are much less likely to develop complications or infections.

With some of the newer biologic agents such as ustekinumab and vedolizumab, the risk of infections is very low, so it becomes more actionable to think about combining these agents with anti-TNF agents. Although biologic agents can be costly, this issue might be mitigated by using biosimilars for anti-TNF agents or companies making more than one biologic agent or small molecule and discounting the price of combinations.

Nevertheless, it is important to note that biologic agents have immunosuppressive properties. Tofacitinib and JAK inhibitors in general are likely more immunosuppressive than other agents because their effects are a bit broader than simply targeting only one cytokine. However, some of the newer JAK inhibitors seem to be safer than tofacitinib.

G&H What research is currently available on combining biologic agents in IBD?

MA Most of the data are observational, involving case reports. At present, I have seen 2 biologic agents approved by insurance only very occasionally, usually for IBD and another condition such as ankylosing spondylitis or rheumatoid arthritis. Currently, we do not have a lot of experience with combination therapy because it is avoided in studies of these agents. One of the challenges with clinical trials in their current structure is that a protracted washout of prior drugs is required. In real life, it is unlikely

that patients would have a drug washout. Researchers are taking the risk that a sick patient might become sicker by the time he or she enters the clinical trial. Moreover, the safety signal of combination therapy is not really being tested. Once the drug is approved, patients will not have a washout period before taking the next drug.

G&H Is it known if combining biologic agents might be more effective in certain patient subgroups?

MA It would be ideal, but may not be possible, to perform functional molecular analysis of individual IBD patients and to predict which drug or combination is needed. There are very few tools to predict who will respond to anti-TNF agents. Because anti-TNF agents are very effective, it is difficult to have a biomarker that can identify the smaller subset of patients who will not respond.

Recently, there have been examples of different pathways that predict a lack of response to anti-TNF therapy. A study by West and colleagues found that patients who had high levels of oncostatin M (which is in the IL-6 family) before receiving anti-TNF therapy were less likely to respond to anti-TNF therapy. Likewise, in a study of an IL-23 inhibitor in Crohn's disease, patients with higher baseline serum concentrations of IL-22, a cytokine induced by IL-23, were more likely to respond.

More research is needed on biomarkers. Piecing together various biomarkers is more likely to predict which is the best target or targets for a given patient. Even an assay in tissue that involves performing a colonoscopy and biopsies might be less expensive than using some of these biologic agents for months.

G&H What other research is needed?

MA Clinical trials that combine biologic agents are needed, although it can be difficult to get such research funded. In addition, there should be improved tracking of complications that might develop in patients on combination therapy, particularly nongastrointestinal complications that may be treated by primary care doctors.

Dr Abreu has received grant/research support from Prometheus Laboratories, Takeda, Eli Lilly Pharmaceuticals, and Pfizer. She has served as a consultant for AbbVie Laboratories, Prometheus Laboratories, Takeda, Janssen Pharmaceuticals, Focus Medical Communications, Celgene Corporation, Eli Lilly Pharmaceuticals, Pfizer, Shire Pharmaceuticals, Roche Pharmaceuticals, Boehringer Ingelheim Pharmaceuticals, Amgen, Gilead, Allergan, Landos Biopharma, and Nestec Ltd - Switzerland. She has also served on the speakers bureau for Takeda, Focus Medical Communications, Cornerstones Health Inc, Imedex, and Vindico Medical Education.

Suggested Reading

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