EDITORIAL

Heading Back to the Trough (Levels of Biologics in IBD)

We are now into the 16th year of the biologic era for treating inflammatory bowel disease (IBD) since infliximab was introduced into the US market in 1998. We can no longer consider biologics targeting tumor necrosis factor \(\alpha\) (anti-TNFs) as new or novel therapies. We have learned a great deal about this class and we still are learning how to optimize monotherapies and how to optimize anti-TNF therapy in conjunction with corticosteroids, thiopurines, and methotrexate.

Getting it Right

We have not always gotten it right. For example, even today less than 50\% of patients started on infliximab or adalimumab persist with therapy for 6 months, and only approximately 30\% remain on treatment for a year.\(^1\) We made some big mistakes in the beginning back in 1998 when infliximab was approved as a single infusion for patients with active luminal Crohn’s disease and for 3 infusions for patients with fistulizing disease. It was not until the ACCENT study published in 2002\(^2\) that maintenance therapy was recognized to be important to sustain the initial clinical responses. Until then, episodic therapy was the standard and was compromised by high levels of antidrug antibodies (ADAs), which led to shortened responses\(^3\) and infusion reactions that could be modulated by pre-infusion corticosteroids.\(^4\) In the setting of maintenance therapy with infliximab (and all subsequent anti-TNF biologics) concomitant thiopurines were shown to reduce immunogenicity, but in post hoc analyses there were no differences in clinical outcomes for patients who were receiving monotherapy or combination therapy.\(^5\) Of course, the questionable validity and imprecision of post hoc and retrospective studies have been exposed by the recent SONIC study, which randomized immunosuppressive and biologic naive patients to infliximab or azathioprine monotherapies, or combination infliximab and azathioprine, and showed a 13\% absolute benefit for combination therapy compared with infliximab monotherapy.\(^6\) Similar results were identified with ulcerative colitis in the SUCCESS trial.\(^7\) An important finding in SONIC was the association between combination therapy and higher trough levels of infliximab, which also were associated with the improved outcome of corticosteroid-free remissions. In rheumatoid arthritis, drug levels, likewise, are increased with the concomitant use of methotrexate and ADAs are reduced,\(^8\) and there is evidence of improved outcomes with combinations of infliximab and methotrexate.\(^9\) Most recently, similar results were found outside the class of anti-TNF biologics in IBD because drug levels with vedolizumab, an anti-integrin, were higher and levels of ADAs were lower in patients on combination therapy with azathioprine.\(^10\)

Optimization

Numerous problems with combining biologics with immunosuppressives remain, not the least of which is the necessity of optimizing 2 different therapies and the most important of which is combining potential toxicities. Despite interest in a top down approach with early introduction of biologics, most of the time biologic therapy is initiated for patients who are not responding to conventional therapies, including thiopurines. Nevertheless, there may be a rationale to optimize monotherapy with a biologic according to drug levels to minimize perceived risks of combination therapy. Although this may increase the cost of biologics as a result of the potential for higher dosing, the safety of combination therapy\(^7\) is a rationale to improve the pharmacoeconomics of biologics by reducing the cost of dose intensification.

Four retrospective analyses highlight many of these principles regarding anti-TNF therapy for IBD and provide bases for designing prospective studies to optimize (individualize) therapy in Crohn’s disease and ulcerative colitis.\(^11-14\)

Loss of Response

Despite their remarkable impact, retention, or lack thereof, of anti-TNF therapies has been disappointing in both clinical trials and clinical practice. In clinical trials, successful maintenance therapy with infliximab has been correlated loosely with absent ADAs and higher trough levels.\(^15-17\) In short-term inductions studies with adalimumab serum levels correlated with remissions,\(^18\) but adalimumab trough levels were not evaluated in the Crohn’s disease maintenance study (CHARM study).\(^19\) However, in the phase III maintenance study in moderate to severe ulcerative colitis the median serum trough concentrations were higher in remitters than in non-remitters.\(^20\) In clinical practice, loss of response to individual anti-TNF agents has necessitated approaches to evaluate mechanisms of loss of response.\(^21,22\) Once the presence of active disease has been confirmed, drug levels and ADAs can be determined, usually by simple enzyme-linked immunosorbent assays.\(^23\) Afif et al\(^24\) assessed a management strategy for approaching loss of response to infliximab according to the presence of serum concentrations and ADAs. Patients with absent infliximab and ADAs responded to substitution of adalimumab, patients with low infliximab levels and no ADAs responded to escalating doses of infliximab, and patients...
with adequate levels of infliximab without ADAs failed to respond to substitution of adalimumab.

Yanai et al\textsuperscript{11} confirmed the experience regarding loss of response to infliximab, and expanded it to loss of response to adalimumab, in a retrospective study of both pediatric and adult patients with IBD. Among 247 patients, higher trough levels of adalimumab and infliximab identified patients who failed to respond to a dose increase or a switch to the alternative anti-TNF. Similarly, the presence of ADAs to adalimumab or infliximab also identified patients who failed to respond to a dose increase but were associated with a longer response to a switch to the alternative agent. As expected, the results of the therapeutic decision (dose escalation or switching) were most robust in the subpopulation of patients with a definite inflammatory loss of response. Hence, as long as serum concentrations can be determined by either commercial or local laboratories the majority of patients losing response in the presence of active inflammation can be assessed and treated appropriately. There remains a smaller proportion of patients in whom the enzyme-linked immunosorbent assay is less accurate, often in the presence of low-titer ADAs, for which more sophisticated techniques may be required to determine underlying immunogenicity or adequacy of serum concentrations.\textsuperscript{22}

Thus, with assessment of loss of response nearly in the bag, the next important question is whether loss of response can be prevented. Since the revelational study by Maser et al\textsuperscript{25} that showed that for Crohn’s disease patients treated with scheduled maintenance infusions of infliximab, trough serum concentrations predicted clinical outcomes, it increasingly has been recognized that, in addition to immunogenicity (development of ADAs), the pharmacokinetics of anti-TNFs modulate response to biologic therapies. Furthermore, there are many factors that contribute to clearance including ADAs, sex, severity of inflammation, albumin, C-reactive protein (CRP) level, body size, and concomitant immunosuppressants.\textsuperscript{26}

**Prospective Management**

Although numerous reports have described the absence of detectable anti-TNF to be associated with loss of response in IBD (reviewed by Ben-Horin and Chowers\textsuperscript{22}), Loste et al\textsuperscript{13} attempted to develop a “risk panel” to aid in clinical decision making regarding improving long-term outcomes from a series of ulcerative colitis patients receiving infliximab. Rather than passive observations of individual patients during the course of treatment they identified independent predictors of relapse-free survival that included the following: a complete clinical response, mucosal healing, and the absence of perinuclear anti-neutrophil cytoplasmic antibody. Short-term clinical response, mucosal healing, low baseline CRP level, and normal baseline albumin level were predictors of colectomy-free survival. As was shown for Crohn’s disease,\textsuperscript{16} serum infliximab level at week 14 (after induction doses at weeks 0, 2, and 6) also had a predictive value. In other words, adequate induction dosing sufficient to achieve clinical and mucosal remissions were associated with trough levels at the end of induction and predicted long-term responses. One would speculate that dose adjustments for modifiable factors such as an incomplete clinical or mucosal response or low-trough levels early in the course may improve long-term outcomes.

Similar findings were reported in a post hoc analysis of the SONIC study by Reinisch et al.\textsuperscript{14} They found that trough infliximab concentrations at week 30 were higher in patients who achieved steroid-free remissions at week 50, and that trough infliximab concentrations and normalization of CRP level at week 30 were associated with mucosal healing at week 26, once again showing the interactions between active inflammation (mucosal ulceration or CRP) and the presence, or absence, of serum drug levels, whether or not patients were on monotherapy or combination therapy. The implication is the possibility of monotherapy treatment leading to adequate interval drug levels after induction and along the course of maintenance therapy.

**Combination Therapy or Monotherapy**

This brings us back to discussions of combination therapy vs monotherapy with anti-TNF biologics. Although findings from SONIC clearly showed a clinical benefit of combining infliximab with azathioprine, the trial did not distinguish between mechanistic synergies and an immunogenic effect on pharmacokinetics because patients on combination therapy had higher drug concentrations and lower ADA levels. Another implication is the possibility of withdrawing azathioprine once the (early) impact on immunogenicity has been obtained with the introduction of combination therapy. We saw a glimpse of this from a randomized study by Van Assche\textsuperscript{27} in which, despite some impact on pharmacokinetics, withdrawal of azathioprine offered no clear clinical benefit during 2-years of follow-up evaluation. The same group now reports an extended retrospective analysis of 158 patients co-treated with infliximab and immunosuppressives who discontinued the immunosuppressives after at least 6 months (median, 13 mo). They identified that trough levels of infliximab and CRP (a reflection of TNF inhibition) at the time of immunosuppressive withdrawal predicted long-term response with a median follow-up period of 29 months.

**Looking Ahead**

So what have we learned about using anti-TNF agents in IBD and where are we heading? We have learned that they are highly effective therapies when there is sufficient drug available. Low concentrations, whether owing to rapid clearance (eg, active inflammation as reflected
by high CRP or low albumin levels) or ADAs (immunogenicity) are associated with inadequate primary responses or loss of response. Low concentrations are a double whammy because they lead to disease activation and the development of ADAs, as we learned from episodic therapy. We now know that we can predict loss of response by low serum concentrations at the end of induction dosing and many clinicians now are re-dosing early in hospitalized ulcerative colitis patients with transient responses to infliximab predicted by low albumin and fecal losses of infliximab.28 In patients on combination therapy (biologic and immunosuppressive) who have achieved clinical and biologic remissions, and with adequate trough levels of biologic, the immunosuppressive can be withdrawn safely. We also have seen data that during maintenance dosing of infliximab, dose intensification in Crohn’s disease for patients with low trough levels resulted in better disease control, but in the maintenance phase of the trough level adapted infliximab treatment study, despite more “efficient” (ie, cost efficient) use of the drug and reductions in ADAs, subsequent level-based dose adjustments did not show superiority in the proportion of patients in clinical and biologic remission compared with clinically based adjustments.29 What is now needed are prospective studies with anti-TNFs using rational and cost-effective monitoring of drug levels early in the course of induction to ensure adequate neutralization of TNF and prevention of immunogenicity. Subsequently, cost-effective strategies for interval therapeutic drug monitoring should be evaluated to maintain remissions. In addition, clinical effectiveness trials should evaluate monotherapy vs combination therapy with anti-TNF dosing adjustments according to the achievement of similar drug levels. We are now a decade and a half into the biologic era and it is time to try to get it right, just in time for biosimilars.

References


Conflict of interest
The author discloses the following: Stephen Hanauer has been a consultant, served on the advisory board and speaker’s bureau, and received institutional research support from AbbVie and Janssen, and has been a consultant and served on the advisory board for UCB.

http://dx.doi.org/10.1016/j.cgh.2014.10.007