

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Understanding Combination Therapy With Biologics and Immunosuppressives for the Treatment of Crohn's Disease

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G&H Are the issues pertaining to combination therapy the same for all patients?

J-FC No. There are two distinct settings that need to be considered separately. When biologics for inflammatory bowel disease (IBD) were first introduced, they were administered to patients who were refractory to steroids and azathioprine. Following more recent studies, biologics are now sometimes given to patients who have not received azathioprine. Azathioprine-refractory and -nonrefractory patients require different considerations.

Generally speaking, there are two important aspects to weigh when considering treatment with combination therapy: efficacy and safety. What is the right balance for any given patient? The ratio between risks and benefits of combination therapy may be different for azathioprine-refractory and -naïve patients.

G&H For patients who are refractory to azathioprine, has combination therapy been found to be superior to infliximab monotherapy?

J-FC A paper by Lichtenstein and associates published in 2009 reviewed all of the studies of infliximab (Remicade, Centocor) up until that time to evaluate the efficacy of co-immunosuppression versus infliximab monotherapy. This retrospective analysis included data from 4 trials: ACCENT-1, ACCENT-2, ACT-1, and ACT-2. The study found no clear evidence that the combination approach produced better outcomes than monotherapy. Of course,

it does need to be emphasized that this was a post-hoc analysis of these studies with all potential weaknesses.

In 2008, van Assche and colleagues from Leuven, Belgium, published an interesting study in which 80 Crohn's disease patients who had received combination therapy with infliximab and azathioprine for at least 6 months were randomized to continue with combination treatment or to discontinue azathioprine. The investigators reported no clear evidence of benefit associated with continuing immunosuppression after the initial 6 months. Nevertheless, prolonged combination therapy was associated with increased C-reactive protein levels as well as higher median infliximab trough levels, and the long-term results of this study are still awaited. Despite some methodological pitfalls, the study is often used as a basis for clinical practice decisions, and many clinicians are now stopping azathioprine after 6 months of combination therapy.

G&H Have any subsequent reports noted the same result?

J-FC Not necessarily. In fact, many centers have reported that, with regard to efficacy, combination therapy is better than monotherapy. For instance, in a recent study from Paris, France, by Sokol and coworkers, in patients with IBD receiving infliximab maintenance therapy, immunosuppression cotreatment was associated with reduced IBD activity, and infliximab dose and switch to adalimumab (Humira, Abbott). In my estimation, no conclusion has yet been reached on the long-term benefits of combination therapy versus monotherapy for azathioprine-refractory patients.

G&H If the matter is not yet settled, then why are so many clinicians stopping azathioprine after 6 months?

J-FC Often, there is a concern about safety. In general, most clinicians believe that combination therapy

(Continues on page 489)

(Continued from page 486)

is associated with an increased risk of serious infection compared with infliximab monotherapy.

G&H Do the available data support this concern?

J-FC Not all of the available data support this conclusion. For instance, in the last update from the TREAT registry reported by Lichtenstein and colleagues at Digestive Disease Week 2010, which looked at more than 2,000 patients, there was no evidence of an increased risk of serious infections associated with the combination approach. However, the risk was certainly increased among patients who received triple-combination therapy, with prednisone added to the combination regimen.

G&H Are there any populations for which combination therapy does pose a serious risk?

J-FC Yes. Some patients receiving combination therapy have developed a rare and serious form of T-cell lymphoma. A total of 36 cases have been reported worldwide. Of these, 20 were receiving infliximab plus thiopurine for IBD. Twenty-nine of these patients were men, and 27 were under age 35. The development of this lymphoma is not well understood, but clearly there is a heightened risk among this specific population of young men. As a result, in Europe such patients often receive monotherapy with infliximab.

G&H How is the situation different for azathioprine-naïve patients?

J-FC The SONIC study compared infliximab versus azathioprine versus combination therapy for Crohn's disease patients who had not received either of these treatments prior to enrollment. In this double-blind trial, 508 adults with moderate-to-severe Crohn's disease were randomized to receive infliximab, azathioprine, or a combination of both drugs.

The results demonstrated a clear superiority for the combination arm. Of the 169 patients on that arm, 96 were in steroid-free remission at week 26 versus 75 of 169 patients receiving infliximab alone ($P=.02$) and 51 of 170 patients receiving azathioprine alone ($P<.001$). Mucosal healing rates were also higher among patients receiving combination therapy versus either of the drugs as monotherapy. Rates of serious infections were 3.9% for the combination arm, 4.9% for the infliximab arm, and 5.6% for the azathioprine arm. Thus, the conclusion of this study, published in *The New England Journal of Medicine*, is that combination therapy is superior to monotherapy with either infliximab or azathioprine for Crohn's disease patients naïve to these drugs. When con-

sidering all randomized patients, this superiority was still present at 1 year.

G&H What treatment approach should be taken after 1 year for such patients?

J-FC This question is very difficult to answer, and clinicians in the United States and Europe are taking different approaches. In the United States, many centers are continuing combination therapy beyond the first year, whereas in Europe, combination therapy is often stopped after the first year. The latter approach seems to stem from the long-held notion that decreasing the load of immunosuppression carries fewer risks for patients. Often, patients prefer to stop combination therapy if possible, whether due to concerns about potential complications, issues regarding pregnancy, or other matters. Especially in the United Kingdom, clinicians are now allowed to use maintenance therapy with biologics for up to 1 year only, and at 1 year, if there is no evidence of clinical, biologic, or endoscopic activity, the recommendation is to stop infliximab as well. This approach is very different from that taken in the United States.

G&H Are there any clinical data indicating which approach is best?

J-FC A recent French study, known as the STORI trial, evaluated infliximab discontinuation. In this prospective study, more than 100 patients who had been treated with combination therapy for more than 1 year were recruited from various centers in France. All of these patients had been in steroid-free remission for more than 6 months. In the study, infliximab was stopped for all patients, with further maintenance consisting of azathioprine alone. The results showed that after 2 years, approximately 50% of patients relapsed. Based on these findings, it is safe to conclude that this strategy is not appropriate for all patients.

G&H If not all patients relapsed, were there any clear subgroups of patients found to fare better or worse?

J-FC Yes. The data also revealed factors that predicted a low risk of relapse. We are still working on the best model to predict persistence of remission after stopping infliximab. According to our findings, among the most important predictors were a high-sensitivity C-reactive protein level below 5 mg/L and a Crohn's disease endoscopic index of sensitivity equal to 0, thus defining a state of so-called deep remission. One model allowed the classification of the patients in 4 different subgroups

with significantly different risk of relapse over time. The subgroup with the lowest score, and representing a small fifth of the patients, had a very low risk of relapse around 10% over 1 year.

This finding is very important. Each clinician already needs to consider stopping biologics based on clinical, biologic, and endoscopic remission. If there is any evidence of activity through any of these measures, the risk of relapse is high if biologics are stopped.

G&H What other aspects of combination therapy remain to be studied?

J-FC All of the strategies described above have been evaluated in patients with a long history of Crohn's disease. The outcomes might be different among patients with early-stage disease. It might be worthwhile to explore the efficacy and safety of initiating treatment for such patients with a very strong combination regimen. The immunosuppression load could then be decreased later. This concept is not original, but it has not been studied in early-stage patients.

In addition, it is important to explore the possibilities of tailoring therapy to patients' specific characteristics. Patients vary by demographic, disease stage, clinical manifestations, and many other traits. It may be that

different strategies are appropriate for different subgroups of patients. At this point, we have no strong tools for personalizing therapy.

Finally, one point should be clarified regarding lymphoma. In addition to the rare T-cell lymphoma risk described above, there is also a concern that biologic therapy is associated with an increased risk of lymphoma in general. However, based on the available data, it is impossible to determine whether this risk is associated with biologics or azathioprine.

Suggested Reading

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