

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

## The Role of Serologic and Genetic Testing in IBD: Now and Looking Ahead

Dermot McGovern, MD, PhD, MRCP(UK)  
 Director, Translational Medicine  
 Inflammatory Bowel Disease Center and  
 Immunobiology Research Institute  
 Cedars-Sinai Medical Center  
 Associate Professor of Medicine  
 David Geffen School of Medicine  
 University of California, Los Angeles  
 Los Angeles, CA

### G&H What markers have been identified as being associated with inflammatory bowel disease?

**DM** The serologic markers identified thus far include ASCA, anti-I2, anti-CBir1, and anti-OmpC. These serologic markers suggest reactivity to certain microbial antigens and are related, in particular, to small bowel Crohn's disease (CD). The serologic marker known as pANCA has been consistently associated with ulcerative colitis (UC).

### G&H Could you describe the association between pANCA and UC?

**DM** This marker is not exclusively associated with UC; it has also been observed in CD, and its role in distinguishing between these 2 forms of inflammatory bowel disease (IBD) remains unclear. The main utility of this particular marker may be in predicting natural history and response to therapy. A number of studies have demonstrated that individuals with high pANCA titers are less likely to respond to anti-tumor necrosis factor (TNF) antibodies, and this is true for both UC and CD. In addition, there are data that suggest that UC patients with high-titer pANCA are much more likely to develop pouchitis

following colectomy and pouch formation compared to individuals without this characteristic.

### G&H What is the association between the other markers mentioned above and CD?

**DM** The main clinical association identified thus far is that individuals who carry these markers are much more likely to have a complicated course of CD. Importantly, a feature that appears to be consistent throughout all of the studies from both North America and Europe is that the more markers a patient expresses, the more likely the patient is to have this aggressive CD phenotype. This finding has been demonstrated in both adult and pediatric populations. The more markers present, the more likely that a patient will develop a complication or require surgery, and the sooner that complication is likely to occur. The most complete study of this phenomenon thus far, conducted by Marla Dubinsky and colleagues, was a prospective study that evaluated the presence of these markers in a pediatric CD cohort.

### G&H On what aspect of these markers does your research focus?

**DM** One focus of our research is in identifying any particular genetic underpinnings to these markers. Also, as the work advances, we want to see whether combining genetic markers with clinical characteristics will help identify subgroups of patients for which the natural history of UC and CD can be predicted.

### G&H What genetic underpinnings have been identified?

**DM** This work is really in its infancy. However, numerous studies have looked at genetic markers that increase susceptibility to CD and UC in general. This research

is currently moving into the next phase, which is to add genetic markers into predicting the natural history of the disease, and then adding serologic markers to further characterize any subgroups or to help with predicting natural history. This work is ongoing; not many studies have been published yet, though our study of genetic markers associated with the need for surgery in UC is currently in press with *Inflammatory Bowel Disease*. In this paper, we describe a panel of markers that appear to predict the need for surgery among patients with severe disease.

#### **G&H** Are these serologic and genetic markers of IBD relevant yet for the treatment of patients?

**DM** This remains the matter of some debate. We definitely need further studies of both genetic and serologic markers to be published and for these findings to be validated. Only 1 genetic marker is currently available to IBD clinicians. It has been well documented that 1 in 10 individuals are heterozygous for a mutation in the *thiopurine methyltransferase (TPMT)* gene, and these patients are at an increased risk for bone marrow toxicity as a side effect of thiopurine therapy. One in 300 patients are homozygous for mutations in this gene and are at risk for severe bone marrow toxicity. I believe that in the near future additional pharmacogenetic markers and genetic markers that help predict natural history will become available.

The serologic markers mentioned above are available to clinicians and are being used by some clinicians to help distinguish between CD, UC, and indeterminate colitis. A more validated use of these markers may help clinicians adopt a more proactive approach in managing patients with CD. Individuals with a worse prognosis, based upon serology and clinical factors (early onset disease, extensive disease, smoking, and so on), may be better candidates for early aggressive therapy or a “top-down” approach in CD.

In addition, some clinicians are beginning to incorporate the data regarding high-titer pANCA into treatment decisions and counseling patients about their likelihood of response to anti-TNF and their risk of developing pouchitis.

#### **G&H** Are any of these markers relevant to other, nongastrointestinal diseases?

**DM** Not really. Some of these serologic markers have been shown to be elevated in small numbers of other immune-related gastrointestinal conditions—for example, ASCA and celiac disease—but these associations are not clinically useful. Another study has demonstrated an association between I2 and ankylosing spondylitis, suggesting a role for mucosal dysregulation in this condition.

Right now, however, these serologic markers are clinically relevant only to IBD.

#### **G&H** Does the same hold true for the genetic markers?

**DM** Interestingly, many of the genetic associations with CD and UC are shared with other immune-related conditions, including celiac disease. Furthermore, if genetic predictors of a response to, for example, anti-TNF therapy, are identified, this may prove to be useful across all diseases for which anti-TNF therapy is used.

#### **G&H** What is the long-term usefulness of this research for patient care?

**DM** The strategy is very appealing to clinicians and patients because it may enable us to identify which patients are more likely to have an aggressive course of disease and should, therefore, have a more intensive approach to therapy. We may be able to tell patients their genetic and serologic profile and what this profile tells us about the natural history of their disease, what medications they are likely to respond to best, and what side effects they are likely to experience. In other words, this research is aimed toward developing a more individualized approach to treating patients. We currently have a uniform, almost reactionary approach to our patients with IBD, whereas it is clear to clinicians that these are extremely heterogeneous conditions. I think we would all welcome a more proactive strategy for managing patient care.

#### **G&H** Do you foresee this proactive approach becoming a reality in the coming years?

**DM** Yes. The study of genetics in IBD has expanded greatly in the past few years. Five years ago, just 1 or 2 genetic regions indicating a predisposition to IBD were confirmed; today, close to 100 different regions have been identified (from data presented by the International IBD Genetics Consortium at the 2010 Digestive Disease Week). The rate of discovery is hard to keep up with at the moment. The task at hand is to take this research to the next level from a functional point of view, so that we can use these genetic advances to understand the underlying immune and functional defects that lead to the increased risk of IBD. Having an understanding of which pathways are important in any particular patient may also help guide clinicians in determining which therapeutic approach is appropriate for this individual. Combining this with the potential ability to predict response to therapy and natural history, as discussed earlier, allows clinicians to truly move toward personalized medicine.

**G&H** What are some of your immediate next steps?

**DM** Our next study will focus on validating our findings of genetic markers associated with the need for surgery among UC patients. As noted above, we are also adding serologic markers to the genetic profile of both adult and pediatric CD patients to create a whole genome combined with serology approach for predicting which patients will require surgery and which are most likely to develop complications early in the course of their CD. This retrospective study is currently in progress, and once the markers are identified, we hope to conduct a large, prospective study. We are also looking at predictors of some of the complications that we see in IBD, such as osteoporosis.

**G&H** Is it important for the pharmaceutical industry to be involved in these efforts?

**DM** Yes. As companies bring new therapies into clinical trials, we would like to work with them to study serologic and genetic markers as well as other biomarkers that will enable clinicians to determine which patients will respond to a given therapy, and which patients are likely to experience adverse reactions to the therapy. Involvement of the pharmaceutical industry will make this process much easier, and there are potential significant benefits for industry, including the ability to conduct much more targeted (and, thus, smaller and cheaper) clinical trials.

**G&H** Could the study of genetics and IBD change how clinicians think about this collection of diseases?

**DM** I believe so. CD is a very heterogeneous condition. There are patients with perianal fistulizing disease, others with stenotic small bowel disease, and many more. All of these come under the umbrella of CD, yet they likely have different underlying genetic or molecular processes. Understanding more about these features may lead us to think of CD as a variety of conditions with different underpinnings, not unlike what has been happening in oncology. We may discover that one pathway is very important for one type of CD and that this pathway may be amenable to a particular therapeutic approach. Different genetic and immunologic profiles may respond to very different treatments, which goes back to the idea of the individualization of therapy.

**Suggested Reading**

Ahmad T, Amuzzi A, Bunce M, et al. The molecular classification of the clinical manifestations of Crohn's disease. *Gastroenterology*. 2003;122:854-866.

Dubinsky MC, Kagathasan S, Mei L, et al; Western Regional Pediatric IBD Research Alliance; Pediatric IBD Collaborative Research Group; Wisconsin Pediatric IBD Alliance. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol*. 2008;6:1105-1111.

Dubinsky MC, Mei L, Friedman M, et al. Genome wide association (GWA) predictors of anti-TNF alpha therapeutic responsiveness in pediatric inflammatory bowel disease. *Inflamm Bowel Dis*. 2010;16:1357-1366.

McGovern DP, Gardet A, Törkvist L, et al. Genome-wide association identifies multiple ulcerative colitis susceptibility loci. *Nat Genet*. 2010;42:332-337.

Mow WS, Vasiliauskas EA, Lin YC, et al. Association of antibody responses to microbial antigens and complications of small bowel Crohn's disease. *Gastroenterology*. 2004;126:414-424.