ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Why Should We Define and Target Early Crohn's Disease?

Laurent Peyrin-Biroulet, MD, PhD
Head of IBD Unit
Nancy University Hospital
Vandoeuvre-lès-Nancy, France

G&H What is your definition of "early" Crohn's disease?

LP-B In a paper that my coauthors and I recently published in *Gut*, we proposed that early Crohn's disease (CD) be defined as an active inflammatory disease with objective signs of disease activity but no bowel damage—meaning no fistulae, abscesses, or strictures. This proposed definition also stated that patients with early CD are those with a disease duration of less than 2 years; no history of CD-related surgery; and no previous use of potentially disease-modifying agents, such as azathioprine or biologic medications. This definition was proposed after performing a comprehensive data review, but it is not yet a consensus definition.

G&H Why do clinicians need an accepted definition for early CD?

LP-B We need a consensus definition so that we can define the appropriate patient population for a study evaluating whether earlier treatment modifies the course of CD. Biologic medications were introduced 15 years ago, and the efficacy and safety of these drugs have been well evaluated since that time. Even with current therapeutic strategies, however, approximately one quarter of patients will require surgery within 5 years after diagnosis. Thus, current treatments do not modify the natural history of CD. In order to actually modify the course of the disease, we will likely need to introduce biologic agents earlier. Fortunately, CD has some similarity to rheumatoid arthritis—in which there is a window of opportunity before the development of damage and disability—so we have reason to hope that CD may also respond well to earlier treatment.

G&H How does CD compare with rheumatoid arthritis in terms of the possible benefits of early treatment?

LP-B Studies have shown that early treatment of rheumatoid arthritis prevents joint damage and disability, and I think we can expect the same for CD. From a pathophysiologic standpoint, we know that there are some differences between rheumatoid arthritis and CD, but both conditions also share some common pathways. Since both are chronic disabling conditions associated with damage, we can expect that early treatment will be similarly beneficial for rheumatoid arthritis and CD.

G&H Are clinicians and researchers working to develop a consensus definition for early CD?

LP-B Yes, this process is ongoing at the international level. I am currently chairing a panel of up to 20 international experts in the field of inflammatory bowel disease, and we should have the last meeting to reach a consensus on the definition of early CD in late June. The aim of this meeting will be to edit the definition proposed in the aforementioned *Gut* paper and then to reach a consensus on the international definition of early CD. I hope to publish this new consensus definition by the end of the year.

G&H How can clinicians detect patients with early CD?

LP-B Unfortunately, we cannot diagnose CD before the onset of symptoms. Even if a patient has genetic and envi-

ronmental risk factors for CD, we have no way to detect subclinical inflammation and diagnose the disease at the preclinical phase. Thus, all patients with CD are diagnosed in the same manner. After diagnosis, CD patients can be classified as having early CD if they meet certain criteria, including short disease duration, no history of surgery, and no use of potentially disease-modifying agents.

Currently, we know that one fifth of patients have some bowel damage at diagnosis, and we need to be able to identify these patients in order to improve treatment. Because CD is a transmural disease, colonoscopy alone is insufficient for an overall evaluation of bowel damage. Thus, we will probably need to perform magnetic resonance imaging (MRI) of the entire intestinal tract in order to determine the degree of bowel damage at diagnosis.

G&H What is the advantage of using MRI rather than other imaging modalities?

LP-B Studies have shown that MRI technology is accurate for visualizing both the colon and small bowel, and this procedure is nonirradiating; the only real disadvantages associated with MRI are its higher cost and sometimes limited availability. In countries where physicians do not have easy access to MRI technology, computed tomography (CT) can also be used to aid in diagnosis. Caution should be used when employing CT scans, however, as repeated scans may be associated with an increased risk of cancer.

G&H How might earlier use of biologic therapies help clinicians to modify the course of CD?

LP-B Subgroup analyses from large randomized controlled trials of both adalimumab (Humira, Abbott) and certolizumab pegol (Cimzia, UCB) have shown that anti–tumor necrosis factor agents are much more effective in early CD than in the later stages of the disease. At earlier stages of CD, the disease has a more inflammatory phenotype and minimal complications (such as stenosis, strictures, and fistulae), and we know that biologic agents are more effective in this setting. Some immunologic changes also occur over the course of the disease; early CD has more of a Th1 phenotype, for which biologic drugs are more effective.

Because biologic medications are more effective in early CD, these medications are more likely to change the natural course of the disease at this stage. By treating CD earlier, we can hopefully prevent the development of bowel damage, rather than having to treat complications after they occur. Earlier treatment should also allow us to reduce or prevent CD-related disability, which is another priority when managing CD.

G&H Are there disadvantages to earlier use of biologic therapies?

LP-B There is always a risk of overtreatment in some patients. Studies of the natural history of CD have shown that approximately 10–20% of patients can achieve sustained clinical remission without treatment. In these patients, early introduction of biologic therapies might be unnecessary, as these individuals are likely to have a milder disease course. While we know that approximately half of CD patients will have disease complications requiring surgery within 10 years after diagnosis, the other half will not have bowel damage and will not require surgery within this period. These latter patients still have inflammatory disease that may be associated with disability, but we do not know the extent of this disability, so aggressive therapy may be overtreatment in some cases. For this reason, our efforts to establish a consensus definition on early CD have involved much discussion about whether recommendations for treatment should include predictors for worse outcomes. Factors that predict a poor prognosis include severe rectal disease, extensive small bowel disease, upper gastrointestinal involvement, young age at diagnosis, and perianal disease. One possibility is that we may recommend treatment of early CD only in patients with predictors of poor outcomes.

G&H Have any studies evaluated treatments for early CD?

LP-B There have not been any good studies regarding treatment of early CD. One study by D'Haens and colleagues evaluated infliximab (Remicade, Centocor) in patients with early CD, but the study had several limitations. First, the study used an empiric definition of early CD: disease duration less than 4 years. In addition, patients in this study received episodic treatment with infliximab rather than a consistent regimen. Thus, we cannot conclude from this study that earlier treatment is more effective.

Another study, the SONIC study, was published in *The New England Journal of Medicine* in 2010; while this study did not evaluate early CD specifically, it may shed some light on treatment of these patients. In the SONIC study, all enrolled patients were naïve to immunosuppressants; thus, we could expect that these patients are likely to have earlier disease. In this study, combination therapy with azathioprine and infliximab was more effective than azathoprine monotherapy in terms of steroid-free remission at 6 months.

While limited data suggest that earlier treatment of CD is beneficial, we still need to perform a disease modification trial in order to compare early aggressive treatment

with a step-up approach. A key first step in this process is to establish an international definition of early CD, as this definition will be needed to standardize the patient population for such trials. Currently, we cannot promote early aggressive treatment of CD because we have insufficient evidence, but once we have an agreed-upon definition of early CD, then we can begin trials to determine whether aggressive treatment can effectively modify the disease course.

Suggested Reading

Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, Sandborn WJ. Early Crohn disease: a proposed definition for use in disease-modification trials. *Gut*. 2010;59:141-147.

Schreiber S, Colombel JF, Bloomfield R, et al; PRECiSE 2 Study Investigators. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am J Gastroenterol*. 2010;105:1574-1582.

Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis*. 2010 Nov 28. Epub ahead of print.

Peyrin-Biroulet L, Cieza A, Sandborn WJ, et al. Disability in inflammatory bowel diseases: developing ICF Core Sets for patients with inflammatory bowel diseases based on the International Classification of Functioning, Disability, and Health. *Inflamm Bowel Dis*. 2010;16:15-22.

D'Haens G, Baert F, van Assche G, et al; Belgian Inflammatory Bowel Disease Research Group; North-Holland Gut Club. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomized trial. *Lancet*. 2008;371:660-667.

Colombel JF, Sandborn WJ, Reinisch W, et al; SONIC Study Group. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383-1395.