ADVANCES IN IBD

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Step-Up Versus Top-Down Therapy in the Treatment of Ulcerative Colitis

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G&H Can you describe the typical step-up treatment algorithm for ulcerative colitis as it differs from Crohn's disease?

WS The first line of therapy for ulcerative colitis (UC) is the safe and effective 5-aminosalicylate (5-ASA) class of drugs. These include sulfasalazine, delayed-release mesalamine (Asacol, Procter & Gamble), controlled-release mesalamine (Pentasa, Shire), olsalazine (Dipentum, Pfizer) and balsalazide (Colazal, Salix), as well as the forthcoming multimatrix formulation. These drugs are clearly effective for the induction and maintenance of clinical remission in patients with mild-to-moderate UC. This is in contrast to Crohn's disease, where the efficacy of mesalamine is not clear. Antibiotic therapies, which are used in Crohn's (although of questionable efficacy) are not effective in UC.

Thus, in patients with UC, there is a clear first-line therapy that satisfactorily treats a substantial fraction of patients, both inducing and maintaining remission. In contrast, in Crohn's disease, there is no safe and effective first line for inducing and maintaining remission. Further, it has been documented that over a disease course of 20 years, 80% of patients with Crohn's disease will require at least 1 surgical resection. In the modern era, in comparable patients with UC, rates of surgery are not more than 15–20% and thus the prognosis for avoiding surgical resection is very different.

G&H Are there specific subgroups among UC patients who may have a different prognosis and might benefit from a top-down approach to therapy?

WS Among UC patients, approximately 30–40% have pancolonic UC or total colonic involvement and a substantial proportion (40–50%) of those pancolitis patients will require colectomy. Many of these colectomies will occur within the first 5 years of disease. Further, among UC patients in general, approximately 40–50% will require treatment with steroids. Of the patients who require steroid treatment, within the first year, one third of them will require colectomy.

Patients with pancolitis, those who require corticosteroids and those who are hospitalized for UC, all have prognostic indicators for a more severe and refractory course of disease. Hypothetically, these are the patients who may benefit from top-down therapy, but no studies have yet evaluated such a treatment strategy.

G&H Could you describe the studies that have led to the recent approval of biologic therapy for induction and maintenance of UC remission?

WS The studies that led to the approval of infliximab (Remicade, Centocor) in UC are very robust. One could argue that they are even more robust than the trials that led to the initial approval of infliximab in Crohn's disease. In the UC trials, the investigators selected patients with moderate-to-severe disease. In the ACT I study, the patients were required to be failing steroids and/or immunosuppressives. In the ACT II trial, patients had to be failing steroids, immunosuppressives, or 5-ASA therapy for inclusion. However, most of the patients in ACT II were failing steroids or immunosuppressives. At enrollment, patients received induction treatment with 3 doses

of infliximab or placebo over 6 weeks and then continued with every-8-week maintenance therapy.

In the original Crohn's disease trials, induction and maintenance were separated. Patients were treated in short-term induction trials first. Later trials employed open-label induction, followed by long-term maintenance only in patients who showed an initial response. In contrast, in the UC trials, patients were treated continuously for 6–12 months with no selection for responders in the maintenance phase. Despite this incrementally much tougher trial design, the overall efficacy results were similar in the UC trials and the Crohn's disease trials.

G&H Given the demonstrated efficacy of infliximab therapy in UC, can any of the chemopreventive properties recently ascribed to 5-ASA drugs be extended to biologics?

WS We know that there are some remote structural similarities between 5-ASA and aspirin, which may denote a directly chemopreventive chemical attribute inherent to 5-ASA compounds. There is also the possibility that 5-ASA therapy simply leads to better disease control and resultant reduced inflammation, which is chemopreventive in and of itself.

With regard to the immunomodulators azathioprine and 6-mercaptopurine (6-MP), Dr. Thomas Ullman from the Mt. Sinai School of Medicine recently published data suggesting that those drugs are not chemopreventive against colorectal cancer in patients with ulcerative colitis. Conversely, those agents have actually been associated with an elevated risk of lymphoma in this patient population. However, they are effective for inducing remission and treating inflammation. Whether the potential chemopreventive effect of reduced inflammation is cancelled out by a slightly raised risk of cancer, or the lack of an inherent chemical chemopreventive effect is responsible for Dr. Ullman's data, we cannot yet be sure.

Regardless, there is a discordance between 5-ASAs and the immunomodulators azathioprine and 6-MP in terms of the ability to induce chemoprevention of colorectal cancer. I think this tells us that each agent will need to be examined individually and that applies to infliximab as well. Theoretically, it is possible that treatment of the disease and inhibition of tumor necrosis factor (TNF) will be chemopreventive, but study is required to show that.

G&H Is there any currently ongoing research regarding the top-down use of biologic therapies for UC?

WS Currently, infliximab is approved for induction and maintenance of UC remission. There are several other biologic agents directed against TNF and α4 integrin that will soon be available for Crohn's disease, including adalimumab (Humira, Abbott), certolizumab pegol (Cimzia, UCB), and, potentially, natalizumab (Tysabri, Elan). At least two, and perhaps all three of these agents, will ultimately go into clinical trials for UC. As more agents come into play and top-down trials are staged on a larger scale with biologic agents in Crohn's disease, there will be an attempt to do the same kind of research in UC. If I had to guess, I would think that those studies would appear within the next 3–5 years.

G&H Is there any current research of chemoprevention with biologic therapies?

WS Our current understanding of the chemopreventive properties of 5-ASAs are based on observational study instead of randomized trials. It is almost impossible to conduct a chemoprevention trial with an agent that also serves as a primary therapy. These drugs need to be introduced into practice, and in diseases such as UC, where associated cancer and dysplasia occur more slowly, the drugs need to be used in clinical practice for 5–10 years, so that a retrospective analysis of dysplasia rates can be performed. Because infliximab was formally adopted for UC only 18 months ago, we are most likely at least 5 years out from making those sorts of assessments with biologic therapy.

Suggested Reading

Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462-2476.

Matula S, Croog V, Itzkowitz S, et al. Chemoprevention of colorectal neoplasia in ulcerative colitis: the effect of 6-mercaptopurine. *Clin Gastroenterol Hepatol*. 2005;3:1015-1021.

Sandborn WJ. What's new: innovative concepts in inflammatory bowel disease. *Colorectal Dis*. 2006;8:3-9.

Sandborn WJ. Treatment of ulcerative colitis with oral mesalamine: advances in drug formulation, efficacy expectations and dose response, compliance, and chemoprevention. *Rev Gastroenterol Disord*. 2006;6:97-105.