Optimal use of biologics in the management of Crohn's disease

Remo Panaccione and Subrata Ghosh

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Abstract: Crohn's disease (CD) is a chronic relapsing and remitting disorder of the gastrointestinal tract with no known cure. The inflammation that drives the disease can lead to debilitating symptoms and a number of complications that may lead to surgery. The introduction of biologic therapy a decade ago has offered a new option for patients failing conventional therapy. Over time, biologic therapy has also led to the desire to achieve treatment goals beyond the control of symptoms. In order to achieve short-term and long-term goals with these new agents, it is important to review how these therapies may be optimized for the best results.

Keywords: adalimumab, biologic therapy, certolizumab, Crohn's disease, infliximab, natalizumab, prognostic factors

Introduction

The introduction of biologic therapy, and particularly the use of anti-tumor necrosis factor alpha (TNF- α) therapy, has significantly changed the treatment and management of Crohn's disease (CD). The addition of a selective adhesion molecule (SAM) inhibitor has further expanded therapeutic options. Several large-scale, randomized, controlled trials have clearly shown that anti-TNF therapy and SAM inhibition are effective in the treatment of the symptoms and signs associated with moderate-to-severe CD. Anti-TNF therapy has been associated with steroid sparing and mucosal healing, and may contribute to fistula closure or a reduction in fistula drainage. Infliximab (IFX) (Remicade[®] (infliximab) for IV injection; prescribing information, Centocor, Malvern, PA, 2008), a murine-chimeric monoclonal antibody directed against TNF- α , was approved by the US Food and Drug Administration (FDA) in 1998 and has been shown to have significant benefits in patients with refractory luminal and fistulizing CD [Sands *et al.* 2004; Hanauer *et al.* 2002; Present *et al.* 1999; Targan *et al.* 1997]. Since the release of IFX, other anti-TNF blocking strategies have undergone investigation with positive results. More recently, adalimumab (ADA) (Humira[®] (adalimumab); prescribing information, Abbott Laboratories, North Chicago, IL, 2008), a fully human monoclonal antibody directed against TNF, has been shown to be effective

for induction and maintenance of remission of moderate-to-severe luminal CD [Colombel *et al.* 2007; Hanauer *et al.* 2006a,b]. Finally, certolizumab (CZP) (Cimzia[®] (certolizumab pegol); prescribing information, UCB, Smyrna, GA, 2008), a Fab fragment attached to polyethylene glycol (PEG), has also been shown to be effective in this patient population [Sandborn *et al.* 2007c; Schreiber *et al.* 2007a,b]. Both ADA and CZP have been approved for the treatment of moderate-to-severe luminal CD by the FDA. Natalizumab (NTZ) (Tysabri[®] (natalizumab); prescribing information, Elan Pharmaceuticals, San Francisco, CA, 2008), the first non-TNF- α inhibitor biologic compound approved by the FDA for the treatment of moderate-to-severe CD, is a humanized monoclonal IgG4 antibody directed against α -4 integrin which has been shown to be effective in moderate-to-severe luminal CD [Targan *et al.* 2007; Sandborn *et al.* 2005]. NTZ is approved for inducing and maintaining a clinical response and remission in patients with moderately-to-severely-active CD with evidence of inflammation and who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- α [Panaccione *et al.* 2004]. With these agents come the promise of mucosal healing and possibly the 'holy grail' of treatment, which is changing the natural history of this chronic relapsing disease. In order to achieve this, it is important that the data from clinical

Correspondence to:

Remo Panaccione, MD, FRCPC

Director, Inflammatory Bowel Disease Clinic, Assistant Professor of Medicine, University of Calgary, Rm. 6D32, TRW Building, 3280 Hospital Drive NW, Calgary, Alberta T2N 4N1
rpanacci@ucalgary.ca

Subrata Ghosh, MD, FRCP, FRCPIE

Professor of Medicine, Inflammatory Bowel Disease Clinic, Division of Gastroenterology, University of Calgary, Calgary, Alberta, Canada

trials be adequately translated into clinical practice including proper patient selection, optimal dosing regimens, and most importantly proper timing with respect to the introduction of these agents. Moving forward, we need to consider incorporating markers reflecting modification of organ damage, and not just clinical improvement, in guiding such optimal use.

Selecting patients properly for biologic therapy

Classical use of biologic therapy

At present, all three anti-TNF therapies are indicated as second-line therapy following failure of conventional nonbiologic treatment and NTZ is indicated for similar patients who have also failed or are intolerant to at least one anti-TNF agent. This adheres to the traditional treatment paradigm in CD, which is based on a 'step-up' approach, whereby the least toxic agents are used early in the course of the disease, with subsequent therapies then added when there is a lack of response or toxicity. Indeed, most guidelines advocate aminosalicylates, and more recently oral corticosteroids with low systemic bioavailability in the form of budesonide, for short-term induction in mild-to-moderate CD. Systemic corticosteroids are indicated for induction therapy for patients with moderate-to-severe CD, or for patients failing therapy for mild-to-moderate CD. Immunosuppressant therapy is reserved for those patients with steroid-refractory or steroid-dependent disease [Travis *et al.* 2006; Hanauer and Sandborn, 2001]. Only after these agents have failed are patients considered for biologic therapy. This classical use of biologics is consistent with the types of patients that were treated in the pivotal clinical trials, but there is rising concern that many patients are receiving biologics too late in the disease course at a time when many have developed complications such as fibrostenosis or penetrating disease. However, these guidelines do not adequately take into account certain patient-specific parameters such as prognostic factors, burden or location of disease, previous exposure and response to medications, and surgical history. In addition, the exact definition of failure of conventional agents is imprecise and this may lead to futile cycling of conventional agents without considering other effective therapies early on. As a result, this treatment paradigm has come under increasing scrutiny in recent years; much of this due to the experience

gathered not only in clinical trials but also by experienced clinicians globally.

Identifying patients for 'early biologic use'

There is accumulating evidence to support earlier use of biologic therapy. A recent study by D'Haens *et al.* suggests that earlier use of biologics may be linked to important long-term outcomes [D'Haens *et al.* 2008]. They conducted a 2-year open-label randomized trial in which 133 patients with new onset moderate-to-severe CD were randomized to receive either early combined immunosuppression or conventional treatment. Many of the patients were treated shortly after diagnosis. Sixty-seven patients were assigned to receive early combined immunosuppression and received three infusions of IFX (5 mg/kg) at weeks 0, 2, and 6, in combination with azathioprine (AZA) (2.0–2.5 mg/kg/day). Additional treatments with IFX were given if necessary to control disease activity. Sixty-six patients assigned to conventional management received corticosteroids, which were tapered after patients responded. Patients whose symptoms worsened during the corticosteroid taper were re-induced with another course of corticosteroids. Those whose symptoms continued to worsen despite this were started on AZA (2.0–2.5 mg/kg/day). Patients who relapsed after withdrawal of corticosteroids were given a second course of corticosteroids in combination with AZA. Patients who remained symptomatic after 16 weeks of AZA treatment received an induction course of infliximab (5 mg/kg) at weeks 0, 2, and 6, and continued immunosuppressive treatment. At week 26, 39 (60%) of 65 patients in the combined immunosuppression group were in remission without corticosteroids and without surgical resection, compared with 23 (35.9%) of 64 in the conventional therapy group, for an absolute difference of 24.1% ($p=0.0062$). Corresponding rates at week 52 were 40/65 (61.5%) and 27/64 (42.2%) ($p=0.0278$). Twenty of the 65 patients (30.8%) in the early combined immunosuppression group had serious adverse events, compared with 19 of 64 (25.3%) in the conventional therapy group ($p=1.0$). Most importantly, at week 104, no ulcers were seen for 19/26 (73.1%) patients assigned to the combined immunosuppression group, compared with 7/23 (30.4%) of the conventional therapy group ($p=0.0028$) despite a similar proportion of patients being in clinical remission. Therefore, early introduction of IFX resulted in faster rates of induction, less exposure to corticosteroids, and a significant

difference in the ability to achieve complete mucosal healing. Furthermore, the strategy tested in the trial may be improved upon by utilizing scheduled use of IFX rather than episodic use.

In addition, emerging evidence suggests that early use of biologic therapy in CD increases rates of response and remission. In a study evaluating the use of different dosing regimens of IFX in pediatric patients with moderate-to-severe active CD, the response and remission rates at week 10 were 88% and 59%, respectively, which is approximately 20% higher than was shown in adult studies [Hyams *et al.* 2007]. Sub-analyses of the CHARM (Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance; maintenance therapy with ADA) and PRECiSE 2 (Pegylated antibody fRagment Evaluation in Crohn's disease Safety and Efficacy; maintenance therapy with certolizumab) studies show higher rates of response and remission with anti-TNF- α therapy among patients with shorter disease duration [Schreiber *et al.* 2007a,b,c]. In the PRECiSE 2 sub-analysis, for responding patients [≥ 100 -point decrease from baseline in Crohn's disease activity index (CDAI)] at week 6 who were randomized to CZP *versus* placebo every 4 weeks, the rates of remission (CDAI ≤ 150) at week 26 for CZP and placebo were 68% and 37%, respectively, for patients with disease duration of less than 1 year. In comparison, the rates of remission at week 26 were 44% (CZP) and 24% (placebo) for patients with disease duration of greater than 5 years. Although, there is the potential for unrecognized cofounders to also explain these differences, these data suggest that there may be a window of opportunity in which biologic therapies may have the most impact.

Therefore, in order to achieve the most benefit from the currently available biologic therapies, patient populations need to be identified that would benefit from early use of these agents. Several types of patients who would benefit from early introduction of biologic therapy include patients with prognostic factors of poorer outcomes, and patients with disease of undesirable location or burden.

There are several lines of evidence that have identified clinical, endoscopic, and serologic variables which make patients at higher risk for poor prognosis and disease progression. A recent study

from France identified young age at diagnosis (<40 years of age), presence of perianal disease, and need for steroids with first flare-up as predictors of poor prognosis [Beaugerie *et al.* 2006]. The presence of any two or all three of these factors was particularly associated with a disabling disease course which included chronic steroid use, need for hospitalization or surgery, early need for immunosuppressives, or chronically active disease. The presence of deep ulceration at colonoscopy has also been shown to be an independent factor associated with a high rate of surgery [Allez *et al.* 2002]. The authors found that patients with severe endoscopic lesions defined as deep ulcers in greater than 10% of the mucosal area of any colonic segment was associated with high rates of surgery, with rates being 31%, 42%, and 62% at 1, 3, and 8 years, respectively. Patients without severe endoscopic lesions fared much better with surgical rates of 6%, 8%, and 18% over the same time horizon. These differences were statistically significant. Finally, the presence of multiple antibodies to gastrointestinal luminal flora (ASCA, ANCA, CBir, Omp C) has been associated with an increased risk of developing complications such as fibrostenotic or penetrating disease and requiring surgery [Dubinsky *et al.* 2006].

Patients with a large burden of disease and those with disease in undesirable locations should be considered as candidates for earlier use of biologic therapy. In particular, patients with extensive small bowel disease, patients with duodenal involvement, and those with anorectal involvement should be considered as strong candidates to receive biologic therapy early in their course because surgery in these patient populations is associated with a high likelihood of postsurgical lifelong morbidity due to either the length of resection or the need for a stoma or diversion. In the pediatric CD population, children with growth retardation or pubertal development delay should be considered for early biologic therapy, as corticosteroid therapy is especially detrimental in such patients.

In 2009, corticosteroids are frequently used as the treatment of choice for induction of remission in patients with a flare-up of CD. As discussed earlier, the requirement for corticosteroid induction therapy is a poor prognostic factor in itself, but it has also been demonstrated that approximately one-fifth of patients will be corticosteroid refractory and approximately one-third of patients

achieve steroid-free remission at 1 year [Faubion *et al.* 2001; Munkolm *et al.* 1994]. Early in the induction phase, it is paramount that these patients are assessed in a timely (every 4 weeks) and routine fashion. The expectation is that these patients should have a substantial improvement in symptoms at this time point. If they have not improved, then the patient requires an alternative induction of remission strategy and in 2009 the only other class of drug that has robust induction properties is the anti-TNF- α class. A recent study has demonstrated that in patients requiring corticosteroids for induction, the addition of IFX plus methotrexate (MTX) was no better than the addition of IFX alone in inducing and maintaining steroid-free remission [Feagan *et al.* 2008]. However, the study demonstrated high steroid-free remission rates (78% and 57% at 14 and 50 weeks, respectively), raising the possibility that the combination of corticosteroids and an anti-TNF during induction therapy may result in synergy and lead to substantially higher rates of remission than either agent alone. Hitting patients with predicted poor prognosis hard and early with multiple effective agents may be a way to optimize efficacy, rather than waiting for patients to become refractory to one agent before introducing another in a sequential manner.

In summary, when selecting patients for biologic therapy, the classical patients that should be started on biologic therapy are those with complicated fistulizing CD and patients with moderate-to-severe disease who are failing traditional nonbiologic therapy. With emerging evidence clinicians should begin identifying patients in whom earlier use of biologic therapy might be beneficial and these include patients failing induction therapy with corticosteroids, patients with poor prognostic factors, and those with undesirable disease burden or location.

Optimal dosing strategies with biologic therapy

Once patients have been properly identified and selected to start biologic therapy, it is important to utilize the correct dose for induction and maintenance of remission, employ strategies to deal with patients who are primary and secondary nonresponders to anti-TNF- α therapy, and decide in which patients there is a benefit of using combination therapy with an immunosuppressant.

Induction and maintenance dosing

The induction and maintenance dosing schedule is outlined in the prescribing information for each of the anti-TNFs and NTZ. After patients have successfully responded to induction dosing, scheduled maintenance dosing is recommended. Episodic dosing with any monoclonal antibody for the treatment of CD is not recommended due to the potential of developing anti-dug antibodies.

For IFX, the induction dosing is 5 mg/kg intravenously (IV) given at weeks 0, 2, and 6. Infusions are carried out in a hospital or outpatient setting. Most patients will respond within the first 4 weeks or the first two doses. Following induction dosing, patients should be maintained on 5 mg/kg IV every 8 weeks. For ADA, the induction dosing is 160 mg subcutaneously (sc) at week 0 (given as four 40 mg sc injections on day 1, or two 40 mg sc injections on days 1 and 2) and 80 mg sc at week 2. Patients should be taught to self-administer ADA by a healthcare professional during the first four injections. Self-injection can usually proceed thereafter. Maintenance should be continued at 40 mg sc every other week. It should be appreciated that although the induction dosing with ADA described above covers only 4 weeks of therapy, the full benefit may not be realized until 12–16 weeks into the ‘maintenance’ dosing phase and, therefore, one should consider this prior to dose escalation [Panaccione *et al.* 2008a,b,c; Sandborn *et al.* 2007]. The authors do not dose escalate prior to week 12 as long as the patient is having a step-wise response to ADA. For CZP, the induction dosing is 400 mg sc administered at weeks 0, 2, and 4, followed by maintenance dosing of 400 mg sc every 4 weeks. CZP can be administered by a healthcare professional or self-administered by the patient. NTZ is approved for IV infusion only at approved infusion centers that partake in the TOUCH program. The induction dosing is 300 mg IV at weeks 0, 4, and 8. For patients who respond to induction dosing maintenance dosing is 300 mg IV every 4 weeks.

Approaches to primary nonresponse to anti-TNF therapy

Despite the shift in treatment paradigms ushered in by the arrival of anti-TNF therapy for CD, it is important to remember that one-third of patients will not respond to anti-TNF therapy [Sandborn *et al.* 2007a,b; Hanauer *et al.* 2006a,b; Targan *et al.* 1997]. This proportion may decrease as we start to treat patients earlier

and with combinations of effective therapy. Patients exposed to anti-TNF therapy and who have failed to respond are referred to as primary nonresponders. In clinical trials, this is defined as failure to achieve a 70- or 100-point reduction in the CDAI score. In clinical practice this may be established by the physician's clinical judgment. Most of the issues surrounding primary nonresponse surround IFX and CD; which is not surprising given that IFX has been available in clinical practice for longer than the other anti-TNF agents.

Patients with primary nonresponse to anti-TNF therapy should be evaluated to determine why they failed to respond. The most important practice point is to exclude the possibility of an underlying irreversible structural lesion, such as a fibrostenotic stricture, or a possible co-infection (e.g. with *Clostridium difficile* or cytomegalovirus) or absence of 'true' inflammation with symptoms driven by irritable bowel syndrome-like symptoms. If these CD complications or concomitant conditions have been ruled out, then it is generally accepted that primary nonresponse would result from a different underlying CD pathobiology in which TNF is not an important component of the inflammatory cascade. Therefore, choosing an agent with a different mechanism of action would be scientifically rational in this setting. There are data supporting the use of NTZ in this patient population. In subgroup analyses of pivotal trials, there were no statistical differences in the efficacy of NTZ for the induction or maintenance of response/remission in patients who were primary nonresponders to IFX as compared with the intent-to-treat population [Panaccione *et al.* 2004]. NTZ has been approved by the FDA as monotherapy for the treatment of patients with moderate-to-severe CD with biologic evidence of disease activity and who have failed to respond to conventional therapy and at least one anti-TNF agent. In the ENCORE (Efficacy of Natalizumab in Crohn's Disease Response and Remission) trial, which evaluated the efficacy of NTZ induction therapy in patients with CD, subgroup analysis demonstrated that the overall efficacy of NTZ was similar for patients who had been exposed to, or failed to respond to, previous anti-TNF therapy and patients who were anti-TNF-naïve [Targan *et al.* 2007]. In patients who have never been exposed to MTX or the purine antimetabolites, introducing these agents or optimizing their use may be considered. This likely

represents a small minority of patients and there is no data to support this practice, but it may be rational.

Despite the rationale for switching mechanisms of action, many clinicians will attempt a second or even a third anti-TNF agent in primary nonresponders, or even a dose escalation (e.g. 10 mg/kg of IFX). In the case of IFX, one could check for early antibody formation by testing for IFX levels and anti-IFX antibodies at week 6 prior to a third induction dose or dose escalation. There are very limited data to support this practice or switching to an alternate anti-TNF in primary nonresponders [Lofberg *et al.* 2008; Mozziconacci *et al.* 2008]. It has been clearly shown that the overall response and remission rates are lower when attempting to use a second or third anti-TNF in clinical trials and therefore the risk-benefit equation is shifted with decreasing benefits while assuming a similar risk. Clinicians should reconsider this strategy and wait for better evidence to be available. Most of this practice surrounds physicians' and patients' concerns about the issue of toxicity associated with NTZ, particularly with regards to the incidence of progressive multifocal leukoencephalopathy (PML) [Yousry *et al.* 2006]. Although PML is a serious and often life-threatening disease, it is estimated that the risk for PML in patients treated with NTZ is between approximately 1 in 5,000 and 1 in 10,000 patients, from the postmarketing reports and the number of cases treated in multiple sclerosis and CD. If this estimate is accurate, the risk of developing PML and dying is extremely low and does not make NTZ any less safe than the anti-TNF class of agents. Recent evidence in multiple sclerosis suggests that PML may be stabilized after its onset by plasma exchange to deplete NTZ and permit immune reconstitution.

Approaches to secondary nonresponse to anti-TNF therapy

In addition to primary nonresponders, there are secondary nonresponders who may initially respond to an anti-TNF agent and then lose response or become intolerant to their initial TNF inhibitor over time. Secondary nonresponders may represent 30–40% of patients during the first year of therapy [Colombel *et al.* 2007; Schreiber *et al.* 2007a,b,c; Hanauer *et al.* 2002]. Secondary loss of response may be due to disease-related factors or drug-related factors. Disease-related factors include the development

of a complication of CD, such as a fibrostenotic stricture or abscess formation. Once again, disease-related factors and co-infection should be ruled out before deeming secondary nonresponse to be a drug-related phenomenon. Drug-related factors include the formation of neutralizing antibodies, which are associated with decreased serum IFX levels, altered clearance of drug, or possibly biologic escape mechanisms. It is important in this patient population to obtain drug and antibody levels if available (currently only available for IFX) and to then re-evaluate disease activity to ensure that symptoms are not arising due to irritable bowel syndrome, bile acid diarrhea, development of fibrostenotic strictures, or postsurgical causes. The majority of data available on the treatment of this patient population is, once again, focused on patients who developed secondary nonresponse to IFX. If patients have developed intolerance to IFX, challenging them with a second anti-TNF agent is appropriate. Most of the experience with this approach is in switching to ADA. Sub-analysis of the CHARM trial demonstrated that patients who were previously exposed to IFX still responded to ADA therapy, but with response rates approximately 10% lower than those of patients who were naive to anti-TNF agents [Colombel *et al.* 2007]. Similar data exist for CZP from a sub-analysis of the PRECiSE 2/3 trials [Schreiber *et al.* 2007a,b,c]. The interdependence of this reduced response rate to duration of disease is not entirely clear.

The options for patients who are losing response to IFX are to 'optimize' the dosing of the drug by increasing the dose or shortening the dosing interval, or to switch from IFX to an alternative anti-TNF agent [DeSilva *et al.* 2008]. The measurement of antibodies to IFX and IFX trough levels is useful in guiding treatment strategy. In patients with no detectable anti-IFX antibodies and low serum trough levels of IFX, optimizing the dosing of IFX is recommended. A study conducted at the University of Pittsburgh has shown that many patients with CD receiving long-term IFX required an increase in dose or a decrease in dosing interval to regain lost response to the agent [Regueiro *et al.* 2007]. Concomitant immunosuppressant therapy did not prevent the need for escalated IFX dosing. In the ACCENT (A Crohn's disease Clinical trial Evaluating IFX in a New Long-term Treatment regimen) I trial, 88% of patients with active CD who had initially responded to IFX but then lost response during

maintenance therapy regained response by increasing the IFX dose to 10 mg/kg [Rutgeerts *et al.* 2004]. The phenomenon of regaining IFX efficacy by dose escalation and shortening the dosing interval is in part explained by data from a study conducted by Maser and colleagues, which demonstrated that the major factor influencing the clinical efficacy of IFX during scheduled maintenance therapy was the serum trough level of this agent [Maser *et al.* 2006]. This study found that patients with higher trough levels of IFX have better outcomes and that the use of concomitant immunosuppressants did not alter outcomes. One must consider that these data are from an open-label study and therefore are inherently biased. In this series, it appears that shortening the interval may be more cost-effective than doubling the dose. In cases where there is a loss of response to ADA dosed at 40 mg every other week, shortening the dosing interval to 40 mg weekly has been shown to re-establish response in approximately 75% of patients [Sandborn *et al.* 2008a,b]. The optimal strategy for managing patients who lose response to CZP is unclear. Data from a small group of patients who lost response to CZP during PRECiSE 2 suggest that a single re-induction dose with CZP 400 mg may re-establish response [Lichtenstein *et al.* 2008], but whether this strategy can be translated into clinical practice remains debatable.

The only randomized controlled trial specifically designed to address the issue of secondary nonresponse to IFX is the GAIN (Gauging Adalimumab efficacy in Infliximab Nonresponders) trial [Sanborn *et al.* 2007a,b,c]. In GAIN, 325 patients with moderate-to-severe CD who had previously been exposed to IFX and lost response and/or become IFX intolerant were randomized to receive either ADA 160 mg and 80 mg subcutaneously at weeks 0 and 2, respectively, or placebo. In the group receiving ADA, 21% of patients entered remission (CDAI < 150), 52% had a CDAI decrease of 70 points or more, and 38% had a CDAI decrease of 100 points or more at week 4, compared with 7%, 34%, and 25% of patients in the placebo group, respectively ($p < 0.05$). There was no difference in overall efficacy if the patients lost response to, or were intolerant to, IFX upon study entry. Although the 4-week remission rates reported in GAIN may appear low at first glance, recently presented data from an open-label extension of this trial demonstrated

that, over time, remission and response rates increased during the maintenance phase with ADA therapy [Panaccione *et al.* 2008c]. At 6 and 12 months, 57% and 40%, respectively, of the week 4 responders to ADA were in clinical remission. Thus, 4 weeks may be too short a time point to assess induction of response in CD patients with prior exposure to IFX. Results from a similar open-label study of CZP in IFX nonresponders were also presented recently [Vermeire *et al.* 2008]. In WELCOME (26-Week open-label trial Evaluating the clinical benefit and tolerability of certolizumab pegol induction and Maintenance in patients suffering from Crohn's disease with prior loss of response or intolerance to IFX), secondary nonresponders to IFX were treated with CZP 400 mg subcutaneously at weeks 0, 2, and 4. At week 6, 62.2% of patients achieved response (CDAI score reduction of 100 points or more) and 39.3% achieved remission. The long-term outcome of these patients has not yet been reported.

Primary and secondary nonresponse to anti-TNF therapy is a reality of treatment with this drug class. In patients with primary nonresponse, serious consideration should be given to switching to another class of biologic agent. The only option for switching to another class (i.e. a biologic agent with a different mechanism of action) at this time is NTZ. However, this decision should be made in concert with the patient, and many patients may choose to try a second anti-TNF agent. For patients who become intolerant to one anti-TNF agent, switching to another anti-TNF agent makes sense and is supported by clinical data. For patients who lose response to IFX, measurement of anti-IFX antibodies and IFX trough levels can be used to optimize the treatment strategy. In the presence of antibodies to IFX, the most robust (placebo-controlled) data at this time suggest a switch to ADA therapy.

Combination versus monotherapy with biologics

The issue of combination therapy or monotherapy with biologics pertains only to the anti-TNF class. NTZ can only be used as monotherapy for CD in keeping with the FDA labeling. Most experts will stop immunosuppressive therapy and initiate NTZ immediately with no washout once a patient has been deemed a candidate for NTZ therapy. Corticosteroids should be withdrawn as quickly as possible and it is

recommended that patients be off corticosteroids within 6 months of initiating NTZ. On the other hand, despite the substantial evidence demonstrating that anti-TNF agents are an effective part of treatment strategies, their role is still evolving. Several questions still remain regarding the optimal use of anti-TNF agents in CD as monotherapy or combination therapy with immunosuppressive agents. The central issues regarding this controversy surround immunogenicity, efficacy, and safety.

Immunogenicity

Immunogenicity can occur with all biologic agents. The principal reason for originally advocating combination therapy with anti-TNF therapy and an immunosuppressant was to reduce immunogenicity and this practice evolved from experience in rheumatoid arthritis. In CD, it has been demonstrated that concomitant use of an immunosuppressant with biologic therapy may prevent the formation of anti-drug antibodies. In patients undergoing episodic IFX therapy it has been clearly demonstrated that the use of either AZA or MTX is associated with a significant reduction in antibody formation [Hanauer *et al.* 2004]. In a study of patients treated concomitantly with IFX plus either AZA or MTX, 48% and 49% exhibited antibodies to IFX, respectively, while 73% of the patients in the group not receiving immunosuppressant therapy demonstrated anti-IFX antibodies [Vermeire *et al.* 2007]. These data support results seen in a previous study which demonstrated that concomitant use of an immunosuppressant in IFX episodic therapy was associated with decreased antibody formation, decreased infusion reactions, and increased sustained responsiveness to IFX [Baert *et al.* 2003]. Current data suggest that the effect of continuing immunosuppressant therapy on reducing immunogenicity in patients receiving biologic therapy is more pronounced in patients undergoing episodic biologic therapy: a strategy that has been largely abandoned due to lack of efficacy.

Enhanced efficacy

The question of whether immunosuppressive therapy enhances the efficacy of anti-TNF therapy or is synergistic has been debated for the last decade. More recently, the debate has become increasingly confusing due to many sub-group analyses of the key pivotal trials which suggested that combination therapy did not lead to increased efficacy. However, the result of a

recent large randomized trial has brought some clarity to this gray area. To understand the data completely it is important to understand the populations that have been studied. In patients with established CD who have active disease despite therapy with immunosuppressants, post-hoc subgroup analyses of the major trials with all three anti-TNF agents and with NTZ did not demonstrate significant differences in efficacy between patients receiving the biologic plus concomitant immunosuppressants and those not receiving concomitant immunosuppressants [Wolf *et al.* 2007; Lichtenstein *et al.* 2007; Schreiber *et al.* 2007a,b,c; Hanauer *et al.* 2006a,b]. The key points here are that in order to enter the trials these patients had to be on stable doses of medications therapy (AZA, 6-mercaptopurine, MTX) and despite this have symptoms of a moderate-to-severe CD flare. It must also be remembered that these are subgroup analyses and, although large numbers of patients were studied, the power calculations were not meant to allow for this comparison. Furthermore, a number of biases have to be considered, including the possibility of variable exposure to concomitant steroids in the two subgroups. In a similar group of patients who failed immunosuppressants prior to starting IFX, an 18-month follow-up study (the IMID study) in 80 patients with CD found no clinical benefit from continuing immunosuppressant therapy beyond 6 months [Van Assche *et al.* 2008]. The trial was designed to study the benefit of immunosuppression during maintenance therapy with IFX. Eighty patients with CD in clinical remission were randomized to continue or to interrupt immunosuppression with AZA, 6-mercaptopurine, or methotrexate, at least 6 months after the start of IFX maintenance therapy. At 2 years, there was no significant difference in the clinical endpoint (defined as the need to change the IFX dosing regimen or discontinue IFX) between patients who continued with immunosuppressants and those who interrupted immunosuppressant therapy. However, there was a difference in the rate of occurrence of anti-IFX antibodies and mean IFX trough levels, with patients continuing immunosuppressants having a lower frequency of antibodies to IFX as well as higher trough drug concentrations. The major criticisms of the study are that it was underpowered and cannot be definitively interpreted as showing that the two strategies were equivalent. There does not appear to be an added advantage of adding MTZ to the combination of

corticosteroids and IFX for induction therapy in patients with active CD. In the recent COMMIT (Combination Of Maintenance Methotrexate-Infliximab Trial) study, there was no difference in steroid-free remission rates in patients taking corticosteroids, IFX, and MTX *versus* patients taking IFX and corticosteroids alone [Feagan *et al.* 2008]. This was in contrast to the study by Lémann *et al.*, which showed that IFX therapy with concomitant AZA appeared to be superior to AZA monotherapy for inducing and maintaining remission and complete steroid withdrawal in patients with active CD, despite 6 months of steroid therapy [Lémann *et al.* 2006]. In all, 63% of patients treated with IFX were able to achieve steroid-free remission, compared with 37% in the placebo group ($p=0.001$) [Lémann *et al.* 2006]. However, during long-term follow-up, there was an 80% relapse rate over a median of 54 weeks. This argues strongly against any type of bridging strategy.

The recent SONIC (Study of Biologic and Immunomodulator Naive Patients In Crohn's Disease) study has provided valuable lessons in the value of combination therapy. SONIC enrolled patients with early CD (median duration of disease 2.3 years) who were naive to immunosuppressant and biologic therapy to either full weight based AZA alone, IFX alone, or the combination of IFX and AZA [Sandborn *et al.* 2008a,b]. The primary endpoint was steroid-free remission at 26 weeks. Major secondary endpoints included complete mucosal healing at 26 weeks. The study demonstrated that in early disease, the combination of IFX and AZA was superior to IFX alone or AZA alone in patients with early CD refractory to mesalamine, budesonide, or prednisone. At week 26, 57% of patients receiving IFX and AZA combination therapy and 44% of patients receiving IFX monotherapy achieved steroid-free remission, compared with 31% of patients receiving AZA alone ($p<0.001$ IFX with AZA *versus* AZA monotherapy; $p=0.009$ IFX monotherapy *versus* AZA monotherapy; $p=0.022$ IFX with AZA *versus* IFX monotherapy). Mucosal healing (absence of ulcers) occurred at week 30 in 44% of patients receiving combination therapy with IFX and AZA, 30% of patients receiving IFX monotherapy, and 16% of patients receiving AZA monotherapy. Mucosal healing with AZA at week 30 was remarkably modest and it will be interesting to await further analysis to demonstrate whether

this was associated with higher hospitalization and surgical interventions.

The therapeutic guidelines still focus on the conventional step-up therapy for CD. However, the options provided by biologic therapies and emerging data suggest that an updated consensus may be needed which reflects the growing body of evidence that suggests that the benefits of anti-TNF- α therapy extend beyond just the measure of clinical efficacy. While it is too early to fully advocate a top-down approach, data suggests that earlier treatment may have a disease-modifying effect similar to what has been shown in rheumatoid arthritis. Moreover, results from the current SONIC study, in which the treatment of IFX with and without AZA is being compared in CD patients naive to both immunosuppressants and biologic therapy should provide answers to some questions raised by the top-down *versus* step-up study by D'Haens *et al.* Data presented at this digestive diseases week (DDW) from the COMMITT study evaluating IFX alone *versus* IFX and MTX will also provide further insights. Ultimately, the field will need to concentrate its efforts on strategies which identify those patients who would receive the most benefit from early intervention with biologic therapy.

Conflict of interest statement

Remo Panaccione has served as a speaker, a consultant and an advisory board member for Astra Zeneca, Procter & Gamble Pharmaceuticals, Shire, Prometheus Laboratories, Centocor, Schering-Plough, Elan Biogen, Bristol Myers Squibb, Ferring Pharmaceuticals, Glaxo-Smith Kline, UCB Pharma, Axcan Pharma and Abbott Laboratories, and has participated in continuing medical education events indirectly sponsored by Astra Zeneca, Elan Biogen, Procter & Gamble Pharmaceuticals, Shire, Axcan Pharma, Centocor, Schering-Plough, and Abbott Laboratories, and has received research funding from Procter & Gamble Pharmaceuticals, Elan Biogen, Centocor, Schering-Plough, Millenium, Bristol Myers Squibb, and Abbott Laboratories.

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