ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

The Present and Future of Inflammatory Bowel Disease Treatment

William J. Sandborn, MD
Professor of Medicine and Adjunct Professor of Surgery
Chief, Division of Gastroenterology
Director, UCSD IBD Center
University of California San Diego and UC San Diego Health System
La Jolla, California

G&H Could you briefly summarize the current pharmacologic options for inflammatory bowel disease?

WS For Crohn's disease, mesalamine products are sometimes used, but they are not approved by the US Food and Drug Administration (FDA) and are not very effective. Corticosteroid formulations, both conventional corticosteroids and ileal-release budesonide, are effective and used for induction. Azathioprine, 6-mercaptopurine, and methotrexate are oral immunosuppressive drugs that are sometimes used, even though they are not approved for Crohn's disease. These agents are of modest efficacy and are relatively slow-acting, so they are better for maintenance than for induction. Anti–tumor necrosis factor (TNF) drugs currently include infliximab (Remicade, Janssen), adalimumab (Humira, AbbVie), and certolizumab pegol (Cimzia, UCB). These agents are effective for both induction and maintenance of Crohn's disease, but they do not work in all patients. Approximately 2 years ago, the anti–alpha-4 beta-7 integrin antibody vedolizumab (Entyvio, Takeda) was approved for induction and maintenance of Crohn's disease. This drug is fairly slow-acting, so it is somewhat better for maintenance than for induction. It is selective in its targeting, even though it is administered intravenously, so it does not have black box warnings for serious infection and malignancy as anti-TNF agents do. There is emerging use of vedolizumab as first-line biologic therapy because it tends to show better results in patients who have not previously had anti-TNF drugs and because it is likely safer than anti-TNF drugs.

For ulcerative colitis, mesalamine is clearly effective for both induction and maintenance in mild to moderate patients. For the approximately 50% of patients who fail mesalamine therapy, the next line of treatment is either conventional corticosteroids or multimatrix budesonide (Uceris, Salix), which delivers the drug to the colon. From there, there is sometimes off-label use of azathioprine and 6-mercaptopurine, neither of which is approved for ulcerative colitis. Their efficacy is modest, and there may be toxicity in the form of non-Hodgkin lymphoma, drug-induced pancreatitis, skin cancer, bone marrow suppression, infection, and other side effects. Then, there are 3 anti-TNF drugs approved for induction and maintenance of remission of ulcerative colitis: infliximab, adalimumab, and golimumab (Simponi, Janssen). These agents have black box warnings for tuberculosis and other opportunistic infections, as well as lymphoma. Finally, vedolizumab is effective for induction and maintenance of remission of ulcerative colitis and is corticosteroid-sparing. Even more than in Crohn's disease, there is emerging use of vedolizumab as a first-line biologic agent for ulcerative colitis owing to its good efficacy profile and its improved safety over anti-TNF drugs.

G&H What are the most significant unmet needs in current inflammatory bowel disease treatment?

WS With the current biologic drugs, approximately 20% to 35% of patients will achieve remission, and approximately 45% to 60% of patients will achieve response or remission. Conversely, this means that 40% to 55% of

patients have no response to therapy, and 65% to 80% of patients do not experience a full remission. In addition, patients who respond to biologic drugs can lose response over time. For example, they may develop antidrug antibodies to the biologic drug, which can lead to loss of response. Thus, there is a substantial number of patients who fail to respond or fail to fully remit, or who lose response. The associations of azathioprine, 6-mercaptopurine, and anti-TNF agents with lymphoma and serious and opportunistic infections, as well as the associations of azathioprine and 6-mercaptopurine with skin cancer, are not ideal either. Therefore, having drugs or drug combinations for all patients that are highly effective and that do not have infectious or malignant side-effect profiles is an important unmet need.

Also, having additional oral therapies and having biologic therapies that are administered subcutaneously on an infrequent basis would be desirable from a patient compliance and convenience standpoint.

G&H Are there any promising anti-integrin drugs in the pipeline?

WS Etrolizumab (Genentech) is an interesting drug in the same general class as vedolizumab that is currently being tested in phase 3 trials in patients with ulcerative colitis as well as in patients with Crohn's disease. Like vedolizumab, etrolizumab blocks alpha-4 beta-7, but it also blocks alpha-E beta-7, which affects lymphocyte trafficking to the skin and to the gut. Blocking alpha-4 beta-1 can lead to progressive multifocal leukoencephalopathy (PML), but both etrolizumab and vedolizumab do not impact lymphocyte trafficking to the brain, which is mediated vs alpha-4 beta-1 integrins. Thus, these 2 drugs are seen as brain-sparing and are not associated with PML.

G&H Which sphingosine-1-phosphate receptor modulators are currently under clinical investigation?

WS Sphingosine-1-phosphate (S1P1) receptor modulators lead to internalization of the S1P1 receptor, which is located on surface C-C chemokine receptor type 7–positive lymphocytes, resulting in an inability for these lymphocytes to follow the S1P1 gradient on the lymphatic endothelium, thus functionally trapping the lymphocytes in lymph nodes until they die.

One promising S1P1 receptor modulator is RPC1063, or ozanimod (Celgene). This drug was shown to be effective in a phase 2 trial in ulcerative colitis and is currently being tested in a phase 3 trial in ulcerative colitis and a phase 2 trial in Crohn's disease. There are 2 other S1P1 modulators in development for patients with inflammatory bowel disease: APD334 (Arena Pharmaceuticals) and MT-1303 (Biogen Idec).

G&H Are there any promising agents that block interleukin-12 and/or -23?

WS Anti-P40 and anti-P19 antibodies block signaling through the Th1 and Th17 pathways. Ustekinumab (Stelara, Janssen) is an anti-P40 antibody that blocks the P40 subunit of interleukin (IL)-12 and -23. This agent is currently approved by the FDA for psoriasis and psoriatic arthritis and has finished phase 3 testing in Crohn's disease. Clinical trial data have recently been presented in abstract form showing that ustekinumab is effective for induction of remission in patients with inflammatory bowel disease who are failing conventional therapy (not anti-TNF drugs) and separately for induction of remission in patients who have failed anti-TNF drugs. A maintenance trial mixed these 2 populations and showed that the drug is effective for maintaining remission for over a year. Ustekinumab is currently under review for FDA approval, and a decision is expected in the third quarter of this year.

A number of other drugs are being developed that have anti–IL-23 antibodies directed toward P19. LY-2525623 (Lilly) is being evaluated in a phase 2 trial in ulcerative colitis. Boehringer Ingelheim just partnered with AbbVie to develop BI 655066, an anti–IL-12 antibody that has been tested in Crohn's disease and has positive phase 2 data. AstraZeneca MedImmune, in partnership with Amgen, has an anti-P19 antibody drug called AMG 139/MEDI2070. A phase 2 study in Crohn's disease showed that this drug was able to achieve clinical remission and improve blood and stool biomarkers. Janssen is developing a drug for psoriasis comprised of an anti-P19 antibody to IL-23 (guselkumab) that could be tested in Crohn's disease in the future.

G&H Which Janus kinase inhibitors show promise?

WS Janus kinase (JAK) inhibitors block a variety of proinflammatory cytokines by blocking the JAK/Signal Transducer and Activator of Transcription signaling pathway. Tofacitinib (Xeljanz, Pfizer), which is currently approved by the FDA for rheumatoid arthritis, is a small molecule that blocks predominantly JAK1 and JAK3 receptors but also has some JAK2 effects at higher doses. A phase 2 study showed that the drug was highly effective in ulcerative colitis, and two phase 3 studies recently showed that the drug was effective for inducing response, remission, and mucosal healing, both in patients with moderate to severe ulcerative colitis who are failing anti-TNF drugs

as well as in patients who are naive to anti-TNF therapy. A phase 3 maintenance trial will be completed in the third quarter of this year, which means that tofacitinib may be sent for FDA review sometime next year.

In addition, ABT-494 (AbbVie), a JAK inhibitor that is more JAK1-selective, is being evaluated for both ulcerative colitis and Crohn's disease. The JAK inhibitor filgotinib (GLPG0634, Galapagos and Gilead) has positive phase 2 data in Crohn's disease and will undergo phase 3 testing in ulcerative colitis and Crohn's disease.

G&H Are there any other promising inflammatory bowel disease agents in the pipeline?

WS A metalloproteinase-9 antibody (GS-5745, Gilead) showed some evidence of efficacy in a phase 1A study in ulcerative colitis and will be undergoing phase 2/3 trials in ulcerative colitis and Crohn's disease.

The oral SMAD7 antisense oligonucleotide drug called mongersen (GED-0301, Celgene) showed significant evidence of efficacy for inducing clinical remission in Crohn's disease. It is now in another phase 2 trial and will soon be in a phase 3 trial for Crohn's disease.

G&H Where would these drugs fit in the treatment algorithm?

WS Most of these agents are being studied in patients who have failed mesalamine, corticosteroids, and perhaps immunosuppressants. Some, but not all, of the protocols require failure of a biologic agent as well. These agents are not being examined for first-line treatment in Crohn's disease or ulcerative colitis.

G&H How have outcome measures for drug development been changing?

WS Historically, drugs were developed primarily for the treatment of symptoms. We are increasingly understanding that the treatment of symptoms is necessary but not sufficient. Other factors are being tracked in clinical trials now; the FDA is requiring that treatments show not only an improvement in the signs and symptoms of the disease, but also an improvement in endoscopic disease activity and, ideally, healing of the bowel mucosa. However, in clinical practice, there is still a widespread tendency to treat patients based on symptoms without performing endoscopy to ensure that the symptoms patients are experiencing are truly due to active ulcerative colitis or Crohn's disease before major treatment decisions are made. It is important to rescope patients after 4 to 6 months of treatment to ensure that the bowel is completely healed because some patients will feel better clinically but will not experience bowel healing, and it looks like bowel healing leads to a better prognosis in the longer term. This concept of treating to target has not come into widespread use in clinical practice yet, but it should.

G&H Will the gut microbiome play a role in future treatment for inflammatory bowel disease?

WS It may very well. It is clear that fecal microbiota transplantation is an effective therapy for recurrent *Clostridium difficile* infection. Research is currently being conducted to see whether that effectiveness carries over to inflammatory bowel disease as well. The results of a study on fecal microbiota transplantation in ulcerative colitis were presented at the 2016 Digestive Disease Week. Using multiple donors, the researchers pooled together stool and administered multiple fecal transplants over a period of months. Such an intensive regimen may not be feasible in clinical practice, but it did provide benefit to the patients, giving the procedure some proof-of-concept. In contrast, studies of single fecal transplants from individual donors have been much less effective in patients who have ulcerative colitis.

In the future, there will likely be additional controlled trials with microbiome products, whether stool or microbiome-oriented products. Although I do believe that the concept has promise, there is still much to be done to figure out an accessible and practical regimen to study, and we are far from bringing microbiome products into routine clinical practice.

G&H Will biosimilars be a common treatment option in the future?

WS The FDA recently approved a biosimilar for infliximab, and more are expected. I recently heard that there are 19 adalimumab biosimilars in development, and I suspect that there are at least that many with infliximab. Biosimilars will end up in the armamentarium for inflammatory bowel disease. The question that clinicians still have, to some degree, is whether biosimilars are therapeutically interchangeable with the innovator compound, and we are still learning whether patients can be switched back and forth between an innovator compound and a biosimilar, or between biosimilars. Not much is known about these issues yet, so more research is needed.

G&H Is any research being conducted on other future treatment possibilities, such as stem cell transplantation?

WS There has been some work with systemically administered stem cells, but this has not panned out too well

thus far. However, injections of stem cells into and around perianal fistula tracts have been shown to help close the fistulas in patients with Crohn's disease.

G&H What are the most important next steps in research in terms of future treatment for inflammatory bowel disease?

WS It turns out that there is quite a bit of variation among patients in terms of how fast biologic drugs are cleared. Clearance can be affected by the formation of antidrug antibodies, although not in every case. Differences in clearance and the resulting drug concentration lead to important differences in efficacy, so more research is needed on the use of therapeutic drug monitoring. This concept is coming into clinical practice, but only gradually thus far.

Another important area of research involves personalized medicine. The drugs mentioned in this column have different mechanisms of action. It can be difficult to know which drugs to use and in which order. Biology could inform such treatment decisions. More research is needed to determine which gene signature profiles might be able to predict whether a particular patient will respond to a particular drug.

Dr Sandborn consults for all of the companies listed in this column.

Suggested Reading

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