ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Optimizing Biologic Therapy for Treatment of Inflammatory Bowel Disease

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G&H What are the major benefits of currently available biologic therapies in the management of inflammatory bowel disease?

GVA Gastroenterologists need to know that biologic agents have been under study for more than 15 years now, and a lot has been learned about their benefits and risks. The anti–tumor necrosis factor (TNF) agents are currently dominating the field of biologic therapy in inflammatory bowel disease (IBD). The armamentarium is relatively small for gastroenterologists compared with that for rheumatologists who have a lot of options in terms of currently available biologic agents. Approved anti-TNF agents that are now on the market include infliximab (Remicade, Janssen Biotech), adalimumab (Humira, AbbVie), and certolizumab pegol (Cimzia, UCB). These agents have been dominating the field and will probably do so for a few more years, although new agents are coming. In addition, the anti-integrin antibody natalizumab (Tysabri, Biogen Idec) is a therapeutic option.

We know that the benefits of currently available biologic agents outweigh the risks in patients with refractory Crohn's disease and ulcerative colitis. The risks are manageable and mostly related to development of infections.

There may be a potential for disease modification in the long term with these agents. The ability of biologic agents to be disease-modifying has yet to be proven prospectively, but indirect evidence suggests that the biologic agents have the capacity to modify disease. The current concerns are optimizing available biologic therapies and patient selection. Should every patient with Crohn's disease be treated with a biologic agent? Probably not, but we have yet to discover those clear predictors of response that would help identify the patient who would most benefit from biologic therapy. We do have some indicators, though. Patients with perianal disease, extensive small bowel disease, or rectal ulcerations would be candidates for primary therapy with a biologic agent before corticosteroids or immunosuppressive agents are considered.

G&H How far are we in studying the association between biologic agents and disease modification?

GVA The prospect of disease modification with biologic agents is an exciting area. The challenge is to define the targets that are measuring damage in the bowel. Development of a scoring system is in process, but it needs to be validated. We know that mucosal healing is probably a very good surrogate marker, but we still do not know for sure how well mucosal healing reflects disease modification. Other major outcomes to explore include prevention of surgery, mortality, and hospitalization rates. Accumulating data can take 5 to 10 years, and a large patient cohort is needed, so these are challenges to the study of whether biologic agents are disease-modifying drugs.

G&H What have we learned about dosing and optimization of treatment response?

GVA Gastroenterologists have 3 or 4 agents to work with for the next 2 years. With these few options, dose optimi-

zation is at stake. Forty percent of patients lose response with any anti-TNF agent when treated beyond 1 or 2 years, so we need to be ready to act. Increasing the dose of a biologic agent may overcome loss of response, but this strategy will not work in all patients. More data are needed about which patients would be candidates for dose escalation or treatment shortening via a subcutaneous or intravenous route, but we do not have clear indications on which patients would benefit. This is where therapeutic drug monitoring will become increasingly important in the near future.

G&H Are there groups of patients in whom response to biologic agents can be predicted?

GVA Hard criteria about which patients are best candidates for biologic therapy are lacking, but the general gestalt in relation to findings from recent clinical trials is that, if a patient has predominantly inflammatory disease, that patient will do better with a biologic agent or with any anti-inflammatory therapy, especially in relation to primary response. As for predictors of response, studies of genetics and proteomics have not given us clarification about which patient is likely to respond.

In the absence of rock-solid evidence, physicians are already making decisions about patient selection in clinical practice. In patient selection, physicians are looking for signs of active inflammation via tools such as endoscopy, biomarkers, and/or imaging because these physicians have been informed that patients with inflammatory disease will respond better. Surgery might be a better option for patients with purely fibrocystic disease. Patients are also screened for potential contraindications for biologic therapy.

G&H What are the contraindications to biologic therapy?

GVA There should be red alerts in the mind of every physician regarding use of immunosuppressive agents, including biologics, methotrexate, and azathioprine. As for immunosuppressive agents, contraindications would include previous malignancies, especially lymphoma, melanoma, and renal cell carcinoma. For other malignancies, consultation with an oncologist about the patient's situation is warranted. Other contraindications include ongoing infections and sepsis. Contraindications more specific to biologic agents include advanced cardiac failure (stage 3 or 4), a history of demyelinating neurologic disease, including optic neuritis, and lupus-like disease. Infection and ongoing sepsis are also contraindications, specifically in patients with Crohn's disease, who can have either perianal or intra-abdominal sepsis.

G&H How can immunosuppressive strategies be balanced against the risk of adverse events?

GVA Evidence from the SONIC trial is strong that combination infliximab and azathioprine for at least 1 year is the best treatment strategy for azathioprine-naive patients with Crohn's disease. There is less evidence for the use of adalimumab or certolizumab pegol in combination with azathioprine. Evidence is also weaker on whether all patients require combination therapy if they have already been exposed to immunosuppressive agents, although the general momentum is moving toward use of combination therapy.

Concomitant immunosuppressive therapy may prevent infusion reactions and antibody formation, but is there a price to pay in terms of safety? Determination of harmful effects of concomitant immunosuppressive therapy is difficult because the available clinical trials include only 1 year of drug exposure, and the patient population has been too limited to look at subtle differences in safety issues. However, computer modeling and extrapolation of data from clinical trials suggest that the benefit outweighs the risk. Preliminary evidence suggests that there may be a limited increase in the risk of malignancy—specifically lymphoma or nonmelanoma skin cancer—with adalimumab and azathioprine used in combination. Although evidence is scarcer regarding infliximab, a slight risk of malignancy may be associated with its use as well, but the benefits most likely outweigh the limited increase in risk with combination therapy.

G&H What is expected to happen after 1 year if combination therapy is discontinued?

GVA If azathioprine is discontinued after the first year of treatment and the biologic agent is continued, there is a risk of early loss of response and need for dose intensification of the biologic agent or else a switch to another anti-TNF agent. This risk, however, is probably limited. Discontinuation of the infliximab has been studied in a French prospective cohort study, with the result that 50% of the patients required treatment again within 1 year. In other words, half of the patients no longer needed therapy after a year. Most of the other half of patients who relapsed within a year of cessation of therapy were able to be retreated with infliximab. Data regarding cessation of therapy are not available for natalizumab, adalimumab, or certolizumab pegol, so care must be taken about decisions regarding discontinuation of therapy with these agents.

G&H What agents in development are you most intrigued by?

GVA New anti-TNF agents are coming, which is good, because I think anti-TNF agents have proven to be rock-

solid agents for refractory IBD. Also creating excitement is the prospect of new findings about mechanisms of action, which will help us understand why some patients fail anti-TNF therapy across the board. For those patients, agents with other mechanisms of action are being developed, such as gut-selective anti-integrin agents. Preliminary data are quite promising—specifically in patients with ulcerative colitis—and, so, these agents are expected to come to the market fairly soon.

The anti-interleukin (IL)12/anti-IL23 antibody ustekinumab also looks promising as do some small-molecule therapies. Janus kinase inhibitors, which are oral compounds, seem to also be working, notably in ulcerative colitis. Given these new agents in development, the next 2 or 3 years seem brighter regarding treatment strategies for ulcerative colitis than Crohn's disease, which is a bit of a reversal of the situation seen 4 years ago.

G&H What is your view of growth factor and helminth therapies? Are these modalities on the fringe or areas of serious investigation?

GVA As regards helminth therapy, 2 clinical trials were conducted in the United States about 5 years ago. The findings showed that eggs of *Trichuris* were able to help patients with ulcerative colitis and Crohn's disease. I want to see more data before I say that helminth therapy is a new way to go. There have been issues with the eggs hatching, causing concern about patient exposure to the adult worms. The worms are parasitic in pigs, not humans, but nevertheless, more efficacy and safety data are needed before helminth therapy can be considered a viable option.

As for growth factors, they have been under study for more than 10 years, but evidence about their value in IBD is limited. The most recent large clinical trial of a growth factor failed to meet its endpoint, which was to stimulate immune function. Topically delivered, growth factors that have been directed against ulcerative colitis seem to have some efficacy, but clinical trials have been small and not all of them have been well controlled. There is also a question of whether growth factors promote dysplasia of the colonic epithelium in the long term.

Suggested Reading

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