ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Combination Therapy for Inflammatory Bowel Disease

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G&H What are the traditional treatment strategies for inflammatory bowel disease, and where does combination therapy fit among them?

SH The current algorithms for treating inflammatory bowel disease (IBD), both ulcerative colitis and Crohn's disease, depend upon several factors, including the severity of the symptoms as well as the prognosis and the patient's response to prior therapy. Thus, for mild to moderate disease in ulcerative colitis, clinicians typically start with aminosalicylates. If these agents are successful at inducing remission, they are continued as maintenance therapy.

In patients who do not respond to aminosalicylates for induction or for individuals who present with more moderate to severe symptoms or a bad prognosis, clinicians typically initiate corticosteroids. I often call corticosteroids a tipping point because after their use, mesalamine is not as effective as a maintenance treatment. Typically, clinicians also use an immunosuppressive agent such as a thiopurine agent (eg, azathioprine or 6-mercaptopurine) or methotrexate to maintain corticosteroid-induced remission.

In patients who do not respond to corticosteroids as an inductive therapy or if patients fail maintenance therapy with a thiopurine agent or methotrexate, biologic therapy is currently indicated with either an anti–tumor necrosis factor agent, anti-integrin agent, or most recently ustekinumab (Stelara, Janssen) for Crohn's disease. Biologic therapy can be started either alone or in combination with an immunosuppressive agent. Combination therapy with a biologic agent and an immunosuppressive agent can be initiated at the same time as the biologic agent alone would be or in patients who are failing corticosteroids. Or, the biologic agent may be added to patients who are not responding to an immunosuppressive agent.

G&H What is the historical precedence of using combination therapy in IBD?

SH There is historical precedence to using a biologic agent in combination going back to the original phase 3 trials of biologic agents. To this point, biologic agents have been studied in moderate to severe disease, both ulcerative colitis or Crohn's disease, that is not responding to conventional therapeutic agents. In clinical trials with infliximab (Remicade, Janssen), adalimumab (Humira, AbbVie), certolizumab pegol (Cimzia, UCB), golimumab (Simponi, Janssen), natalizumab (Tysabri, Biogen), vedolizumab (Entyvio, Takeda), and most recently ustekinumab, patients who were failing immunosuppressive therapy continued that therapy during and after the introduction of the biologic agent. Although patients were not randomized according to concomitant immunosuppressive agents, retrospective analyses of all these studies showed that patients who were on immunosuppressive agents did not do any better on the biologic agent than patients who were not on immunosuppressive agents. However, it was noted that in patients receiving immunosuppressive agents, biologic drug levels were higher and antidrug antibody levels were lower. With the recent interest in therapeutic drug monitoring of biologic agents using trough levels, the explanation for why the patients did not do better clinically often came down to the fact

that these studies were not powered to see a difference in immunosuppressive-naive vs -exposed patients.

Subsequently, the risk of certain complications, in particular lymphoma, was attributed more to the immunosuppressive (thiopurine) agent rather than the biologic agent. With this risk, pediatricians especially were reluctant to use combination therapy in children because there were no identified clinical benefits and the patients were at an increased risk of lymphoma because of the thiopurine agent. Thus, pediatricians started using monotherapy with the biologic agent alone or substituting methotrexate for a thiopurine agent.

This has changed since the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) study, which was led by Dr Jean-Frédéric Colombel. This was the first comparative effectiveness study that enrolled patients with Crohn's disease who were naive to immunosuppressive agents and biologic agents. In this study, patients were randomized to receive either infliximab alone, azathioprine alone, or the combination of infliximab and azathioprine. In study findings reported several years ago, patients receiving combination therapy had superior clinical and endoscopic outcomes compared to patients who were receiving infliximab monotherapy. At the same time, it was recognized that drug levels were indeed higher in patients receiving combination therapy, and there were fewer antidrug (anti-infliximab) antibodies. These study findings changed the treatment approach for most adult gastroenterologists back to what they were accustomed to—using combination therapy of a biologic agent and a thiopurine agent to improve clinical outcomes and also improve the pharmacokinetic aspects of the biologic agent by increasing drug levels.

G&H What is the most recent research on combination therapy for IBD?

SH Most recently, Dr Colombel and I presented a new SONIC analysis at this year's European Crohn's and Colitis Organisation annual congress and will also be presenting the findings at this year's Digestive Disease Week. We wanted to know whether there is synergy between the biologic agent and the immunosuppressive agent or whether the benefit of combination therapy is simply raising drug levels of the biologic agent. To find out, we and our colleagues reanalyzed the SONIC study according to the drug levels in each group (monotherapy vs combination therapy). We found that as long as the patients had the same drug level of infliximab, their outcomes were actually equal. In addition, there was no benefit associated with azathioprine, the thiopurine agent that was used, beyond raising the drug level. Thus, we did not identify synergy between the 2 agents in the majority of patients. The better results were primarily due to the thiopurine agent's increase in the drug level of infliximab.

G&H What is the clinical relevance of these new findings?

SH It should be noted, first of all, that these results have not yet been replicated, so additional data are needed. Nevertheless, these findings still have clinical relevance. They afford the option of treating patients with a biologic agent alone so that clinicians do not need to optimize 2 different therapies (the biologic agent as well as the immunosuppressive agent). In this scenario, patients who are not on an immunosuppressive agent would not have to undergo blood draws every 3 months for therapeutic drug monitoring of the immunosuppressive agent.

On the other hand, this therapeutic approach would require more intensive monitoring of the blood levels of the biologic agent in order to minimize antidrug antibody development that occurs in low levels of biologic agents and to optimize the biologic agent by increasing dosing in order to achieve therapeutic blood levels.

G&H Are there plans to replicate this research?

SH At the moment, I am not aware of any plans to repeat a SONIC-like study with other biologic agents. However, there are many efforts ongoing to try to optimize how clinicians can perform proactive therapeutic drug monitoring of a biologic agent to minimize the number of patients losing response.

G&H In light of all these findings, how should gastroenterologists currently view combination therapy in IBD patients?

SH The current evidence is that combination therapy is superior in patients who are naive to either biologic agents or immunosuppressive agents. However, the majority of patients who are started on a biologic agent are already on an immunosuppressive agent. Thus, the majority of gastroenterologists at the present time are continuing with that combination therapy for a minimum of 6 to 12 months before they would withdraw the immunosuppressive agent.

G&H Should the immunosuppressive agent always be withdrawn, or are there any cases in which immunosuppressive therapy can continue for the long term?

SH This is an important question. What should we do for a patient who is in remission on combination therapy?

Should we stop the biologic agent because that is the more expensive agent, or should we stop the immunosuppressive agent because that has the greater risk of malignancy? Studies have looked at both options. It turns out that the results are approximately the same. If a clinician stops the immunosuppressive agent or instead stops the biologic agent, approximately 50% of the patients will stay well for several years if—and this is the important part—they are in a deep remission. This means that they are clinically well, have mucosal healing, and have no laboratory test results suggesting active inflammation (ie, they have a normal C-reactive protein level, a normal white blood cell count, and no anemia).

On the other hand, patients who are in a clinical remission and have residual signs of inflammation, either endoscopically or via laboratory test results, are at greater risk of relapsing with withdrawal of either of the drugs used in combination such that combination therapy and optimization of both agents should be attempted.

G&H How safe is combination IBD therapy in the short and long term?

SH In a short-term (ie, 1-year) SONIC safety analysis, combination IBD therapy was actually the safest approach in adult patients as far as infections and other adverse events. Part of the explanation for this finding is that many of the side effects of IBD therapy are related to active disease. Thus, the more effectively a clinician treats active disease, the more side effects related to Crohn's disease (including perianal disease and other infections) will be minimized.

Long-term risks of combination therapy have been evaluated less in prospective controlled trials but have undergone assessment via registries. For example, the TREAT (Crohn's Therapy, Resource, Evaluation, and Assessment Tool) registry demonstrated that the biologic agent, at least for infliximab, and the immunosuppressive agent used in combination therapy were safe; corticosteroids led to the greatest risk of infections, hospitalizations, and death.

G&H Has combination therapy been examined in pediatric IBD patients?

SH Combination therapy has not been tested in the same way in pediatric patients, although clinical trials of biologic agents in pediatric IBD patients have included patients who were not responding to immunosuppressive agents and were continued on the agent along with the biologic agent. As mentioned previously, due to the risk of lymphomas in young men treated with thiopurines, most pediatricians are switching to methotrexate as a preferred agent for combination therapy despite a lack of prospective data.

G&H What are the next steps in research?

SH An important next step is to expand the methods of performing therapeutic drug monitoring proactively to optimize initial clinical response and minimize loss of response. At the same time, alternative immunosuppressive agents such as methotrexate, which does not have the same risk of lymphoma as thiopurine agents, may be used in combination therapy in both ulcerative colitis and Crohn's disease to help boost drug levels and reduce antidrug antibody levels. This may be more cost-effective than using monotherapy, in which the clinician has to give higher doses of the biologic agent over longer periods of time, leading to increased expense. In other words, using methotrexate to reduce the dose of the biologic agent without any additional risk would help optimize clinical results and obviate the risk of lymphoma associated with thiopurine agents.

Dr Hanauer is a consultant for Janssen and Prometheus Labs.

Suggested Reading

Colombel JF, Jharap B, Sandborn WJ, et al. Effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in patients with Crohn's disease or ulcerative colitis who had failed conventional therapy. *Aliment Pharmacol Ther*. 2017;45(1):50-62.

Colombel JF, Reinisch W, Mantzaris GJ, et al. Randomised clinical trial: deep remission in biologic and immunomodulator naïve patients with Crohn's disease—a SONIC post hoc analysis. *Aliment Pharmacol Ther*. 2015;41(8):734-746.

Dulai PS, Siegel CA, Colombel JF, Sandborn WJ, Peyrin-Biroulet L. Systematic review: monotherapy with antitumour necrosis factor α agents versus combination therapy with an immunosuppressive for IBD. *Gut*. 2014;63(12):1843-1853.

Jones JL, Kaplan GG, Peyrin-Biroulet L, et al. Effects of concomitant immunomodulator therapy on efficacy and safety of anti-tumor necrosis factor therapy for Crohn's disease: a meta-analysis of placebo-controlled trials. *Clin Gastroenterol Hepatol*. 2015;13(13):2233-2240.e1-e2; quiz e177-e178.

Torres J, Boyapati RK, Kennedy NA, Louis E, Colombel JF, Satsangi J. Systematic review of effects of withdrawal of immunomodulators or biologic agents from patients with inflammatory bowel disease. *Gastroenterology*. 2015;149(7):1716-1730.