ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

New and Emerging Therapies for Inflammatory Bowel Disease

Silvio Danese, MD, PhD
Head of the IBD Center
Department of Gastroenterology
Istituto Clinico Humanitas
Milan, Italy

G&H What has recent research revealed about the pathophysiology of inflammatory bowel disease?

SD One of the major discoveries in Crohn's disease over the past few years has been the realization that the innate immune system plays a key role in the disease mechanism. Following an initial defect in the innate immune system, there is overreaction of the adaptive immune system, which leads to the classical inflammatory response that has been described in these patients.

Ulcerative colitis has classically been described as a disease involving T helper 2 cells and increased levels of interleukin (IL)-13, which seems to be a key cytokine, but the pathophysiology of ulcerative colitis has not been studied as much as that of Crohn's disease.

Finally, another concept that is very relevant is that most diseases are dependent not only on T cells but also on nonimmune cells. While a primary defect in epithelial cells seems to be a key step in the disease process, the development of inflammatory bowel disease (IBD) also depends on the immune response and on nonimmune cells such as fibroblasts and endothelial cells.

G&H Given our current understanding of these disease mechanisms, what new treatment approaches might be effective for IBD?

SD The drugs currently used to treat IBD deactivate the immune system in a very nonspecific manner. Specifically, the available biologic therapies include anti-integrins and various antibodies against tumor necrosis factor α (TNFα), such as infliximab (Remicade, Janssen Biotech), adalimumab (Humira, Abbott), and certolizumab pegol (Cimzia, UCB). In addition to the drugs that are currently on the market, a new anti-TNFα drug should be available soon: Golimumab (Simponi, Janssen Biotech) is a humanized anti-TNFα drug that can be administered subcutaneously. This drug is currently indicated for treatment of moderately to severely active rheumatoid arthritis, active psoriatic arthritis, and active ankylosing spondylitis, and it has been reported to be effective as a treatment for ulcerative colitis.

Also in the pipeline are several other new drugs, all of which appear to be very effective. For example, anti-adhesion molecules such as vedolizumab are being developed that can block the homing of reactive T cells, and these drugs have been shown to be very effective for the treatment of both Crohn's disease and ulcerative colitis. The specificity of these drugs for T cells that express in a selective manner the integrin α4β7 is an important advantage because it both promotes efficacy and improves safety. One of the major concerns with early trials of anti-integrins was the possibility of significant side effects, such as progressive multifocal leukoencephalopathy (PML), but the specificity of newer anti-integrins suggests that this concern will be greatly reduced with the next generation of drugs such as vedolizumab. A similar safety profile should occur with anti–MAdCAM-1 or anti–recombinant β7 antibodies.

Another interesting molecule that has recently been described in the literature is ustekinumab (Stelara, Janssen Biotech), which is an antibody against IL-12 and IL-23 that is currently indicated for treatment of psoriasis. A phase II trial showed this drug to be effective for treatment of Crohn's disease, and a phase III trial is now ongoing.

Finally, tofacitinib (Xeljanz, Pfizer) is an inhibitor of Janus kinase (JAK) 3, a signaling molecule that acts as a hub

for many inflammatory cytokines. Tofacitinib is currently approved for treatment of moderately to severely active rheumatoid arthritis and is being investigated for treatment of ulcerative colitis. Inhibiting the signaling of JAK3 should allow for inhibition of inflammation by broadly inhibiting multiple inflammatory cytokines.

G&H What are the results of early research on these drugs?

SD Trials of vedolizumab, which acts against the α4β7 integrin, have shown this agent to be very effective for inducing and maintaining remission in patients with ulcerative colitis; this finding was first reported at the 2012 Digestive Disease Week meeting. At the 2012 United European Gastroenterology Week meeting, researchers provided further data showing that vedolizumab is also very effective for treating patients with Crohn's disease, especially in terms of maintaining remission at 1 year. Of note, no safety issues were observed in these studies. Other anti-integrins have been associated with a risk of neurologic complications, such as PML, but the results with vedolizumab have been very promising to date, suggesting that safety is not likely to be a problem with this drug.

Data on ustekinumab were recently published in *The New England Journal of Medicine*. This dose-ranging, phase II trial showed ustekinumab to be effective in inducing response and maintaining remission at 22 weeks.

Finally, a phase II trial of tofacitinib was recently published in which this drug was shown to be very effective for inducing remission in patients with moderate-to-severe ulcerative colitis.

G&H How soon do you think some of these drugs will be available for clinical use?

SD I think golimumab will be available in approximately 1 year. Vedolizumab will also probably be available in 1 year —or a few years from now, at the latest. For ustekinumab and tofacitinib, approval will take somewhat longer, as these drugs are still being evaluated in phase III trials.

G&H Which of these drugs do you think will have the biggest impact on clinical practice?

SD It is very difficult to predict which new drugs will have the biggest impact. We will need to see efficacy data on these new drugs to determine whether we should change our treatment strategy for patients with IBD. At the moment, I think anti-TNFα drugs will continue to be the mainstay of treatment. In fact, generic anti-TNFα drugs will likely become available soon, which could prompt more widespread use of this class of medications.

G&H What nonmedical therapies are being considered for the treatment of IBD?

SD One interesting approach that has recently been reported is stem cell transplantation for treatment of Crohn's disease. This therapy is being evaluated in a European trial called ASTIC, which stands for Autologous Stem Cell Transplantation for Crohn's Disease. This trial enrolled patients with Crohn's disease who were extremely resistant to conventional therapy, and these patients were randomized into 2 groups. Patients in the first group were assigned to receive immune depletion therapy followed promptly by autologous bone marrow transplantation; patients in the second group were assigned to immune depletion therapy alone, and then autologous bone marrow transplantation was performed 1 year later. The preliminary results of this study are very promising, with data showing a high remission rate. While 1 fatality has been reported with this therapy, it nonetheless remains an interesting approach.

G&H Assays are now available that can measure the levels of anti-TNFα drugs and antidrug antibodies. Do you think that the availability of such tests will change how clinicians use these drugs?

SD The problem is not the lack of reliable assays, but rather the lack of good clinical studies proving that patients benefit when clinicians adjust anti-TNFα therapy in relation to trough levels and/or the presence of antidrug antibodies. We need studies to show that such a scheme will be both cost-effective and clinically effective in terms of improving patient outcomes. Several laboratories have been working to determine the best test for measuring drug and antidrug antibody levels, but we need more information on optimal trough levels for various drugs, the levels at which antidrug antibodies become neutralizing, and how we should change clinical management in relation to levels of drugs and antidrug antibodies.

G&H What further research is needed in this area?

SD Research in ulcerative colitis should look at many aspects of the disease. For example, we need studies that adjust treatment in a prospective manner to determine whether using mucosal healing as a target endpoint is better than simply aiming to remission. Studies of ulcerative colitis patients should also assess bowel function.

For Crohn's disease, we need more studies in patients with early Crohn's disease, and we also need studies in which researchers step up treatment in relation to intestinal damage rather than treating based on symptoms alone. In particular, studies should not only focus on the relationship between therapy and mucosal

healing but should also aim to prevent bowel damage progression in order to change the natural history of the disease. Researchers are currently working to create tools that will allow quantification of bowel damage in patients with Crohn's disease, and these tools should aid in the planning of future studies. A consensus on the definition of Crohn's disease was also published just a few months ago, and good studies are now needed to evaluate therapies in this context.

Finally, many challenging areas of Crohn's disease require further study; for instance, we need studies showing that anti-TNFα drugs are effective in the postoperative setting. Such trials are now ongoing, and their results should show us whether patients who receive anti-TNFα therapy have better outcomes, which would suggest that these drugs can prevent recurrence of disease. Studies of fistulizing disease are also needed, as we have very few studies on treatment in this subpopulation of patients.

Suggested Reading

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