Risks and benefits of combining immunosuppressives and biological agents in inflammatory bowel disease: is the synergy worth the risk?

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Since the introduction of infliximab to treat Crohn's disease, combination therapy with immunosuppressants has reduced immunogenicity, without impacting efficacy. The availability of novel anti-TNF agents and potential combined toxicities question the risk/benefit of combination therapies.

Vermeire and colleagues have furthered our understanding of the effectiveness of concomitant immunosuppressive therapy in suppressing formation of antibodies to infliximab in Crohn's disease (see page 1226).¹ The Leuven group has continued to demonstrate that immunosuppressive therapy reduces antibody formation to infliximab when the biological agent is administered on an episodic basis, and that antibody formation against infliximab correlates with lower infliximab blood levels and an increased risk of infusion reactions. In a year in which we can anticipate the introduction of two additional biological agents targeting tumour necrosis factor (TNF) α (adalimumab and certolizumab) and, possibly, a third monoclonal antibody targeting $\alpha 4$ integrins (natalizumab) for the treatment of Crohn's disease in the USA and Europe, the benefits and risks of combination therapy have become a primary focus of both efficacy and toxicity studies.

Monoclonal antibodies targeting TNF α are highly effective therapies for the treatment of Crohn's disease (and, as shown with infliximab, ulcerative colitis). The initial studies of these biological agents have been performed in patients who have active Crohn's disease despite ongoing treatment with aminosalicylates, corticosteroids and immunosuppressants.²⁻⁴ In these short-term trials, response to the induction dosing has been independent of the concomitant therapy. However, in this patient population (refractory disease despite ongoing therapy) short-term treatment without maintenance dosing of the biological therapy has not translated into long-term results without maintenance dosing.⁵⁻⁸ Furthermore, scheduled maintenance

dosing of infliximab has been more effective than episodic therapy.⁹ Whether maintenance therapy with a biological versus an immunosuppressive will be necessary after induction therapy with a biological¹⁰ in different patient populations (eg, new onset disease, steroid-naïve patients, or individuals treated for extraintestinal presentations), remains to be determined in ongoing clinical trials.

We have also learned that patients who develop antibodies to biological agents have a greater likelihood of acute and delayed infusion reactions, a shorter duration of response to each infusion,^{8 11-13} and a higher likelihood that long-term therapy will be compromised by eventual loss of response to an individual agent,¹⁴ which can be regained by use of an alternative biological agent targeting the same^{15 16} or a different molecule.¹⁷ Not surprisingly, rheumatologists have recognised similar findings with availability of an expanded number of biological options used to treat rheumatoid arthritis (RA) and other inflammatory arthropathies.^{18 19} An important lesson for current and future therapies with biologicals is that all biological agents have the potential to induce immunogenicity.¹⁹ Several factors contribute to an individual patient developing antibodies to a biological agent. These are incompletely understood but include host factors (genetics, age, gender, and immune status); structure of the biological treatment and its route of administration; dosing schedule; and concomitant medications. The degree of "human-ness" of a biological is not necessarily the sole determinant of immunogenicity, as fully human monoclonal antibodies or antibody fragments can be engineered to have greater (or lesser) protein structure (and post-translational carboxylation) similarities or differences

compared with inherent human proteins. In addition, attempts to compare immunogenicity between biological agents are compromised by differences in trial designs, assays of anti-drug antibodies (often proprietary), time-points of antibody determination, routes of administration and concomitant medications.

Despite the development of antibodies to anti-TNF α monoclonal antibodies and pegylated Fab fragments (certolizumab), and the documented effects of antibodies on the pharmacokinetics of the individual biological agent, immunogenicity has yet to translate into a statistically significant effect on the efficacy of regularly scheduled maintenance therapy after 1 year.¹³ Furthermore, despite the observation that concomitant immunosuppressives reduce the development of antibodies against biological agents, they have not significantly altered the response to infliximab,⁶ adalimumab,⁵ certolizumab,² or natalizumab¹⁷ in the treatment of Crohn's disease, particularly when these agents are administered as an induction course followed by scheduled maintenance treatment. In contrast, concomitant immunosuppressives do improve 1-year outcomes for patients treated in an episodic manner.^{8 9 20} Furthermore, the likely reason for recommendation of concomitant therapy has been to "optimise" treatment with infliximab, the sole biological therapy available to date for the treatment of Crohn's disease.^{8 20} Presently, with numerous biological agents available for RA, it is not uncommon for rheumatologists to switch between anti-TNF agents, in which case there is often a reduced response to the second or third agent.²¹ Early experience with second-generation anti-TNF agents in Crohn's disease have demonstrated similar results with both adalimumab and certolizumab; long-term responses are less likely in patients who have previously lost response to infliximab (SB Hanauer and WS Sandborn, personal communications). Potential mechanisms for the lowered response to a second anti-TNF agent include a more refractory disease, increased predilection to develop antibodies to biologicals, or escape from a "primary" TNF mechanism of inflammation.

Despite the outstanding vision of the Leuven group in studying aspects of individual responses to biological therapy, the study by Vermeire and colleagues does not help us greatly in answering additional practical questions. The study population has been divided into many small subgroups (use of azathioprine, methotrexate or no immunosuppressive; <3 months or >3 months of immunosuppressive use, and luminal vs fistulising disease). In addition, the decisions for

episodic treatments were made by individual clinicians rather than by a through established protocol. Furthermore, the outcomes were also clinical and not based on a standardised index.

Thus, both practical and theoretical questions arise from the observations that immunosuppressives reduce antibody formation and improve outcomes for episodic treatment. The first is the mechanism of effect. It is known that antibodies against the biologicals decrease clearance and increase blood levels of the circulating monoclonal antibodies and antibody fragments. Whether the reduced clearance is completely due to antibody-monoclonal antibody interactions or occurs by another mechanism is not known. In addition, there is the potential for synergistic mechanisms of action for the immunosuppressives and biologicals, as has been proposed for methotrexate in RA.¹⁹

Another practical question pertains to the possibility of discontinuing the immunosuppressant after an "induction" period. Antibodies to infliximab occurred early in the treatment, as shown by early (4-week) reduced trough levels of infliximab, denoting an 81% positive predictive value of high antibody to infliximab levels. A preliminary report from the Leuven group suggested that the immunosuppressive could be stopped after 6 months with no effect on the "loss of response" to infliximab over 2 years.²² However, the clinical results must be interpreted with caution, as blood levels of infliximab fell over time in patients in whom the immunosuppressive was discontinued. An ultimate effect on the clinical response may simply lag behind the pharmacokinetic data.

The patient populations may also make a significant difference in appropriate treatment strategies. For patients who have been refractory to therapy with immunosuppressives, we²³ and others⁸⁻¹⁰ have determined that maintenance therapy with infliximab is necessary to prevent relapse. In contrast, early ("top-down") therapy with infliximab induction followed by azathioprine/methotrexate maintenance may be efficacious for newly diagnosed or steroid-naïve patients and allow long-term "mucosal healing."²⁴ Improved outcomes have also been demonstrated for steroid-dependent, immunosuppressive-naïve patients who are "induced" with infliximab and maintained with azathioprine.¹⁰

Finally, from a practical standpoint, the Vermiere study was performed in the setting of episodic therapy with infliximab. Although some country funding sources continue to require episodic (rather than maintenance) therapy with

infliximab, it has clearly been demonstrated that maintenance therapy is more advantageous at preventing relapse⁹ and fistula drainage²⁵ and in inducing mucosal healing;²⁶ both of the latter end-points correlate with improved pharmacoeconomic outcomes (reductions in surgeries and hospitalisations).

Of course, the issues pertaining to concomitant immunosuppressives with biologicals go beyond the reduction of antibody to biological formation and efficacy, and are beginning to focus on safety. Given that induction and maintenance therapy with biologicals are efficacious, with low proportions (~10%) of antibodies to biologicals and no clinical differences in efficacy with concomitant immunosuppressives versus scheduled maintenance therapy after 1 year, what, then, are the risks of long-term concomitant therapy?

The publications regarding 1-year outcomes of biological therapy for Crohn's disease^{5-6,17} or ulcerative colitis²⁷ do not provide subgroup data on combined toxicities related to combination therapy and it is likely that the sample size in each group would not be able to identify anything other than a very strong toxicity signal. Further, registry data on adverse events related to infliximab for the treatment of Crohn's disease have primarily identified corticosteroids as a risk for serious infections and mortality.²⁸

The risks of treatment with biological therapy continue to be elucidated,²⁹⁻³⁰ and there is an expanding compendium of data on the risks of immunosuppressive therapy for the treatment of irritable bowel disease (IBD)³¹⁻³³ and, in particular, the risk of lymphoma.³⁴ It must be kept in mind that there is a variety of different lymphoma subtypes that may be related to the thiopurines³⁴⁻³⁶ and methotrexate.³⁷⁻³⁸ Most recently, a report by Mackey *et al* described eight cases of a rare form of hepatosplenic T cell lymphoma (HSTCL) occurring in young male patients (age 12–31 years) treated concurrently with infliximab and a thiopurine immunosuppressant.³⁹ Most of the cases were fatal and, although there have been rare reports of HSTCL in patients with Crohn's disease treated with thiopurines alone,⁴⁰ the clustering of cases in paediatric patients treated concomitantly with infliximab and a thiopurine has led to the sponsorship of a prospective paediatric observational registry similar to the TREAT²⁸ registry for adult patients.

The issue related to safety of concomitant immunosuppressive therapy with biologicals is not limited to anti-TNF therapy, as can be seen by the recent identification of an infectious complication of progressive multifocal leucoencephalopathy in a

patient with Crohn's disease treated with a combination of natalizumab and azathiopirine.⁴¹

Thus, while many leading clinical investigators (including me) have advocated the use of combination immunosuppressive therapy with biologicals, primarily to reduce the induction of anti-biological antibodies,⁴²⁻⁴³ this concept needs to be re-evaluated in light of the expanding reports of potential increases in severe, life-threatening infections and neoplasms, particularly in children.⁴⁴ We must continue to balance the risks of the disease burden on individual patients according to their clinical course, predicted disease behaviour,⁴⁵ response to conventional therapy and the option for surgical resection to treat a diseased segment. Furthermore, we still need to determine how to optimise biological therapies to induce and maintain remissions according to disease subgroups. Whether "top-down" or "step-up" therapies will require short-term or long-term concomitant immunosuppressive and biological therapy to optimise not only efficacy but the overall risk-benefit ratio for individual patients still requires better predictive criteria and additional clinical trials and observational series. In addition, as gastroenterologists welcome the addition of novel biological agents for induction and maintenance therapy of IBD, these considerations should be applied to the performance of individual agents both within and outside the different therapeutic classes. In the meantime, we may be entering an era where switching between agents, in cases of loss of response due to immunogenicity to specific agents, may be a safer option than long-term concomitant therapy with a biological and immunosuppressive. Meanwhile, studies to determine safe and effective means of minimising immunogenicity to biologicals should be a clinical research priority.

In summary, over the past near-decade since the introduction of infliximab, we have learned a great deal regarding biological therapy for IBD and other immune-mediated inflammatory disorders. To date, infliximab is the only biological, anti-TNF agent available for the treatment of Crohn's disease and ulcerative colitis. To optimise its efficacy and long-term use, doctors have recommended an induction and maintenance regimen, and concomitant therapy with an immunosuppressive agent. Most recently, with the recognised marginal benefit of an immunosuppressant in conjunction with induction-maintenance therapy with biologicals compared with the increased risks of infections and neoplasia, and at the same time that

several alternative biologicals (without cross-immunogenicity) are approaching marketing, these recommendations are coming under greater scrutiny. At present, either short-term concomitant therapy (eg, 6–12 months) or monotherapy with a biological agent, alone, appear to offer the best balance between short-term and long-term safety and efficacy for the treatment of IBD. In settings in which episodic therapy is (inappropriately) demanded by regulatory or funding authorities, the benefit appears to favour concomitant therapy; although the risks related to both disease progression and potential toxicities exceed those related to monotherapy with an induction and maintenance regimen.

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Competing Interests:
Declared (the declaration can be viewed on the Gut website at <http://www.gutjnl.com/supplemental>).

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