ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Disease Clearance in Inflammatory Bowel Disease

Jean-Frédéric Colombel, MD
Professor of Medicine
Director of the Susan and Leonard Feinstein IBD Clinical Center
and the Leona M. and Harry B. Helmsley Charitable Trust IBD Center
Icahn School of Medicine at Mount Sinai
New York, New York

G&H How have therapeutic goals evolved over time in inflammatory bowel disease?

J-FC Several years ago, the main goals of inflammatory bowel disease (IBD) treatment were essentially to improve symptoms as well as quality of life in patients because drugs were not available that could modify the course of the disease. These goals have evolved into more ambitious ones by targeting the natural history of the disease and blocking disease progression to prevent complications leading to surgery, disability, and risk of cancer in patients with Crohn's disease and ulcerative colitis. In order to achieve these goals, the endpoints of clinical trials have evolved. For example, in ulcerative colitis, endpoints have changed from clinical remission to endoscopic remission, and, more recently, mucosal healing has combined endoscopic remission with histologic remission. The most recent concept that has been proposed in ulcerative colitis is disease clearance, which is essentially a combination of clinical, endoscopic, and histologic remission. The definition of disease clearance in Crohn's disease is less clear and may also encompass transmural healing as best appreciated by cross-sectional imaging such as magnetic resonance enterography.

The main reason for achieving disease clearance and treating patients beyond symptoms is that many doctors are convinced, even though the evidence is mostly based on retrospective data, that achieving the components of disease clearance may block the progression of the disease in the long term and prevent complications.

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G&H How is each of these 3 types of remission best measured in patients with ulcerative colitis?

J-FC In patients with ulcerative colitis, validated indices are available to measure clinical remission (Mayo score), endoscopic remission (Mayo endoscopic subscore

and Ulcerative Colitis Endoscopic Index of Severity), and histologic remission (Robarts Histopathology Index, Nancy Index, and Geboes score). These indices can then be combined to evaluate disease clearance.

G&H Could you discuss any research that has looked specifically at disease clearance in patients with IBD?

J-FC Disease clearance is a new concept and has not yet been well studied. There are no prospective data yet proving that disease clearance actually matters in terms of long-term outcomes of patients. The research on disease clearance thus far has been preliminary and is mostly based on post hoc analysis of clinical trials or retrospective data from international cohorts. It is important to note that regardless of the drug used in clinical trials, the percentage of patients with ulcerative colitis able to reach the stage of disease clearance remains relatively low; after 1 year, no more than 20% of patients are able to do so. Thus, it is a very difficult endpoint to reach.

G&H Are there any studies currently underway on disease clearance?

J-FC The ongoing VERDICT (Determination of the Optimal Treatment Target in Ulcerative Colitis) trial is the first multicenter, prospective, randomized, controlled trial in moderately to severely active ulcerative colitis to determine whether using a treatment target of corticosteroid-free symptomatic plus endoscopic plus histologic remission is superior to a treatment target of just corticosteroid-free symptomatic remission. The primary endpoint is time to a complication associated with ulcerative colitis within up to 80 weeks of follow-up after reaching the target. This is a disease modification trial, which means that it examines whether the course of the disease can be changed; thus, it looks at long-term outcomes (80 weeks). In contrast, most clinical trials are limited to 1 year of follow-up, which may not be sufficient to appreciate the impact of a treatment strategy on long-term outcomes.

> … I believe that true disease clearance will require targeting the disease even before the first symptom.

G&H Is disease clearance a realistic goal for all patients with IBD?

J-FC I think that it is a realistic goal when patients are treated early, at diagnosis. In those cases, doctors are more ambitious because they know that medications work best when used early. When IBD has already progressed, disease clearance is a much less realistic goal because response to medications may be suboptimal and damage has already been caused that may be irreversible.

G&H What appear to be the best predictors of disease clearance?

J-FC This issue has not been very well studied. These predictors would probably encompass those of drug response, which are not known yet either. The best predictor of disease clearance may still be early therapy. Catching a patient very early in his or her disease history may increase the likelihood of clearing the disease. It is also likely that disease clearance is easier to reach when the disease is not as severe and has less endoscopic or histologic activity, for example. When disease starts very severe with an acute flare, deep ulcerations, and substantial endoscopic activity, disease clearance is more difficult to attain.

G&H How does disease clearance differ from cure?

J-FC It is very important to differentiate between disease clearance and cure. Disease clearance does not equal cure because cure means no disease and no treatment. Once IBD has started, it is very difficult to obtain cure. A patient may be able to clear the disease on therapy (ie, achieve combined clinical, endoscopic, and histologic remission), but as soon as the patient stops treatment, the risk of relapse is very high. That is why I believe that true disease clearance will require targeting the disease even before the first symptom. This is the domain of prediction and prevention, which has started to be explored in IBD as well as in other immune-mediated diseases.

G&H Can surgery help achieve disease clearance or cure?

J-FC It has been argued that a proctocolectomy can cure ulcerative colitis. I disagree because removing the colon has a significant long-term functional impact. However,

there have been some interesting recent observations suggesting that when surgery is performed in some patients with limited, noncomplicated ileal Crohn's disease close to diagnosis, approximately one-third may no longer have disease and may not need treatment (ie, they may achieve cure). This is an interesting concept that has to be confirmed.

G&H What are there any other challenges to targeting disease clearance?

J-FC There is always a need to balance the risks and benefits of drugs that may achieve disease clearance. That is why some doctors may be reluctant to step up therapy when a patient is in clinical remission but has not achieved endoscopic and histologic remission.

G&H What are the next steps in research in this area?

J-FC As mentioned, disease clearance is an endpoint that is difficult to achieve with the drugs that are currently available, so it is important to find predictors of clearing the disease. We also need to optimize strategies to increase the efficacy of drugs, for example, by finding biomarkers of response to a drug and/or by combining drugs to increase the likelihood of healing and of achieving disease clearance. In addition, as previously noted, it is important to confirm in prospective studies that targeting disease clearance is associated with better long-term outcomes than clinical remission and has a favorable risk-benefit ratio.

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Suggested Reading

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