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When Should Combination Therapy for Patients with Crohn's Disease Be Discontinued?

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G&H When is combination therapy appropriate for patients with Crohn's disease?

J-FC Right now, there are 3 potential treatment strategies in patients with Crohn's disease (CD): The first strategy, which is the classical step-up approach, involves starting with steroids, switching to an immunosuppressant such as azathioprine if steroid therapy fails, and finally resorting to an anti–tumor necrosis factor (TNF) agent if the immunosuppressant fails. The second strategy is a more rapid step-up approach in which an immunosuppressant is added to the steroid at diagnosis. The third strategy is combination therapy, in which both an immunosuppressant and an anti-TNF agent are administered simultaneously. When combination therapy is used, it typically consists of an anti-TNF agent plus azathioprine, as this is the combination that has been explored in most clinical trials.

Data now show that combination therapy with an anti-TNF agent and an immunosuppressant is the most effective strategy for treating CD. However, it is reasonable to propose that the most intensive therapy should not be used in all patients, given that CD is a very heterogeneous disease. For example, a patient who has mild CD localized to a short segment of the bowel and no criteria that would predict increased disease severity could likely be treated effectively with a less intensive strategy.

The big problem clinicians now face when treating CD is that the course of a patient's disease in the years following diagnosis is difficult to predict. In many cases, clinicians cannot accurately predict whether a particular patient will have severe CD with a very aggressive course that leads to complications or whether the disease will remain mild. Ongoing studies are examining a range of clinical, serologic, and genetic predictors that might be able to answer this question in the future; at present, however, clinicians must select treatments based on clinical criteria.

The patients in whom I use combination therapy very early after diagnosis are patients with diffuse extensive disease involving the small bowel and colon; patients with disease that involves the upper gastrointestinal tract; patients with complex perianal fistulizing disease, who often present with complications of CD at diagnosis; patients with very severe endoscopic lesions that predict a higher risk of surgery; and pediatric CD patients who are at risk of growth problems.

G&H What is the benefit of continuing combination therapy?

J-FC The goal of combination therapy in patients with CD is to induce deep remission, which includes not only remission of clinical symptoms but also full healing of the transmural inflammatory process that occurs in CD. Some data show that patients who are able to achieve deep remission will be able to avoid complications of CD, surgeries, and disability linked to surgery.

The idea of deep remission is a very important evolving concept because clinicians are now treating patients with the goal of not only obtaining clinical remission but also achieving full bowel healing. Rheumatologists have adopted exactly the same approach for treating

rheumatoid arthritis because they want to not only obtain remission of clinical symptoms but also avoid bone loss. Similarly, gastroenterologists want to avoid bowel damage in patients with CD.

This rationale supports the use of combination therapy, as it is the most effective treatment option available. The efficacy of combination therapy offers a huge potential benefit, and use of combination therapy is most advantageous in patients with the most severe disease. In selecting a treatment for a specific patient, however, clinicians must consider the risk-benefit ratio for that individual.

G&H What are the risks of combination therapy?

J-FC Unfortunately, we do not know much about the risks of this therapy because we are still in the early days of its use. Clinicians have only been using combination therapy for 3–4 years, and establishing the full safety profile of combination therapy will require long-term studies.

Currently, infection is one of the main risks thought to be linked to combination therapy. Also, because combination therapy is associated with a state of immunosuppression, combination therapy potentially puts patients at increased risk for some forms of cancer and lymphoma. However, evaluating these risks is difficult. There is no clear evidence that the risk of infections is higher with combination therapy than with monotherapy, and it is also not clear whether the risk of lymphoma and cancer is higher with combination therapy than with monotherapy. Nonetheless, there is a theoretical concern that adding immunosuppressants together could increase the risks associated with immunosuppressive therapy, the most important of which are infection and cancer.

G&H Does a longer duration of combination therapy increase these risks?

J-FC It is not well known whether long-term use of combination therapy is associated with higher risks. We know that some types of lymphoma occur after 2–3 years of use, but it is not clear if the risk of lymphoma is still increasing after 4–5 years.

G&H What did SONIC show regarding the use of combination therapy?

J-FC SONIC was a pivotal study because it was the first study to compare the reference drug for maintenance of remission in CD, which at that time was azathioprine, versus anti-TNF monotherapy, specifically infliximab (Remicade, Janssen Biotech), versus combination therapy involving infliximab plus azathioprine. SONIC showed without any doubt that combination therapy is the most effective treatment in terms of both clinical remission and mucosal healing. Based on these results, many clinicians have started to change their practice.

In terms of safety, SONIC did not find any evidence that patients in the combination therapy arm experienced more side effects than those in the infliximab monotherapy arm or the azathioprine monotherapy arm. While there was no safety signal linked to combination therapy in SONIC, clinicians should bear in mind that this study only followed patients for 1 year, and it was not designed to assess the risks of treatment.

G&H Have other large studies assessed the safety and/or efficacy of combination therapy in patients with CD?

J-FC So far, SONIC is the largest and most important such study. Another study, called the COMMIT study, evaluated patients who were receiving infliximab and methotrexate, but it did not find any benefit of combination therapy. However, I think the results of the COMMIT study are not easy to interpret because steroids were also given to patients in the combination therapy arm, and evidence suggests that use of steroids may have blurred the results.

G&H How does prior monotherapy impact the safety and efficacy of subsequent combination therapy?

J-FC This is an important question because clinicians often add an anti-TNF agent to azathioprine. In SONIC, all patients were naïve to both immunosuppressants and biologic agents, but in clinical practice, anti-TNF agents—frequently infliximab or adalimumab (Humira, Abbott)—are often added when patients have failed azathioprine monotherapy. I suspect that the results of SONIC still apply in this situation: that combination therapy is still the most effective strategy, even in patients who have failed azathioprine monotherapy. However, the reverse scenario—adding an immunosuppressant to anti-TNF monotherapy—has not been studied. Overall, there is a lack of data regarding how prior monotherapy impacts the safety and efficacy of subsequent combination therapy.

G&H What clinical milestones can clinicians use to determine when to discontinue combination therapy?

J-FC The debate about how long to continue combination therapy and when to stop this therapy is not yet solved. Some key opinion leaders, especially in North America, believe that once a patient has been started on combination therapy, the patient should remain on

combination therapy forever. However, other clinicians remain concerned about long-term use of combination therapy and want to de-escalate therapy in some patients. Also, patients sometimes request the discontinuation of combination therapy because they are concerned about side effects or they find combination therapy to be a financial burden.

Unfortunately, very few studies have looked at outcomes in patients who have stopped combination therapy. One study that I conducted with colleagues from France assessed outcomes following discontinuation of combination therapy in patients who had been in clinical remission for more than 1 year. These patients were initially receiving both infliximab and azathioprine; after being weaned from steroids, infliximab was stopped, and patients were maintained on azathioprine monotherapy.

Overall, approximately 50% of these patients relapsed within 2 years. When we considered predictors of relapse, however, we were able to show that the risk of relapse was much lower in patients who had mucosal healing and normal levels of biologic markers, such as C-reactive protein (CRP). In this subgroup, the relapse rate was approximately 20% within 2 years. The take-home clinical message is that clinicians who are considering a de-escalation of treatment in patients on combination therapy need to be certain these patients are in full remission—meaning they have normal CRP levels and mucosal healing. If combination therapy is stopped in a patient who is doing well clinically but who still has endoscopic evidence of inflammatory activity, then the risk of relapse is very high.

G&H What factors may prompt discontinuation of combination therapy?

J-FC For patients who are receiving combination therapy, clinicians have 3 options: They can stop infliximab, stop azathioprine, or stop both drugs. In practice, very few clinicians stop both drugs; typically, clinicians either stop infliximab and maintain the patient on azathioprine or stop azathioprine and maintain the patient on anti-TNF monotherapy.

Likewise, clinicians have several options regarding the timing of de-escalation. From the point of view of efficacy, there is actually no reason to ever stop combination therapy; combination therapy is the most effective strategy available, so if efficacy is the primary concern, combination therapy should be maintained. Practically speaking, discontinuation of combination therapy may be considered for various reasons: Patients may want to stop combination therapy for financial reasons, they may be tired of the treatment, they may be concerned about side effects, or they may be planning a pregnancy.

Additionally, some countries have guidelines that call for de-escalation after a fixed duration of therapy; in the United Kingdom, for example, national guidelines state that clinicians must stop infliximab after 1 year if patients are in remission. Given that the use of combination therapy is highly variable among different countries, there is no standard duration of combination therapy, so the decision to stop combination therapy must be made on a case-by-case basis. Personally, I think clinicians should not consider stopping combination therapy until the patient has been receiving combination treatment for at least 1 year.

G&H What further research is needed regarding combination therapy?

J-FC Research comparing different de-escalation strategies is needed. Toward this end, my colleagues and I are planning a randomized clinical trial in which we will compare various de-escalation strategies; this study will also have a control arm in which combination therapy will be maintained. Some of the de-escalation strategies we might study include stopping azathioprine, increasing the interval between injections or perfusions of the anti-TNF agent, and stopping infliximab. We are still working on the design of this study, but having a control arm will be an important aspect of this trial.

Another important consideration for future clinical trials is that patients should be stratified based on disease duration, as we may find different results for different groups. For example, if a patient was started on combination therapy very early, maybe at diagnosis, then subsequently halting combination therapy might not be associated with any harm to the patient. In contrast, if combination therapy was started later—for instance, after the patient had already been refractory to several treatments and/or had already developed complications, such as stenosis and fistulae—then de-escalation may be more difficult. I think that stratification by disease duration will therefore be a very important parameter to include in future clinical trials.

G&H Overall, what is the current status of combination therapy for CD?

J-FC Use of combination therapy is still an evolving field. I have worked both in Europe and the United States, and I have seen a huge variance in the way doctors consider this problem. In some countries, parameters such as financial resources are very important; in other countries, the cost of therapy is less of an issue. Likewise, doctors in some countries are very concerned about safety, while doctors in other countries think mainly about efficacy. Given these differences, it is difficult to speak a universal language when talking about how best to employ combination therapy.

Suggested Reading

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