ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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When Should Therapy for Inflammatory Bowel Disease Be Stopped?

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G&H Why has the question of when to stop treatment for inflammatory bowel disease been of particular interest recently?

DR Patients with chronic inflammatory bowel disease (IBD) have always asked whether and when they can stop treatment. No one wants to be controlled by medical therapy, and yet we do not currently have a curative treatment for these chronic diseases. Therefore, patients frequently want to know whether it is safe to stop treatment.

This question recently has become particularly relevant for a few reasons. First, we are able to obtain deeper levels of remission than previously, which could allow us to de-escalate therapies in some way, whether by reducing the dose or stopping one of several medications, or even stopping all of the medications. The second issue is cost. The most effective therapies for IBD are biologic drugs, which are very expensive, so prolonged use carries a direct financial burden. Third, long-term use of immunosuppressive and immune-modifying drugs may pose risks, and there is a fear about these risks even in the absence of evidence. For all of these reasons, patients and clinicians are very interested in whether de-escalation of therapy can be performed safely.

G&H What are the risks associated with stopping treatment?

DR There are multiple safety concerns. Most proximate is that the patient may experience a relapse, which disrupts not only health but also quality of life and the ability to function both socially and professionally.

Another risk is that if the disease does return, complications may occur. For example, uncontrolled inflammation could create scar tissue, which typically does not respond well to anti-inflammatory therapy.

If a patient stops treatment and the disease relapses, the medication may not work as well or at all the next time. In the case of biologic therapies, the body may have an immunogenic reaction to the monoclonal antibody, leaving the disease unresponsive to the drug.

As clinicians, we need to be able to quantify the risks of stopping treatment and develop strategies to avoid complications. Stopping drugs and hoping nothing bad happens is not a sound way to proceed.

G&H How can these issues be studied without putting patients at risk?

DR As this question implies, there are ethical considerations in designing a study to examine de-escalation and/or treatment withdrawal. One approach has been to study de-escalation very incrementally. One well-known study from France, the STORI (Infliximab Discontinuation in Crohn's Disease Patients in Stable Remission on Combined Therapy With Immunosuppressors) trial, investigated incremental withdrawal among patients who were taking infliximab (Remicade, Janssen) plus either azathioprine or methotrexate, were in stable remission for at least 1 year, and were off corticosteroids for at least 6 months. These patients stopped taking infliximab but not azathioprine or methotrexate. With this study, the investigators were able to examine whether infliximab could be stopped and the other agent used as

maintenance therapy. The protocol allowed for patients to resume infliximab if any problems arose.

The key attributes of this study were that the patients were well characterized in terms of their disease state and that there was a strategy to monitor patients for signs of clinical relapse, such as the initiation of inflammation, before the patient experienced any symptoms. Detection of subclinical relapse can allow for intervention to prevent clinical recurrence and avoid complications.

G&H Are such signs of early relapse well recognized by clinicians?

DR In general, clinicians agree that patients on medical therapy for IBD should have some type of follow-up. However, the concept of disease monitoring is somewhat new to many gastroenterologists. The goal of disease monitoring is to obtain objective information on disease activity in order to know whether the treatment needs to be adjusted to prevent relapse and complications.

Disease monitoring leaves room for some drift—a patient can de-escalate treatment, for example—but only after having decided upfront the threshold for reinitiating therapy or making another change. What we need to determine is how much give-and-take to allow before restoring a drug dose to a prior level or recommending another intervention.

The approach is somewhat new, but not unfamiliar. With diabetes, physicians measure blood sugar periodically and monitor glycated hemoglobin (HbA1c level). With hypertension, physicians measure blood pressure periodically to check a patient's status. With IBD, we can perform endoscopy, measure fecal calprotectin, or measure C-reactive protein.

G&H Is it difficult to secure funding for a clinical trial aimed at de-escalating or stopping a medication?

DR A trial such as this can benefit industry sponsors in multiple ways. The study can be designed to ask not only is it safe to de-escalate therapy, but also when should therapy be escalated?

Everyone involved in treating IBD needs to play a role in figuring out the best strategy. Interestingly, the STORI trial demonstrated that it was safe to remove some patients from infliximab and also showed that, contrary to popular teaching, patients could resume infliximab therapy safely and effectively. The investigators theorized that continuing with the immunosuppressant prevented the development of antibodies against infliximab, enabling the infliximab to be reintroduced if patients needed it again.

G&H Are insurance companies interested in de-escalation studies?

DR Beyond being just interested, insurance companies should be logical sponsors for these trials. Insurers are always concerned about the bottom line. If companies are interested in saving money, they should fund a study to see whether therapy can be de-escalated safely and how to monitor patients effectively. If insurance companies do not want to pay for such studies, then they should at least consider covering the cost of monitoring patients with direct examinations, C-reactive protein level, and fecal calprotectin level. All of these are less expensive than prescribing biologic drugs.

G&H Can you discuss your recent study that demonstrated that patients with ulcerative colitis can achieve a complete histologic remission?

DR The traditional teaching about ulcerative colitis and Crohn's disease is that when a patient has had inflammation, a biopsy will always show microscopic architectural changes even when the patient is in stable remission. We reviewed more than 600 patients with ulcerative colitis treated at the University of Chicago and found that 10% had normal biopsies. For these patients, the disease would not be detected through the biopsy—the pathologist would have needed to know about the prior IBD diagnosis.

This finding raises the question of whether people who achieve normalization of their biopsies have a deeper level of remission than those who have stable clinical disease or even chronic changes on biopsy. In addition, can therapy be safely withdrawn for these patients? Our recently completed study found that patients whose biopsies normalize have statistically more stable disease control than patients who are just in remission with chronic changes, and certainly have better disease control than patients who have active inflammation on biopsies, even if they are not experiencing any symptoms of IBD.

Our next step is a de-escalation trial with patients who have normal biopsies. In this study, patients will stop medication and resume simpler treatments if necessary. Patients on immunosuppressants will be moved to mesalamine-based therapies, for example. Our hypothesis is that certain patients may do well with therapy withdrawal, and now we want to test that hypothesis. Implicit in this approach is the need for disease monitoring in patients who de-escalate.

G&H Can patients do anything to monitor themselves if they de-escalate medications?

DR If we can establish a strategy to monitor inflammation through stool and/or blood tests, then we can also

explore dietary options, whether sleep and exercise affect inflammation, and other measures. It would be ideal for patients to be able to manage their disease, at least to some extent, without needing to come to the clinic.

At-home testing is a current topic of interest for doctors and patients. Most people do not want to deal with stool testing at home. However, there may be other options. We are currently exploring whether we can create a saliva or urine test to measure inflammation. The necessary corollary to that research is whether we can develop therapy adjustments that patients can instigate themselves. The patient is the most motivated party when it comes to the management of IBD, so it makes sense to find more ways to help patients help themselves.

All of this being said, we also need to remember that just because a patient wants to stop medication does not mean that that decision is the best one for that person's health. Many of the safety concerns about long-term drug use do not reflect the evidence, so I do not always support that concern as a reason to stop treatment. In addition, we have to identify patients for whom de-escalation is likely a safe option, and then find ways to monitor their progress. We cannot wait until blood counts plummet to reinstate treatment, and we cannot send patients away until their next annual check-up. We need a concrete strategy in place.

Dr Rubin is a consultant for and has received grant support from some of the companies that make the products mentioned above, including AbbVie, Janssen, Prometheus Laboratories, Shire, Takeda, and UCB.

Suggested Reading

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