ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Targeting the Preclinical Phase of Inflammatory Bowel Disease

Jean-Frédéric Colombel, MD
Professor of Medicine
Director, Susan and Leonard Feinstein Inflammatory Bowel Disease Clinical Center
Icahn School of Medicine at Mount Sinai
New York, New York

G&H What is the current understanding of the natural history of inflammatory bowel disease?

JFC It is now recognized that inflammatory bowel disease (IBD) is comprised of chronic progressive diseases that lead to bowel damage and disability. This is especially true for Crohn's disease, although it may also apply to ulcerative colitis. Crohn's disease most often starts as an inflammatory disease and then progresses toward complications, such as fistulae, abscesses, and stenosis, which may require surgery or lead to bowel damage and eventually disability. This progression is an important recent concept that changed the way clinicians should think about IBD. In the past, clinicians viewed IBD as an intermittent disease with flares and periods of remission, and treated patients with the goal of improving their quality of life. Now, because of this new understanding, the target of treatment is to block the progression of the disease in the long term.

This same concept of disease progression was adopted many years ago by specialists of autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus, and diabetes. For example, rheumatologists realized that they needed to target the prevention of bone damage in RA instead of merely concentrating on treating symptoms. They built an index to measure bone damage in RA called the Sharp/Van der Heijde Score. Along the same lines, my colleagues and I published a scoring system, the Lémann Index, which enables, for the first time, assessment of bowel damage in Crohn's disease.

Another new, related concept, also following the path of other diseases, is that there is a window of opportunity in which early intervention should occur. If a clinician tackles a disease early (ie, immediately after the first symptoms and diagnosis), drugs such as anti–tumor necrosis factor α agents are much more effective, and the progression of the disease can be blocked. Unfortunately, too often clinicians see patients too late after their diagnosis and patients are undertreated during the first months of their disease; by the time patients finally present to an IBD specialist, irreversible damage has often already occurred.

G&H What is the status of predicting (and then targeting) the preclinical phase of IBD?

JFC The concept of prevention means tackling the disease before diagnosis and the appearance of symptoms. Again, this is not an original notion; there has been increasing interest in preventing diseases with this approach across multiple fields of medicine. There are essentially 3 different kinds of prevention: primary prevention, secondary prevention, and tertiary prevention. Primary prevention essentially means avoiding the development of a given disease in the general population by eliminating specific risk factors or increasing resistance to the disease. A typical example is the early identification of colon cancer through colonoscopy. Secondary prevention is when there is early evidence of disease, although it is not yet clinically apparent, and a preventive strategy is then provided to a specific group of

patients. Tertiary prevention is the treatment of early stages of a disease, when it is already clinically apparent.

We have already started tertiary prevention by tackling patients in early stages of IBD, but primary and secondary prevention of IBD are still untouched. For example, for primary prevention, the goal would be to identify environmental risk factors and then propose appropriate lifestyle modifications. However, even though researchers have identified several environmental factors for IBD, such as smoking or early use of antibiotics, the relative risk carried by these factors is still low, meaning that it is not yet possible to apply this strategy at a population level. This is why there are currently many studies concentrating on secondary prevention. The goal here is to focus interventions on individuals who are at a higher risk of developing overt clinical IBD because of genetic and/or environmental predisposition or who have markers in their blood or stool that indicate the disease is already present at a very early stage without any clinical symptoms. The interventions would try to tackle the disease before it progresses.

G&H What have specific studies reported thus far regarding the possibility of predicting IBD via serology and genetics?

JFC In IBD, several studies have tried to identify which individuals in the general population may be at a higher risk to develop Crohn's disease or ulcerative colitis so that these individuals can undergo preventive strategies. Many of the risk factors currently being explored are genetic risk factors, such as the *NOD2* gene for Crohn's disease.

There is also strong interest in serologic markers. In particular, my colleagues and I and researchers at several other institutions are conducting a large research project with the US Department of Defense. The aim is to examine the US Army's serum repository, in which sera are stored as soon as a recruit is enrolled. Some of those recruits will eventually develop either Crohn's disease or ulcerative colitis during follow-up, and we will have access to samples of these patients before the appearance of clinical symptoms.

Along the same lines, a study involving the Israeli army, published approximately 10 years ago—as well as a study from The Netherlands, published 2 or 3 years ago—showed that patients who develop Crohn's disease have antimicrobial antibodies in their sera 6 to 10 years before diagnosis and the first clinical symptoms. The first data from the ongoing US Army project, which focused on a cohort of 100 patients with Crohn's disease, were presented at this year's Digestive Disease Week and confirmed the data from Israel and The Netherlands.

Even more strikingly, patients in the US Army project who presented with complications such as a fistula or obstruction (which meant that their disease was discovered because they needed surgery) had an even higher number of different antibodies as well as increased levels of antibodies up to 6 years before diagnosis than patients who had a noncomplicated form of Crohn's disease at diagnosis. Further studies are ongoing in a much larger cohort that includes 1000 patients with Crohn's disease, 1000 patients with ulcerative colitis, and 500 controls, with the goals of replicating these findings, expanding them by looking at other markers, and performing proteomic analysis on the sera.

The ultimate aim of such research would be to identify a population at risk for developing an aggressive form of IBD, in which we could propose appropriate preventive strategies, such as a lifestyle modification (eg, a change in diet) or a drug therapy as long as the risk/benefit ratio of the strategy remains favorable.

G&H Are there any studies examining the prediction of IBD in families?

JFC There are currently several ongoing projects in this area. The largest one started in Canada and is called the GEM (Genetics, Environmental, and Microbial) project. The strongest risk factor for Crohn's disease has been shown to be having a family member with the disease. In the GEM project, first-degree relatives of individuals with Crohn's disease are identified; undergo comprehensive assessment of genetics, serology, and the microbiome; and are followed prospectively. Eventually, some of these subjects will develop Crohn's disease, and some will not. The goal is to find the difference(s) between these 2 groups in the hope of identifying a predictive metric for the risk of Crohn's disease.

Another ongoing study is being conducted at Mount Sinai on Jewish families who are at high risk of developing IBD. Essentially, this study uses the same concept as the GEM project but concentrates on a higher-risk population.

G&H Can any of these findings be applied to clinical practice yet?

JFC The concept of predicting IBD before the appearance of clinical symptoms is not yet applicable to clinical practice. Thus far, what we know is that if a person has a high number of antimicrobial antibodies when diagnosed with Crohn's disease, then the risk that the disease will progress is higher. There are several studies looking at predictors of disease progression in IBD, with the goal of identifying patients who should be given early intensive therapy from the beginning.

G&H How should this area be studied further?

(Continued on page 717)

(Continued from page 712)

JFC Although the prediction of disease may appear to be an overly ambitious endeavor, it is currently being explored in diseases such as RA, diabetes, and systemic lupus erythematous. IBD is trailing behind these fields, so there is a strong need for more research. A better understanding of the pathogenesis of the disease in the future may improve the strategies for detecting IBD. For example, if we could identify a signature in the microbiome that is associated with the development of Crohn's disease, then we could add this marker to our preventive metrics. Thus far, the problem is that the main tools that are currently available are serologic markers that are not very sensitive or specific. Nevertheless, this concept is a first step. More prospective studies are needed, as well as studies of cost-effectiveness, feasibility, ethics, and risk/benefit ratios for identifying an at-risk population that could benefit from a preventive approach.

Dr Colombel has no relevant conflicts of interest to disclose.

Suggested Reading

Arbuckle MR, McClain MT, Rubertone MV, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med*. 2003;349(16):1526-1533.

Choung RS, Stockfisch TP, Princen F, et al. Longitudinal status of serological markers predict Crohn's disease phenotype before diagnosis: a 'PREDICTS' study. Presented at: Digestive Disease Week 2015; May 16-19, 2015; Washington, DC. Abstract 78.

Deane KD, El-Gabalawy H. Pathogenesis and prevention of rheumatic disease: focus on preclinical RA and SLE. *Nat Rev Rheumatol*. 2014;10(4):212-228.

Israeli E, Grotto I, Gilburd B, et al. Anti-Saccharomyces cerevisiae and antineutrophil cytoplasmic antibodies as predictors of inflammatory bowel disease. *Gut*. 2005;54(9):1232-1236.

James JA, Kim-Howard XR, Bruner BF, et al. Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus. *Lupus*. 2007;16(6):401-409.

Pariente B, Mary JY, Danese S, et al. Development of the Lemann index to assess digestive tract damage in patients with Crohn's disease. *Gastroenterology*. 2015;148(1):52-63.e3.

van de Stadt LA, de Koning MH, van de Stadt RJ, et al. Development of the anti-citrullinated protein antibody repertoire prior to the onset of rheumatoid arthritis. *Arthritis Rheum*. 2011;63(11):3226-3233.

van Schaik FD, Oldenburg B, Hart AR, et al. Serological markers predict inflammatory bowel disease years before the diagnosis. *Gut*. 2013;62(5):683-688.