Exploring the role of monitoring anti-TNF α drug and antibody levels in the management of inflammatory bowel disease

Allen W. Lim, Remo Panaccione and Cynthia H. Seow

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Abstract: Crohn's disease and ulcerative colitis are chronic inflammatory gastrointestinal disorders which often result in significant morbidity or surgery. Current treatment options are not curative and may cause significant adverse effects. The introduction of anti-tumour necrosis factor alpha (anti-TNF α) therapy over a decade ago was a welcome addition to the therapeutic armamentarium and revolutionized the treatment of inflammatory bowel disease (IBD). Despite their relative success, a significant proportion of patients with IBD fail to respond or subsequently lose response anti-TNF α therapy. This review identifies and explores the role of drug levels and immunogenicity (antibody formation) on the efficacy of anti-TNF α therapy and details how monitoring these parameters may help to optimize the management of patients with IBD.

Keywords: anti-TNF α , pharmacokinetics, antibodies, inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD) is a chronic gastrointestinal disease that affects up to 0.5% of the Canadian population [Bernstein *et al.* 2006]. The two common subtypes of IBD are Crohn's disease (CD) and ulcerative colitis (UC). CD is characterized by chronic, relapsing, transmural gastrointestinal inflammation that can involve any part of the gastrointestinal tract while UC only affects the colon and is characterized by contiguous mucosal inflammation. Both conditions primarily manifest in younger patients in their teens and twenties with resultant significant morbidity and reduction in quality of life [Hanauer, 1996].

Biologic therapy and inflammatory bowel disease

There is no known cure for IBD. While proctocolectomy can offer a potential cure in UC, patients may suffer from complications such as pouchitis which can be associated with significant morbidity and impairment in quality of life. Treatment should therefore be directed towards optimizing medical therapy including induction and maintenance of clinical remission, endoscopic mucosal healing and avoiding unnecessary surgery. Conventional nonbiologic therapy includes sulfasalazine and 5-aminosalicylic acid compounds, corticosteroids and the

immunosuppressants azathioprine, 6-mercaptopurine and methotrexate. Unfortunately, these therapies are limited by unwanted toxicity, intolerance or slow onset of action.

The introduction of anti-tumour necrosis factor alpha (anti-TNF α) therapy over a decade ago was a welcome addition to the therapeutic armamentarium and revolutionized the treatment of IBD. TNF α plays a central role in the pathogenesis of a number of chronic inflammatory disorders in the rheumatologic and gastrointestinal disease domains [Papadakis and Targan, 2000]. Infliximab, a murine chimeric anti-TNF α agent, was first approved by the US Food and Drug Administration (FDA) in 1998 for the treatment of moderate to severe CD and leads to steroid sparing, rapid induction and maintenance of clinical remission and promotes endoscopic mucosal healing. Similar efficacy has been demonstrated in UC. In addition, adalimumab, a fully human anti-TNF α has been approved for the treatment of moderate to severe CD. Certolizumab pegol, a pegylated Fab fragment, is approved in the United States and Switzerland but has been denied approval in other jurisdictions.

Natalizumab is a non-anti-TNF α biologic therapy which instead targets α -4 integrin. This agent has shown efficacy but has not been

Correspondence to:

Cynthia H. Seow,
MBBS(Hons), MSc, FRACP
University of Calgary—
Gastroenterology, 3280
Hospital Drive NW,
Calgary, Alberta, Canada
T2N 4Z6
[cynthia.seow@
albertahealthservices.ca](mailto:cynthia.seow@albertahealthservices.ca)

Allen W. Lim, MD, FRCPC
Remo Panaccione, MD,
FRCPC
University of Calgary—
Gastroenterology, Calgary,
Alberta, Canada

approved for general use in IBD due to the rare development of progressive multifocal leukoencephalopathy associated with JC viral reactivation [Sandborn *et al.* 2005; Van Assche *et al.* 2005].

Evidence for biologics

Infliximab is an intravenously administered murine-chimeric monoclonal antibody composed of human constant and murine variable regions. Infliximab works by binding with high affinity to both soluble and membrane-bound forms of TNF α , neutralizing its pro-inflammatory activity [Knight *et al.* 1993]. The efficacy of infliximab has been demonstrated in several landmark trials. In ACCENT I, of 335 CD patients who responded to a single infliximab infusion, 39% entered clinical remission (Crohn's Disease Activity Index Score [CDAI] <150) on 5 mg/kg infliximab scheduled maintenance infusions every 8 weeks, *versus* 21% in the placebo group at week 30 ($p=0.003$). At week 54, 30% were in remission *versus* 17% in the placebo group ($p=0.007$). These patients were also more likely to discontinue corticosteroids (29% *versus* 9%; $p=0.004$). In ACCENT II, scheduled doses of infliximab were also more effective at maintaining and closing perianal fistulae (46% *versus* 23%; $p=0.001$) when compared with placebo [Sands *et al.* 2004]. In the ACT I and II trials, patients with refractory moderate to severe acute UC had a clinical response rate of 45% in the maintenance group *versus* 20% in the placebo group at week 54 following induction and 8-weekly maintenance dosing with infliximab. Similar to CD, infliximab-treated UC patients were also more likely to achieve mucosal healing and to discontinue corticosteroids [Rutgeerts *et al.* 2005].

Adalimumab is a subcutaneously administered recombinant but fully human monoclonal antibody that binds to TNF α . The CLASSIC I trial studied anti-TNF α naïve, moderate to severe CD patients randomized to different induction doses of adalimumab *versus* placebo and evaluated after 4 weeks. Clinical remission (CDAI <150) was attained in 36% of patients on adalimumab *versus* 12% in the placebo group [Hanauer *et al.* 2006]. The CHARM trial, which recruited biologic naïve moderate to severe CD patients on maintenance adalimumab 40 mg weekly or biweekly, demonstrated remission rates of 41% *versus* 12% in the placebo group ($p=0.001$) at week 56, with a higher proportion in the treatment group discontinuing corticosteroid use (29% *versus* 5%; $p<0.001$) and achieving fistula

closure (33% *versus* 13%; $p=0.016$) by week 56 [Colombel *et al.* 2007]. In the GAIN study, a higher proportion of patients receiving adalimumab achieved remission after 4 weeks *versus* placebo (21% *versus* 7%, $p<0.001$) despite a previous intolerance or loss of response to infliximab [Sandborn *et al.* 2007c].

Certolizumab pegol is a pegylated humanized Fab' fragment that also targets TNF α . PRECISE I randomized 662 patients with CD to induction doses of certolizumab *versus* placebo. Patients with an elevated C-reactive protein (CRP) (≥ 10 mg/l) had a significant response at weeks 6 and 26 on certolizumab compared with placebo (22% *versus* 12%, $p=0.05$) [Sandborn *et al.* 2007a]. In PRECISE II, patients who responded to induction doses of certolizumab were randomized to maintenance certolizumab every 4 weeks or placebo and followed to 26 weeks. Remission was achieved in 48% on maintenance certolizumab *versus* 29% in those on placebo ($p<0.001$) [Schreiber *et al.* 2007].

Despite their efficacy, 20–30% of CD patients started on anti-TNF α therapy do not respond and remain symptomatic [Van Assche *et al.* 2005; Sands *et al.* 2004; Hanauer *et al.* 2002]. The proportion is even higher in acute refractory UC at 30–40% [Rutgeerts *et al.* 2005]. Furthermore, patients who respond initially may lose response or become intolerant of the anti-TNF α agent. While switching anti-TNF α agents may be an option in patients who are failing first-line anti-TNF α therapy, patients were less likely to achieve remission after switching therapies [Sandborn *et al.* 2007c]. Factors contributing to primary and secondary anti-TNF α failure include suboptimal dosing, increased rates of drug clearance, development of immunogenicity and mechanistic escape. Despite this, anti-TNF α therapies still have a niche role in managing severe refractory IBD and therefore developing strategies to optimize response seem intuitive. This review explores the current literature on one such strategy, utilizing measurements of drug trough levels and the presence or absence of anti-TNF α antibodies as an aid to clinical decision making in IBD.

Antibody and drug assays in anti-TNF α therapy

At present, in North America, there is one commercially available anti-TNF α antibody and serum assay available through Prometheus Laboratories, Inc., San Diego, CA. While antibodies against TNF α which are more humanized

Table 1. Interpretation of anti-tumour necrosis factor alpha (anti-TNF α) trough serum and antibody levels.

	Drug trough level ($\mu\text{g/ml}$)	Drug trough status	Antibody level ($\mu\text{g/ml}$)	Antibody status
Infliximab	<1.40	Undetectable	<1.69	Negative
	<1.40	Undetectable	>1.69	Positive
	>1.40	Detectable	Uninterpretable	Inconclusive
Adalimumab	<0.094	Undetectable	<0.128	Negative
	<0.094	Undetectable	>0.128	Positive
	>0.094	Detectable	Uninterpretable	Inconclusive

are generally considered less immunogenic, immunogenicity against anti-TNF α agents is primarily a function of their underlying protein structure and therefore antibodies can still develop against fully human or pegylated antibodies such as adalimumab or certolizumab.

Serum drug levels of infliximab or adalimumab are measured using a microplate enzyme-linked immunosorbent assay that consists of human TNF α coated plates that bind to free infliximab or adalimumab. The anti-TNF α antibodies are then detected using antihuman immunoglobulin γ Fc-specific antibodies conjugated with horseradish peroxidase. Antibodies to infliximab (ATI) or adalimumab (AAA) can only be reliably measured when serum concentrations of the drug are undetectable, as the presence of free drug interferes with the antibody assay. Therefore, serum sampling should ideally be performed immediately before the next infusion or injection, to coincide with trough levels of circulating anti-TNF α .

Prometheus Laboratories set cut-off values of serum infliximab at 1.40 $\mu\text{g/ml}$ and antibodies to infliximab at 1.69 $\mu\text{g/ml}$. Serum infliximab is detectable at concentrations above 1.40 $\mu\text{g/ml}$. ATI are described as positive at levels greater than 1.69 $\mu\text{g/ml}$ when serum infliximab levels are less than 1.40 $\mu\text{g/ml}$ (undetectable circulating infliximab). Negative ATI are reported when ATI levels are less than 1.69 $\mu\text{g/ml}$ and serum infliximab levels are less than 1.40 $\mu\text{g/ml}$. Therefore, serum infliximab may be undetectable either in the presence or absence of ATI. When serum infliximab levels are greater than 1.40 $\mu\text{g/ml}$, the ATI status is reported as inconclusive, as the circulating drug interferes with the assay and makes assessment of antibody status uninterpretable [Baert *et al.* 2003].

The cut-off value used for the detection of AAA is 0.128 $\mu\text{g/ml}$. As with ATI, AAA cannot be measured if circulating levels of adalimumab are

elevated above a baseline level of 0.094 $\mu\text{g/ml}$. Therefore, patients with elevated levels of adalimumab above 0.094 $\mu\text{g/ml}$ are classified as antibody inconclusive [Karmiris *et al.* 2009]. Table 1 summarizes the interpretation of anti-TNF α trough serum and antibody levels.

Antibodies to anti-TNF α therapy

ATI have been shown to correlate with infusion reactions and poorer clinical outcomes including a shorter duration of response and less likelihood of attaining clinical remission by neutralizing bio-available infliximab [Hanauer *et al.* 2004]. The proportion of CD patients positive for ATI at week 54 were documented as 14% in the ACCENT I trial, 17% in ACCENT II, both of which involved scheduled maintenance infusions [Sands *et al.* 2004; Hanauer *et al.* 2002]. Antibody formation against infliximab is significantly higher at 61% with episodic compared with 16% with maintenance infusions in CD patients [Hanauer *et al.* 2004]. ATI positivity has been reported to be as high as 41% following induction and scheduled maintenance infusions of infliximab for steroid refractory UC [Seow *et al.* 2010]. While pharmacologic studies indicate that infliximab clearance is similar in rheumatoid arthritis, ankylosing spondylitis and Crohn's disease, the mechanisms underlying the increased immunogenicity in UC patients remain uncertain as pharmacokinetic studies specific to this disease subgroup have not been reported. However, it is possible that disease-specific factors promote early formation of immune complexes in UC patients resulting in a more rapid clearance of infliximab [Seow *et al.* 2010].

Several studies have investigated strategies to reduce immunogenicity. While pretreatment with corticosteroids prior to an infliximab infusion may reduce antibody levels, there was no significant difference in the proportion of patients who developed detectable antibodies nor did this strategy ameliorate infusion reactions [Farrell *et al.* 2003].

Earlier studies have demonstrated that immunosuppressive agents reduces immunogenicity in patients receiving episodic infliximab infusions but not in patients receiving scheduled maintenance infusions [Baert *et al.* 2003]. Emerging data from the SONIC trial presented at the American Society of Gastroenterology meeting in 2008 and the American Association of Gastroenterology meeting in 2009 demonstrated a lower proportion of patients on concomitant maintenance infliximab and azathioprine developed antibodies when compared with scheduled maintenance monotherapy with infliximab in immunosuppressive and biologic naive early CD patients. The concurrently treated patients were also more likely to achieve and maintain clinical and endoscopic remission [Sandborn *et al.* 2008b, 2009]. However, investigators from the COMMIT trial reported at the American Society of Gastroenterology meeting in 2008 that in corticosteroid refractory CD patients, there was no significant difference in the proportion of patients achieving induction and maintenance of remission in patients on combination therapy with infliximab and methotrexate *versus* infliximab alone [Feagan *et al.* 2008]. Important patient differences exist, as the patients in the SONIC trial were started on combination therapy early in the course of their disease suggesting combination therapy may be more successful with early intervention and this may influence future antibody development.

Adalimumab, though once considered less immunogenic because of its fully human structure and subcutaneous administration, is not exempt from antibody development though less information on the prevalence and clinical significance of AAA exists. AAA positivity was reported to be 2–4% in CLASSIC II and as high as 9.2% in a study by Karmiris and colleagues in patients on maintenance adalimumab [Karmiris *et al.* 2009; Sandborn *et al.* 2007b]. AAA positivity was associated with lower drug levels of adalimumab but not injection-site reactions [Karmiris *et al.* 2009].

However, antibodies to anti-TNF α agents may not be the best surrogate marker for bioavailability nor the best predictor of clinical outcome. In CD patients receiving maintenance infliximab up to 52 weeks, there were equal numbers of ATI-positive and ATI-negative patients who discontinued treatment. More importantly, both of these groups had undetectable trough levels of

infliximab and lower rates of clinical and endoscopic remission when compared with antibody inconclusive patients with adequate serum levels of infliximab [Maser *et al.* 2006]. Similar results were found in steroid refractory UC patients receiving infliximab, suggesting that drug trough levels are better at predicting maintenance of remission. It has been demonstrated that low serum trough levels of infliximab 4 weeks after the initial infusion correlated with antibody formation at a later date [Seow *et al.* 2010; Vermeire *et al.* 2007]. These findings suggest that anti-TNF α antibodies serve as a surrogate measure of low drug trough levels and that early drug bioavailability is the predictor of subsequent antibody development.

Serum trough drug levels

Detectable trough levels of infliximab in patients receiving maintenance infusions for CD were associated with significantly higher rates of clinical remission when compared with patients who had undetectable trough levels (82% *versus* 6%; $p < 0.001$) [Maser *et al.* 2006]. In keeping with more favourable outcomes, these patients also demonstrated lower CRP levels and were more likely to achieve mucosal healing at endoscopy. Conversely, treatment failure with lower levels of clinical remission and endoscopic improvement was associated with low serum levels of infliximab. In steroid refractory UC, a detectable serum infliximab trough level was associated with higher remission rates (69% *versus* 15%; $p < 0.001$) and endoscopic improvement (76% *versus* 28%; $p < 0.001$). The same study also demonstrated that undetectable serum trough levels of infliximab were associated with significantly higher rates of colectomy (55% *versus* 7%, odds ratio 9.3; $p < 0.001$) [Seow *et al.* 2010].

Therefore, in both CD and UC, clinical and endoscopic remission are associated with maintaining detectable trough levels of infliximab. Measurement of trough levels therefore can be used to optimize response to infliximab. There is less data available on adalimumab, however, similar to infliximab, an existing study has demonstrated that low serum trough levels of adalimumab in CD were associated with higher failure rates and long-term discontinuation of adalimumab [Karmiris *et al.* 2009].

Diminishing response continues to be a major problem with anti-TNF α therapy. As maintaining detectable infliximab and adalimumab trough

Table 2. Recommended interventions in patients who have failed or lost response to anti-tumour necrosis factor alpha (anti-TNF α) therapy after appropriate disease reassessment.

Detectable trough level	Anti-TNF α antibodies	Recommended intervention
No	Negative	Shorten duration between infusions/injections or dose escalate.
No	Positive	Switch to a different anti-TNF α agent. If persistent nonresponse, switch drug class
Yes	Inconclusive	Switch drug class

levels is associated with higher rates of remission and endoscopic healing, it has been postulated that increasing anti-TNF α levels may recapture patients losing response. This can be achieved with infliximab by escalating the dose from 5 to 10 mg/kg or shortening the dosing interval to 7 or 6 weeks. In both the ACCENT I and II trials, CD patients who had developed recurrent flares on 5 mg/kg of infliximab either had their dose escalated to 10 mg/kg or their dosing interval shortened, the resulting increase in serum trough levels led to recapture of remission in two thirds of the patients [Sands *et al.* 2004; Hanauer *et al.* 2002]. In the ATTRACT trial of rheumatoid arthritis patients on maintenance infliximab, decreasing the interval between doses appeared to be more beneficial in increasing serum infliximab levels than escalating individual doses [St Clair *et al.* 2002].

A recent study by Afif and colleagues examined the clinical utility of measuring infliximab and ATI (termed human antichimeric antibodies [HACA]) in 155 IBD patients (CD, UC and indeterminate colitis). The main indications for testing were loss of response or partial response after the initiation of infliximab. In patients with subtherapeutic infliximab levels (defined by the authors as an undetectable trough concentration or an infliximab concentration <12 μ g/ml at 4 weeks after infusion) and negative ATI, dose escalation was associated with a higher clinical response when compared with switching to a different anti-TNF α (86% *versus* 33% $p < 0.016$). However, in HACA (ATI) positive patients, switching to another anti-TNF α was associated with a 92% response rate *versus* 17% with dose escalation ($p < 0.004$) [Afif *et al.* 2010].

In the CHARM and CLASSIC II trials with adalimumab, 27–46% of patients required their dosing interval increased from biweekly to every week in order to restore response [Colombel *et al.* 2007; Sandborn *et al.* 2007b]. Similarly, Karmiris and colleagues demonstrated that an increment in

serum trough levels from 4.8 to 9.4 μ g/ml could be achieved with a change in dosing schedule from biweekly to weekly with a subsequent improvement in clinical response. Those who failed to respond to dose escalation continued to have low to undetectable levels of adalimumab [Karmiris *et al.* 2009].

To summarize, the recommended interventions in patients who have failed or lost response to anti-TNF α therapy are shown in Table 2. First, the clinician should perform a disease reassessment checking clinical, radiologic or endoscopic parameters to ensure if symptoms are due to active inflammation. In the absence of active disease, then alternative explanations for the patient's symptoms need to be investigated. However, if active disease is documented, the clinician should then determine whether detectable trough levels of the anti-TNF α agent are present. It is recommended that a trough measurement rather than a timed nontrough postinfusion measurement (e.g. a 4-week postinfusion infliximab concentration) is obtained as there is currently insufficient pharmacokinetic data on timed infliximab drug levels in UC, nor timed adalimumab drug levels in CD. If patients have a detectable trough level in the absence of a clinical response, a switch in drug class (different mechanism of action) should be considered. In the absence of detectable trough levels and antibodies, strategies to increase circulating drug levels by shortening the duration between infusions/injections or dose escalating may re-induce response. Lastly, in patients with no detectable drug due to the presence of ATI/AAA, the patient may benefit from a switch to a different anti-TNF α agent or in the setting of persistent nonresponse (continuing active inflammation), then switching to a different drug class.

Conclusion

Over the last decade anti-TNF α biologic therapies have revolutionized the management of IBD, however optimization of these therapies is

still required. Circulating drug levels and antibody status have long been recognized as important biomarkers in predicting clinical response. Scheduled maintenance rather than episodic therapy reduces immunogenicity, however the presence of antibodies should not be used as the primary marker of bioavailability as these antibodies are merely a reflection of low circulating drug levels. Maintaining detectable serum infliximab and/or adalimumab trough levels is vital in retaining clinical and endoscopic remission in both CD and UC, and preventing colectomy in the setting of UC. Concomitant therapy with azathioprine or methotrexate may help maintain higher trough levels of infliximab and the final results of the SONIC and COMMIT clinical trials are eagerly awaited.

Ultimately, the presence of detectable anti-TNF α trough levels is paramount in optimizing remission on biologics. In the setting of nonresponse or diminishing response to anti-TNF α agents, an interpretation of the trough level in combination with anti-TNF α antibody status will allow appropriate decisions regarding escalating doses or switching therapies to be undertaken.

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