

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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The Optimization of Immunosuppressive and Biologic Cotherapies in Inflammatory Bowel Disease

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G&H Can you describe the typical treatment scenario where a patient would be likely to receive biologic and immunosuppressive therapies concomitantly?

GV There are two typical situations where biologics and immunosuppressives tend to be co-administered. The first is in patients bridging to an effective immunosuppressive monotherapy. Increasingly, patients with acute, severe ulcerative colitis (UC) who fail intravenous steroids and have never been exposed to azathioprine (AZA) or 6-mercaptopurine (6MP) will receive infliximab (Remicade, Centocor) for 3–6 months in order to control their disease and avoid colectomy. These patients will start on AZA after they respond to infliximab and are able to leave the hospital. After 3–6 months, they are eligible to stop therapy with infliximab and continue on AZA as maintenance medication.

Another scenario is in patients who receive episodic or on-demand anti-tumor necrosis factor (TNF) therapy, a practice that still takes place in many countries. This is rarely done in the United States. However, in several European countries, this practice is still the rule rather than the exception, particularly in patients with UC but also those with Crohn's disease. In these patients, it is common practice to give AZA in order to avoid the potential immunogenicity caused by episodic biologic therapy administration.

G&H What evidence exists to recommend immunosuppressive cotherapy as a protective measure in avoiding the development of immunogenicity in anti-TNF therapy?

GV All of the available data on this question are based on retrospective cohort studies or post-hoc analyses of controlled trials; no prospective trial has specifically examined the effect of immunosuppressives on biologic immunogenicity. Several papers, most recently by Maser and colleagues, indicate that patients taking on-demand, as opposed to scheduled, maintenance therapy, benefit from immunosuppressive cotherapy, but these are, again, retrospective data. When post-hoc analysis of prospective trials, where immunogenicity was not a defined endpoint, is conducted, there seems to be no effect from immunosuppressive prevention of immunogenicity on overall efficacy. However, most of these trials have been in patients taking scheduled maintenance doses of biologic therapy, a scenario where immunogenicity is of less concern.

G&H Has any one immunosuppressive been shown to be more effective in controlling immunogenicity in episodic biologic therapy?

GV AZA, 6MP, and methotrexate have all been studied. Our group recently published data that show methotrexate and AZA are both clearly protective in episodic biologic use but not in patients taking scheduled maintenance dosing.

G&H How do the immunologic profiles of varying biologic therapies affect the need for possible cotherapy with immunosuppressives?

GV Flexibility of the dosing schedule, which is the real issue, will most likely be more available in humanized anti-TNFs, although humanization does not abolish the risk of development of antibodies to biologic drugs. Erythropoietin, which is a recombinant human protein,

can induce immunogenicity in patients. We also know from data in rheumatoid arthritis patients that for intermittent use or initial use of adalimumab (Humira, Abbott) without methotrexate, the maximum percentage of patients developing antibodies has been 17%. Studies have shown up to 24% of patients developing antibodies to certolizumab pegol (Cimzia, UCB) without concomitant use of immunosuppressives. Therefore, I think that, ultimately, decreased immunogenicity and more flexibility of dosing will be possible with humanized biologics, but the scenario is not all-or-nothing. All therapeutic biologics will face some degree of immunogenicity, but current research provides some indication that in humanized drugs, immunogenicity will remain less of an issue.

G&H Could you describe the current data indicating a heightened adverse event profile associated with biologic/immunosuppressive cotherapies?

GV Evidence exists to indicate that combination therapies increase toxicity in patients. Evidence from the TREAT registry in the United States suggests heightened rates of adverse events, but this has been predominantly in association with steroids rather than immunosuppressives. In rheumatoid arthritis treatment, methotrexate plus infliximab has not shown any increased risk over methotrexate alone. However, virtually no rheumatoid arthritis patients have been treated with infliximab monotherapy. Therefore, we do not have any clear evidence regarding monotherapy, but there is also no clear indication that malignancy or serious infection can be associated with a combination of, for example, AZA and infliximab or AZA and adalimumab.

In inflammatory bowel disease (IBD) patients, 12 cases of hepatosplenic T-cell lymphoma have been seen in pediatric patients taking infliximab, and all of these patients were taking some course of concomitant AZA. This provided a signal that combined therapy could be associated with a very severe adverse event. However, in looking at clinical trials, there is no direct evidence of increased toxicity of the combination of only AZA with infliximab. More research is required to answer this question definitively.

G&H What ongoing research will add to our understanding of the pros and cons of immunosuppressive/biologic cotherapies?

GV Over the last 3 years, our group has conducted a prospective study examining whether patients can withdraw their immunosuppressives when disease is well-controlled with the combination of infliximab and

an immunosuppressive. We have seen no difference for 2 years since the starting point between outcomes in patients where immunosuppression was withdrawn and infliximab monotherapy continued and those continuing combination therapy. We did see differences in levels of C-reactive protein, which may indicate a difference in subclinical disease activity. However, in terms of overall efficacy, the two groups fared similarly. This shows that biologic monotherapy is a possible option, but more data are needed to confirm this practice. Our study was of only a small cohort.

The ongoing SONIC trial will provide additional evidence on this question, as it will compare patients taking scheduled maintenance infliximab monotherapy to infliximab therapy in combination with AZA. Preliminary data from this study will most likely be available by the fall of 2008. This study will allow us to look at trough levels of the agents and at clinical efficacy, but because many of the patients will have high serum levels of infliximab at all times, we will most likely not be able to look at antibody formation.

G&H Will future research focus on ways to stratify patients for monotherapy or combination therapy?

GV In rheumatology, it is generally accepted that combination therapy with biologics and immunosuppressants is required for long-term efficacy and for synergy between the two agents to achieve disease remission. More data are needed to address the same question in IBD. Data may show that some patients benefit from combination therapy whereas others show similar efficacy with monotherapy. However, these need to be large trials, powered to examine both efficacy and safety. In addition, we also need information about pharmacokinetic profiles of all the biologic therapies available and whether they are affected by cotherapy with immunosuppressives. An ongoing Canadian trial is specifically looking at this question.

G&H Could biologic or genetic markers play a future role in determining individual pharmacokinetics that vary from patient to patient?

GV Pharmacokinetics do vary individually among patients. This is another reason why quite a few patients are required in any trial design for biologics, to correct for the high rate of interindividual variability.

What is seen generally is a connection between lower trough levels and the chance of failing biologic therapy, but this is by no means a uniform correlation. Therefore, to make clinical decisions based solely on trough levels is

not advisable. We need more data on other markers to gain more reliable predictive information.

G&H Could an understanding of individual pharmacokinetics and trough levels allow for dose adjustments to further optimize patient outcomes?

GV This is an interesting possibility, but it is hard to know if patients with low trough levels on any biologic therapy metabolize the drug quickly, which could potentially be addressed with a higher dose, or if they have developed immunogenicity, in which case the dose increase will only provide temporary clinical benefit. Until we can pinpoint the factors that drive low trough levels, we cannot use them to determine dosage. As of yet, genetic and phenotypic data cannot be used to make this determination. Research is ongoing but, again, more data are needed.

G&H What other further research is needed regarding biologic/immunosuppressive combination therapies?

GV Because of the lymphoma cases, pediatric patients are almost uniformly receiving monotherapy with inf-

liximab, which is justified, given the incidence of this grave adverse event. However, this practice is not based on a significant amount of evidence. We have seen in the GAIN trial of adalimumab that patients who have lost response or developed intolerance to a first anti-TNF are less likely to respond to an alternative agent in the same class. This can have long-term ramifications, particularly in pediatric patients where a long course of therapy is anticipated. Though it is not the sole factor in the overall success of medical therapy, we need to optimize response to an initial anti-TNF agent, which may require use of immunosuppressive cotherapy, in order to ensure the best long-term outcomes of these patients.

Suggested Reading

Vermeire S, Noman M, Van Assche G, et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. *Gut*. 2007;56:1226-1231.

Hanauer SB. Risks and benefits of combining immunosuppressives and biological agents in inflammatory bowel disease: is the synergy worth the risk? *Gut*. 2007;56:1181-1183.

Vermeire S, Van Assche G, Rutgeerts P. Review article: Altering the natural history of Crohn's disease--evidence for and against current therapies. *Aliment Pharmacol Ther*. 2007;25:3-12.

Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2006;4:1248-1254.