ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Emerging Strategies in the Use of IBD-related Serologic Markers

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G&H Could you describe the historic development of serologic markers in the diagnosis of inflammatory bowel disease?

MD Serologic testing for inflammatory bowel disease (IBD) patients was initially developed in an effort to differentiate disease states in patients with indeterminate colitis. Originally, in the 1990s, there were only two known markers to screen. Initially, *anti-Saccharomyces cerevisiae* antibody (ASCA) was associated with Crohn's disease (CD) and perinuclear antineutrophil cytoplasmic antibody (pANCA) with ulcerative colitis (UC). Eventually it was found that approximately 25% of Crohn's colitis patients are also pANCA-positive, and the term "UC-like CD" was coined to describe them. Thus, our understanding of CD and UC as distinct diseases became slightly muddied. However, as research utilizing these markers continued to develop, patterns of pANCA IBD and ASCA IBD emerged, and the question of the two diseases became less important. Ultimately, with further and more exact serologic definitions of different IBD subtypes, the terms CD and UC may be eliminated altogether.

Ultimately, ASCA and pANCA screening proved sensitive in differentiating disease states in approximately two thirds of patients because two thirds of patients had one or both of these markers present. The other 30% of the IBD population could not be evaluated accurately with these markers because they did not screen positively for either of them. Thus, researchers began looking for other markers that could be detected and added to a profile of serologies to increase their overall sensitivity. All of the new markers that have been identified over the last 4 years have been CD markers. No new UC markers have been found, but we continue to consider pANCA-positive patients as having a predominantly UC-like behavior.

The next marker that was identified in association with CD was the outer membrane porin of gram-negative bacteria, including *Escherichia coli* (OmpC). In 2005, an antibody to the flagellin of a family of *clostridia* (anti-CBir1) was discovered and proved to be present in approximately 50% of CD patients. With all of these markers in place, it became possible to detect CD in anywhere from 80% to 90% of patients.

There are now several laboratories in the United States that are equipped to perform IBD serology screening, and some have proprietary procedures to test for specific markers. Prometheus Laboratories, for example, has a proprietary test for IBD-specific pANCA, as well as OmpC and anti-CBir1. Laboratories originally utilized cut-point–based diagnostic testing where titers, at a certain level, were deemed positive or negative. Eventually, it became very clear that IBD serologies are better interpreted on a continuous spectrum, where some patients have low levels of these markers but the markers are still positive indicators of disease. Prometheus now utilizes a Smart Diagnostic algorithm, which examines pattern-recognition data, rather than using a cutoff for each marker to determine positivity or negativity for CD. Clinicians who need to rule in or rule out IBD in a specific patient can examine patterns of markers in an IBD serology screening to see if they are consistent with IBD. They can also look at the patterns to determine whether the patient has more CD- or UC-like disease. Thus, in their current state, serologic diagnostics reflect a 2-tiered facility.

G&H In what patients and scenarios are serology panels most useful as a diagnostic tool?

MD For pediatric gastroenterologists, these noninvasive tests are useful because we prefer to avoid colonoscopy in

our young patients whenever possible. For adult patients, the utility is less clear-cut, as any adult with rectal bleeding needs to be scoped unless they have a visible hemorrhoid or fissure. A 40- or 50-year-old patient with rectal bleeding of no immediately apparent origin needs to be scoped due to the possibility of malignancy, regardless of the results of a serology panel; there is no real application in these patients. However, in a scenario of IBD versus irritable bowel syndrome (IBS), where patients have a nonspecific presentation of bloating, a little fatigue, a little diarrhea, and/or a little cramping, there is any number of possible diagnoses. In these cases, there may be a role for adding serologic testing to other standard tests like sedimentation rate, platelet levels, C-reactive protein levels, and other inflammatory markers. Taking into account the patient's history, their physical state, the laboratory results, and, additionally, these markers, can be helpful in ruling out IBD and deciding to treat for bacterial overgrowth or IBS before investigating invasively.

G&H Is there a role for serologic panels as a prognostic indicator in patients with an established IBD diagnosis?

MD One of the most important applications of serologic testing is in established IBD patients who are considering complete colectomy. The presence of certain markers, such as ASCA, is an indication for a high risk of postsurgical CD or fistulization of the pouch, whereas patients who are pANCA-positive have a UC-like profile that is more predictive of pouchitis and not CD of the pouch.

Serologies are also helpful as a prognostic tool that allows clinicians to communicate with patients regarding their risk of disease complication and probabilities of rapid disease progression. They create a context for discussing risk of developing strictures or internal penetration that may require small-bowel surgery. Thus, patients have a better understanding regarding recommendations for more effective therapies earlier in the disease course. If a patient is failing conventional approaches and the family or patient is hesitant regarding a switch to more potent medications, clinicians can utilize serologic panels to provide some level of risk stratification for complications and disease course, which can be weighed against lymphoma and/or infection risk associated with more effective therapies.

G&H How can the presence of high titers of a given marker be interpreted versus the presence of multiple markers at lower levels?

MD Magnitude versus presence or absence of serologic markers is an issue of ongoing research. Does the mere presence of any given marker at a very high level trump the presence of other markers at low levels? In other words, what if the patient has very high titers of any one marker? How does a patient with low levels of four markers compare to someone with high levels of only two markers?

Levels of markers are calculated by quartile sums, versus antibody sums, which are the calculation of the total number of different markers a patient has. Current research suggests that higher quartile levels may be more significant and predict more severe disease than the presence or absence of more than one marker. If a patient tests positive for OmpC, anti-CBir1, and both immunoglobulin A and immunoglobulin G subtypes of ASCA, but has low levels of all four, it would still be cause for concern because our experience with antibody sums shows that patients who are positive for four markers have a rapid disease course and high likelihood of complications. However, I would be much more concerned if the same patient displayed levels in the highest quartiles for all four. This scenario would send a strong signal for adamant recommendation of a more aggressive therapeutic strategy.

G&H How can serologic markers potentially be used to predict response to different classes of therapy?

MD There has been no research into the use of serologic markers to predict response to steroids, immunomodulators, or 5-aminosalicylates, though it could be of potential interest, particularly for immunomodulators like methotrexate, 6-mercaptopurine, and azathioprine. The research focus thus far has been on the use of these serologies in conjunction with biologic therapies.

Because biologics target specific inflammatory pathways associated with tumor necrosis factor (TNF) or $\alpha 4\beta 1$ integrins, it would be very helpful to know, upfront, the mechanism of a specific patient's inflammatory response. If we were able to say that, for example, ASCA signals a specifically TNF-driven pathway, we might be able to predict which patients will have the best response to anti-TNF therapies. Conversely, there are currently two or three studies that have shown that pANCA is a negative predictor of early response to anti-TNFs. This information could be crucial in deciding a course of therapy for a hospitalized patient with active disease, where the clinician is presented with a choice between biologic therapy, cyclosporine, and surgery. If a prediction could be made based on serologies, as to which therapy will most likely allow them to avoid surgery and the likelihood of postoperative complications, both in the short- and long-term, it would be a huge advance.

I have had hospitalized patients who are pANCA-positive in the highest quartile, and I have felt comfort-

able presenting them with a scenario where anti-TNF therapy is much less likely to work for them or allow them to retain their colon in the long run. This information provides real guidance in the decision-making process.

G&H How do you predict the use of serologic markers will affect the future individualization of IBD therapy?

MD Given the fact that not all of our patients respond to all therapies and the fact that early, successful intervention is needed to improve long-term outcomes, it is important to begin selecting out those patients who will have complications and severe disease, as well as those who will respond to certain therapies, at the time of diagnosis. This will allow us to intervene early in those patients who most require it and are most likely to benefit from aggressive therapies, simultaneously avoiding exposure to the risks of top-down management in those who do not need it.

One of the most complicated questions to be addressed is that of the mildly symptomatic patient whose serologic profile predicts IBD with a severe and rapid course of disease, ending in surgery within the next 18 months. Should this patient receive an aggressive course of therapy, based entirely on serologic findings, or should we observe how this patient progresses in our traditional step-up approach? I believe that although serologic markers will play an important role, they will need to be integrated into a larger risk assessment algorithm that considers everything from clinical presentation, to symptoms, to family history, to endoscopic findings, and all of the other assessment tools that are available.

G&H Is there a potential future role for other noninvasive evaluations such as fecal and genetic markers?

MD Measurement of fecal calprotectin is an interesting possibility, though its role remains unclear. We are still not sure if it is a marker of postoperative recurrence, relapse, or degree of small- versus large-bowel involvement. Until we have better evaluations of sensitivity and specificity for fecal markers, they will not be of much practical use.

We have reached a point in research and treatment where the use of markers to predict response and disease course has assumed a place of paramount importance, given the widely varying levels of success that we are seeing with current therapeutic options. Of potential promise is current research into proteomics and gene expression. Furthermore, as new bacterial antigen immune responses are discovered and as new genetic markers are identified with the completion of new genome-wide association studies, our understanding of IBD disease pathways will grow and allow us to individualize therapies in ways that are increasingly effective.

Suggested Reading

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