

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Advances in the Treatment of Ulcerative Colitis



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G&H How has anti-tumor necrosis factor therapy changed the treatment of ulcerative colitis?

LP-B We have a new and potent therapeutic option. In the past, when a patient with ulcerative colitis (UC) was refractory to corticosteroid therapy, we had to consider cyclosporine therapy or colectomy. Now, we have the option of using an anti-tumor necrosis factor (TNF) agent, which may avoid the need for a colectomy in some patients. Anti-TNF agents are also an option for patients who fail azathioprine therapy instead of going straight on to colectomy, which was the protocol in the past. We now know that colectomy is not a cure for UC; postoperative issues, such as pouchitis and incontinence, and many other problems can emerge, and the patient may have 6 to 10 stools a day after colectomy. So, now, the first therapeutic option for patients who have failed standard pharmacologic treatment is not surgery but a trial of an anti-TNF agent. Not only are anti-TNF agents a new option in the treatment of UC, but they are also now the most potent option in patients who have failed other forms of therapy. Note, however, that physicians are already using anti-TNF agents as first-line therapy in Crohn's disease (CD), but the situation is different with UC. Physicians delay use of anti-TNF agents and continue to use them as a rescue therapy in UC.

G&H What do we know about the impact of anti-TNF therapy on the need for colectomy?

LP-B Data from the ACT (Active Ulcerative Colitis) trials of infliximab (Remicade, Janssen) show that fewer patients receiving infliximab, compared with

those receiving placebo, required colectomy over the course of a year (10% vs 17%), which translated into an absolute risk reduction of 7% with use of infliximab. Adalimumab (Humira, AbbVie) therapy was associated with reduced risk of hospitalization in patients with UC in randomized clinical trials. A recent observational study that was conducted by me and colleagues from the University Hospital of Nancy also demonstrated that 5-aminosalicylates (5-ASA), azathioprine, or anti-TNF agents are not associated with a reduced need for colectomy. At 5 years, a tenth of patients with UC will still require colectomy. I conjecture that these findings suggest that anti-TNF agents are given too late in the disease course to make a significant impact on colectomy rates and that more clarity about their value will come through large prospective cohort studies with a long-term follow-up.

G&H Is the goal of mucosal healing in UC adequate, or is achieving remission more complex?

LP-B We know that mucosal healing in UC is associated with a better long-term outcome, including a lower rate of colectomy. Mucosal healing can be evaluated with endoscopy, and we know that there is a good correlation between clinical remission and mucosal healing in UC. This is borne out by clinical trial data. The main problem is the definition of mucosal healing. The minimum therapeutic goal is probably an endoscopic Mayo score of 0 to 1. However, data are now showing that a Mayo score of 0 may be better, although confirming this will require further investigation. Importantly, accumulating evidence indicates that histologic remission may be the

ultimate therapeutic goal in patients with UC because, even when endoscopy shows mucosal healing, histologic activity may still be observed. We need a validated definition of histologic remission in UC; however, we do not have controlled data on this, and the definition of deep remission—which I define as histologic and mucosal healing—still needs to be validated. There is a great need for large prospective studies in this area.

G&H How can therapy be optimized to better sustain remission?

LP-B The aim of care of the patient with UC is to have a tight monitoring of disease activity similar to the approach taken with CD. By tight monitoring, I mean achieving and maintaining sustained mucosal healing. This should be the therapeutic goal. If mucosal healing does not occur within 2 to 3 months of initiation of treatment, then the treatment should be reevaluated and optimized to achieve mucosal healing. A rapid step-up approach, similar to what is done in the management of CD, is needed. For example, if the patient is on azathioprine and has not achieved mucosal healing, the clinician should consider switching the patient to an anti-TNF agent. If the patient is on an anti-TNF agent, the clinician should consider increasing the dose and/or adding an immunomodulator. As for use of anti-TNF agents, as mentioned, the main problem is that, so far, these agents are being started too late in the course of UC.

G&H What precautions or preparations are needed to address potential adverse events associated with anti-TNF agents, such as opportunistic infections?

LP-B Anti-TNF agents are quite well tolerated, actually. When we discuss the safety of anti-TNF agents, we are generally doing so in comparison with azathioprine. We know that azathioprine is not well tolerated in terms of increased risks of lymphoma and nonmelanoma skin cancer. Increased risk of malignancy has not been seen with anti-TNF agents used alone, although a slight increased risk of lymphoma is associated with anti-TNF agents used in combination with thiopurines, probably mainly driven by thiopurines. As for opportunistic infections, we have found that anti-TNF agents are not associated with an increased risk of tuberculosis when patients are screened to rule out tuberculosis before initiation of treatment. However, anti-TNF therapy is associated with a slight but, statistically speaking, significant increased risk of opportunistic infection compared with placebo (0.9% vs 0.3%). This underlines the importance of adherence to guidelines for prevention and management of UC.

G&H When do disease-modifying anti-inflammatory bowel disease drugs come into the picture? Should they only be reserved for second-line therapy?

LP-B All drugs that can induce and maintain mucosal healing in UC should be considered to be disease-modifying anti-inflammatory bowel disease drugs (DMAIDs). What drug is used is not as important as whether it is able to induce and maintain mucosal healing. For example, when a patient has a good response to 5-ASA, it is a DMAID. Azathioprine is modestly effective as compared with anti-TNF agents in terms of mucosal healing, and its potential for disease modification is questionable in inflammatory bowel disease. In patients who are refractory to corticosteroids, an anti-TNF agent should be introduced. In patients with corticosteroid-dependent UC, anti-TNF therapy is increasingly being used. If corticosteroid-associated adverse effects occur or in moderately to severely active corticosteroid-dependent disease, an anti-TNF agent should be considered. In patients with mildly active disease and low disability, azathioprine monotherapy can be considered, but patients should be reevaluated for mucosal healing after 3 to 6 months of treatment.

G&H How do Janus kinase inhibitors potentially improve upon or get around some challenges related to anti-TNF therapy in the treatment of UC?

LP-B About one-third of patients with UC will be in remission at 1 year posttreatment, and secondary loss of response is relatively frequent in all patients receiving anti-TNF therapy. Therefore, we need more treatment options. Janus kinase inhibitors may be a new therapeutic option, and it is always good to have an armamentarium of agents that have different mechanisms of action. Tofacitinib (Xeljanz, Pfizer) and other Janus kinase inhibitors are immunosuppressive agents, not biologic agents. Tofacitinib was the first Janus kinase inhibitor to be approved by the US Food and Drug Administration (FDA) for the indication of rheumatoid arthritis. As for its use in inflammatory bowel disease, safety concerns are being studied. The majority of the adverse events reported in clinical trials of tofacitinib were mild to moderate. Overall, tofacitinib has a manageable safety profile. Ongoing phase 3 trials will establish its benefit-risk ratio in UC.

G&H What are the most promising DMAIDs that are currently being studied, and what impact do you think they will have on UC?

LP-B Golimumab (Simponi, Janssen) was just recently approved and is a subcutaneous anti-TNF agent with a

monthly administration. It is the third anti-TNF agent now on the market, joining infliximab and adalimumab. Vedolizumab, an agent with a different mechanism of action, is expected to receive FDA approval for use in UC next year. It has been studied in more than 3000 patients and has demonstrated a good safety profile together with high efficacy in UC. Vedolizumab is administered intravenously, like infliximab, but unlike infliximab and other available anti-TNF agents, it does not exert a systemic effect but, rather, has gut specificity. Hence, it is anticipated that vedolizumab's unique mechanism of action may, in turn, offer a unique safety and efficacy profile in the treatment of UC.

Dr Peyrin-Biroulet has no conflicts of interest to disclose.

Suggested Reading

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