

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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## Emerging Data in the Concomitant Use of Immunomodulators and Biologic Therapies

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**G&H** Historically, who are the patients that have been treated with combination immunomodulator/biologic therapies?

**GL** Concomitant immunomodulator therapy, consisting of azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate, has been used with biologic therapy most often in patients that have been tried on immunomodulator monotherapy but continue to experience low-level or even significant symptoms (ie, they are refractory to medical therapy or flare after they had been in remission with medical therapy).

A beneficially synergistic relationship between immunomodulators and biologic therapy was first suggested by data published by Baert and associates in the *New England Journal of Medicine*, showing a decreased level of antibody formation directed against infliximab (Remicade, Centocor) in patients taking concomitant immunomodulators. In this prospective, sequential study of 125 patients utilizing episodically administered infliximab therapy, those patients taking concomitant immunomodulators experienced a longer median duration of response to infliximab. In addition, the mean serum infliximab level was higher in patients taking concurrent immunomodulators. These findings led to a longstanding practice of continuing immunomodulator maintenance in patients started on biologic therapy. In some scenarios, patients were even started on immunomodulators at the same time as their biologic, in an effort to extend and optimize therapeutic response.

**G&H** How relevant are these data today, given the current standard practice of scheduled maintenance dosing of biologics?

**GL** It is true that in current practice, we do not typically utilize episodic biologic therapy. Episodic administration has been shown to be less successful in terms of patient outcomes and to promote greater biologic immunogenicity, when compared to scheduled maintenance. To date, no adequately powered, prospective, randomized, placebo-controlled trials have been completed to assess the impact of concomitant immunomodulator use on efficacy and serum levels of infliximab in the setting of standard, scheduled maintenance.

**G&H** Why is it important to further study the use of immunomodulators in conjunction with current biologic regimens?

**GL** The proper use of immunomodulators in the setting of current concomitant biologic therapy regimens must be established given the growing data regarding both safety and efficacy as it relates to combination therapy in both Crohn's disease (CD) and ulcerative colitis (UC).

Dr. Lewis and colleagues, here at the University of Pennsylvania, recently demonstrated a 4-fold elevated risk of lymphoma in CD patients taking AZA. Whether this elevation is disease-activity-related or medication-related currently remains unclear. However, this study revealed 1 case of lymphoma per 2,000 patient-years of follow-up in patients on AZA versus 1 per 8,000 patient-years in those patients with CD alone. Similar findings were recently presented at the 2008 Digestive Disease Week (DDW) meeting by the Cancers Et Sur-risque Associé aux Maladies inflammatoires chroniques intestinales En France (CESAME) group, who also reported an elevated risk of lymphoma in patients with CD, suggesting a 2-fold increased risk of lymphoma.

Additionally, there have been recent reports of a specific type of lymphoma. This rare but lethal condition is known as hepatosplenic T-cell lymphoma. This form of lymphoma manifests primarily in patients taking immunomodulators alone or infliximab in conjunction with immunomodulators. Two cases have also been reported

in patients taking infliximab followed by adalimumab (Humira, Abbott), but these patients, again, were on concomitant immunomodulators. Thus it appears that AZA or 6-MP therapy are mandatory for the occurrence of this adverse event.

In addition, recent data published by Sandborn and coworkers in *Gastroenterology* suggest a higher infectious complication rate in individuals that receive multiple immunomodulatory agents. These investigators found that if patients take corticosteroids, a biologic, and an immunomodulator, their risk is highest for the development of severe infectious complications, thus establishing the idea that fewer medications, in general, are safer for the patient.

### **G&H** What other research has been undertaken to consider the risks and benefits associated with concomitant immunomodulator/biologic therapy?

**GL** At the 2007 DDW meeting, our group presented a retrospective analysis of efficacy, safety, serum infliximab concentration, and immunogenicity associated with baseline concomitant immunomodulator use in four prospective, randomized, phase III trials of infliximab for both CD (ACCENT I and II) and UC (ACT I and II). In pooling these studies, we were able to examine a total of 1,383 patients, all of whom were randomized to either placebo or infliximab at 5 mg/kg or 10 mg/kg administered at weeks 0, 2, and 6 and then every 8 weeks as maintenance. Among these patients, approximately one half with UC and one third with CD were taking concomitant immunomodulators.

We found that efficacy, serious infection rates, and serum infliximab levels were comparable in patients receiving scheduled maintenance therapy with or without concomitant immunomodulators. Although the use of immunomodulators lowered the incidence of infliximab-related infusion reactions and immunogenicity, they did not significantly increase efficacy or improve pharmacokinetics in patients receiving maintenance infliximab. Thus, we concluded that, given the potential risks associated with immunomodulators, their use in conjunction with infliximab in IBD should be considered optional.

Additional studies of adalimumab and certolizumab pegol (Cimzia, UCB) reinforce this conclusion, demonstrating similar efficacy rates with or without concurrent immunomodulators. However, it should be noted that these studies were post-hoc analyses that were not powered to differentiate among treatment regimens and a lack of difference in outcomes could be the result of an underpowered assessment. This is why we chose to pool data from the four infliximab trials, in order to provide more conclusive analysis.

More recently, results of the COMMIT trial were announced as a late-breaking abstract at the 2008 DDW

meeting by Feagan and associates. COMMIT was a randomized trial that compared the safety and efficacy of infliximab plus methotrexate to infliximab alone for long-term control of signs and symptoms of CD in patients requiring corticosteroids for disease control at baseline. COMMIT was placebo-controlled, double-blinded, and staged at 15 centers throughout Canada. Patients who had initiated steroid induction in the preceding 6 weeks were randomized, irrespective of Crohn's Disease Activity Index (CDAI) score, into two arms receiving either methotrexate or placebo for 50 weeks in combination with infliximab given for 8 infusions. A total of 63 patients were randomized into each arm. In the methotrexate arm (prednisone, infliximab, and methotrexate) treatment success at week 14 was 76.2% versus 77.8% in the placebo arm (prednisone, infliximab, and placebo). At week 50, treatment success was seen in 55.6% of the methotrexate patients versus 57.1% of those receiving placebo. The authors concluded that treatment success with prednisone, infliximab, and methotrexate was no better than infliximab and prednisone alone and concomitant methotrexate added no benefit.

Finally, Rutgeerts and colleagues published a study in the June issue of *Gastroenterology* that examined CD patients in remission, who were taking concomitant infliximab and AZA maintenance at baseline, via a prospective, randomized, controlled study. These patients were subsequently randomized to continue or withdraw AZA as part of their maintenance regimen. The authors found no difference overall in terms of long-term benefit to patients: response, remission, and adverse event rates were all directly compared. Although this, again, was an underpowered study, it is compelling to see that the aggregate of all of these results provide no clear mandate for the use of immunomodulators in conjunction with biologic therapy.

### **G&H** Could you describe the design and projected outcomes of the currently ongoing SONIC trial?

**GL** SONIC is a trial cosponsored by Centocor and Schering-Plough, which is randomized and double-blinded to measure the outcome of steroid-free remission at week 26 of therapy with infliximab versus infliximab plus AZA versus AZA alone in patients with CD. A secondary endpoint will measure mucosal healing at week 26. Patients are randomized to one of three arms: placebo infliximab infusion plus daily AZA therapy; infliximab infusion at weeks 0, 2, 6, 14, and 22 plus placebo AZA capsules; and combination active AZA daily and infliximab infusion. Thus, there is no possibility of patients receiving placebo only. The total cohort consists of 500 patients, all of whom are age 18 or older, who have received a diagnosis of CD at least 6 weeks previous to enrollment. All have moderate to severe disease activity with CDAI scores ranging from 220

*(Continued on page 502)*

to 400. All are naïve to AZA, 6-MP, or biologic therapy at enrollment, and they are either steroid-dependent or have failed 5-aminosalicylate or budesonide therapies.

It is hoped that with the results of SONIC, the efficacy of immunomodulators as a concomitant therapy with biologic regimens can be determined in a prospective, randomized, double-blind setting that will once and for all lay to rest the controversy surrounding their use.

**G&H** Does the use of concomitant corticosteroid therapy in these trials cloud the issue of safety or efficacy of immunomodulator therapy?

**GL** The use of corticosteroids has been linked to a number of adverse effects, including infectious complications. As per the above data from Sandborn et al, fewer drugs are always safer in this regard. However, at present we believe that CD activity and immunomodulator therapy are the risk factors for lymphoma in these patients, and we believe that corticosteroids are not an associated factor in this regard. In fact, steroids are a treatment option for lymphoma.

**G&H** Regardless of the outcomes of these trials, will there remain a subgroup of patients who require concomitant therapy with immunomodulators and biologics in order to maintain remission?

**GL** Until we have results of prospective trials, examining this issue directly, we will need to individualize therapy. In the past, when only one biologic agent was available, it was crucial that we take every precaution to maintain response and promote remission. With our

current armamentarium of infliximab, adalimumab, certolizumab pegol, and natalizumab (Tysabri, Elan) available, we have more monotherapy options that incur fewer risks upfront. In my practice, I try to withdraw immunomodulators in patients who are successfully in remission on a biologic. Among patients who do flare when the immunomodulator is withdrawn, a subset will require it back to maintain remission. In other patients, however, there is now the option to switch to another biologic and continue monotherapy.

### Suggested Reading

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