EDITORIAL

Strategies for overcoming anti-tumor necrosis factor drug antibodies in inflammatory bowel disease: Case series and review of literature

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Abstract

Anti-tumor necrosis factor (TNF) biologics are currently amongst the most widely used and efficacious therapies for inflammatory bowel disease (IBD). The development of therapeutic drug monitoring for infliximab and adalimumab has allowed for measurement of drug levels and antidrug antibodies. This information can allow for manipulation of drug therapy and prediction of response. It has been shown that therapeutic anti-TNF drug levels are associated with maintenance of remission, and development of antidrug antibodies is predictive of loss of response. Studies suggest that a low level of drug antibodies, however, can at times be overcome by dose escalation of anti-TNF therapy or addition of an immunomodulator. We describe a retrospective case series of twelve IBD patients treated at the University of California-Irvine, who were on infliximab or adalimumab therapy and were found to have detectable but low-level antidrug antibodies. These patients underwent dose escalation of the drug or addition of an immunomodulator, with subsequent follow-up drug levels obtained. Eight of the twelve patients (75%) demonstrated resolution of antidrug antibodies, and were noted to have improvement in disease activity. Though data regarding overcoming low-level anti-TNF drug antibodies remains somewhat limited, cases described in the literature as well as our own experience suggest that this may be a viable strategy for preserving the use of an anti-TNF drug. Low-level anti-TNF drug antibodies may be overcome by dose escalation and/or addition of an immunomodulator, and can allow for clinical improvement in disease status. Therapeutic drug monitoring is an important tool to guide this strategy.

Key words: Inflammatory bowel disease; Adalimumab; Anti-tumor necrosis factor; Infliximab; Therapeutic drug monitoring; Drug antibody; Antidrug antibodies; Dose escalation

Core tip: One of the main challenges of anti-tumor necrosis

factor use in inflammatory bowel disease is immunogenicity, or the immune-mediated formation of drug antibodies. Therapeutic drug monitoring allows for measurement of serum drug levels and antidrug antibodies. Previously it was thought that antibody formation was indication to switch to an alternate agent; however, more recent literature, which we review in this article, suggests that a low level of antidrug antibodies can be overcome by dose escalation of the biologic drug and/or addition of an immunomodulator. We describe a small case series of patients in whom this strategy was used, in conjunction with therapeutic drug monitoring, with some success.

INTRODUCTION

Since the initiation of their use for inflammatory bowel disease (IBD) in the late 1990s, tumor necrosis factor (TNF) inhibitors have drastically changed the face of IBD treatment. Anti-TNFs are monoclonal antibodies that inhibit the pro-inflammatory cytokine tumor necrosis factor[1]. These drugs have shown significant efficacy in the treatment of ulcerative colitis (UC) and Crohn's disease (CD)[2]. Currently approved anti-TNFs for IBD in the United States include infliximab, adalimumab, certolizumab, and golimumab.

As the use of anti-TNFs has become more widespread, we seek out tools that will help us to use these drugs more efficaciously and economically. Therapeutic drug monitoring (TDM) allows for measurement of drug levels and drug antibodies. As inadequate serum drug levels and/or development of immunogenicity are possible etiologies for treatment failure, TDM has become a helpful tool to guide therapy.

DRUG LEVELS

In the United States, there are currently commercially available assays to measure serum drug levels of infliximab, adalimumab, certolizumab and golimumab, though the therapeutic cutoffs for certolizumab and golimumab are overall less certain[3]. There are various types of assays, including enzyme-linked immunosorbent assay (ELISA), homogeneous mobility shift assay (HMSA), radioimmunoassay (RIA), reporter gene assay (RGA), and electrochemiluminescence (ECLIA)[4]. It is beyond the scope of this article to discuss details regarding the mechanism of these various assays; however, although analytic properties of the tests vary somewhat, it is thought that overall detection of drug levels and antidrug antibodies (ADAs) correlate with

each other and result in similar interventions and clinical outcomes regardless of the assay used[5]. It should be noted that the newer generation assays allow for the detection of drug in the presence of drug antibodies or when bound to drug antibodies[4].

Numerous studies have clearly demonstrated that therapeutic levels of drug in the serum are associated with induction and sustaining of clinical remission, decreased inflammatory markers, endoscopic healing, and decreased risk for requiring surgery[6-9].

Anti-TNF drug levels are typically measured as a trough. There have been multiple attempts to identify target therapeutic levels; due to variable study end points (including clinical remission, decreased inflammatory markers, endoscopic and mucosal healing and lack of antibody formation), these studies have yielded mixed results[3]. A retrospective analysis in 2015 by Yanai *et al*[10] using an ELISA-based assay demonstrated trough infliximab levels of > 3.8 mcg/mL and trough adalimumab levels of > 4.5 mcg/mL to be 90% specific in identifying patients who failed to respond to dose intensification. Other studies suggest that slightly higher trough levels are necessary for the end point of mucosal healing[11,12].

ANTI-DRUG ANTIBODIES

Formation of antidrug antibodies occurs as an immune response to exposure to the TNF inhibitor, which is a foreign protein. Immunogenicity results in inability of the TNF inhibitor to bind to TNF molecules and also results in increased immune-mediated clearance of the drug from the body[13,14]. Factors thought to predict development of immunogenicity include episodic anti-TNF dosing, lack of induction dosing[15], chimeric monoclonal antibody drugs[16], route of administration, and possibly the presence of certain genetic alleles[17,18]. Commercially available assays for quantitation of antidrug antibodies are currently available for infliximab and adalimumab only[3]. Due to lack of data on this topic with regard to other biologics, this article will focus on application of TDM for infliximab and adalimumab only.

The significance of ADAs has been evaluated in multiple studies. A relatively early study by Baert *et al*[19] in 2003 showed that antibodies to infliximab were associated with infusion reaction and decreased duration of response to the drug. Subsequent studies confirmed that ADAs are associated with decreased drug levels[20,21], and demonstrated association with flare, loss of clinical response, and discontinuation of the anti-TNF drug[20-23].

Dose escalation of the anti-TNF drug is less successful in patients with antibodies and will be discussed further below. Therefore, determining the presence or absence of drug antibodies is a useful tool to guide decision-making.

Determination of a clinically significant level of antibodies has been evaluated in multiple studies. Baert *et al*[19] determined that patients with antibodies

Table 1 Management of secondary loss of response

	No/low antibody level	High antibody level
Low drug level	Increase drug dose	Change therapy (within class or alternate class)
Normal/high drug level	Change therapy (alternate class)	(Not clinically relevant scenario)

to infliximab in a titer ⩾ 8 mcg/mL (using ELISA) had a reduced duration of drug effect. Mazor *et al*[24] showed an inverse correlation between drug levels and antibodies levels, with antibody to adalimumab ⩾ 3 mcg/mL (using ELISA) predictive of active disease. The Yanai study from 2015 determined that antibodies to infliximab > 9 mcg/mL or antibodies to adalimumab > 4 mcg/mL (using ELISA) identified patients who did not respond to dose escalation with 90% specificity[10].

Given the above, prevention of immunogenicity is regarded to be an important consideration in the approach to using a TNF inhibitor. Strategies to prevent antibody formation include maintenance, rather than episodic, dosing[25], and concomitant use of an immunomodulator[26].

However, if antidrug antibodies are identified, the subsequent management strategy is less clear. Options to salvage the current anti-TNF therapy may include dose adjustment of the TNF inhibitor and/or addition of an immunomodulator.

DOSE ESCALATION OF ANTI-TNFS

Dose intensification of the anti-TNF drug, in the form of increased dosage or frequency, can be a useful strategy for the management of secondary loss of response. The success of this strategy has been described with and without the assistance of drug monitoring, but appears to be more cost-effective when TDM is used as evidenced in multiple reviews[14,15,27]. Additionally, as recapturing of response is only demonstrated in patients who achieve measurable increase in drug levels after dose intensification[28,29], TDM may be helpful to better identify patients who will respond to this intervention.

The usefulness of dose escalation in patients with antidrug antibodies, however, is less certain. A 2010 study found that patients who underwent dose escalation of infliximab had a decreased response when antibodies to infliximab were present[30]. Similar findings were noted during a prospective study of patients on adalimumab done in 2014[31]. Vande Casteele *et al*[28] also reported in 2013 that patients with sustained levels of infliximab ADAs were more likely to fail dose adjustment, with a likelihood ratio of 3.6 to fail dose escalation when antibodies to infliximab were > 9.1 U/mL (using HMSA). Based on these data, some treatment algorithms would advocate changing drug therapy if presence of ADAs is identified.

Though studies have been able to identify with relatively reasonable consistency a cutoff beyond which dose escalation is unlikely to be successful (10, 28), the question remains whether lower levels of ADAs can be overcome by manipulation of therapy. This phenomenon has been described, albeit not in great number, in multiple studies throughout the years. Ternant *et al*[32] described as early as 2008 patients in whom infliximab antibodies resolved with dose adjustment, though disappearance seemed to occur spontaneously in other patients. In another prospective study by Bartelds *et al*[33] in 2011, 6 cases were described in which patients had loss of antibodies to adalimumab after dose escalation. Pariente *et al*[34] described a decrease in antidrug antibody titers after dose intensification. More recently, the previously cited retrospective study by Yanai noted that low level of ADAs were overall less specific for failure to respond to dose escalation[10], and a 2015 study by Steenholdt *et al*[35] demonstrated resolution of anti-infliximab antibodies in patients who underwent dose escalation.

Based on the limited information from (but not limited to) the studies listed above, and the theoretical pharmacokinetics of overcoming the presence of antibodies, more recent treatment algorithms advocate that a low level of antidrug antibodies can be overcome[14,28,36-38]. These algorithms suggest that in patients who are found to have low drug level and low level of ADA, dose intensification be performed in an attempt to avoid changing to an alternate drug (Table 1).

ADDITION OF IMMUNOMODULATOR THERAPY

An alternate strategy to mediate immunogenicity to anti-TNF biologics is to use a concurrent immunomodulator.

Concomitant therapy with an immunomodulator is a strategy already used to prevent immunogenicity. Previous data has shown that use of an immunomodulator, in the form of a thiopurine *vs* methotrexate, when used together with a biologic agent has been associated with decreased formation of antidrug antibodies[26]. Use of dual therapy is associated with lower disease activity, increased mucosal healing, increased rates of steroid-free remission, and decreased need to switch to an alternate drug. These findings are evidenced in multiple studies, including the SONIC trial[39-41]. This benefit has been postulated to be at least in part related to decreased immunogenicity of the biologic therapy when an immunomodulator is used. Additionally, studies do not show significant increase in adverse events such as malignancy, infection or death when using combination therapy *vs* monotherapy[42].

There is limited data regarding the addition of an immunomodulator drug after antidrug antibodies have already formed, but it suggests that this may be a viable strategy. In a small retrospective study of 5 patients who developed antidrug antibodies and loss of response to infliximab, Ben-Horin *et al*[43] showed

that after addition of an immunomodulator (either azathioprine/6-mercaptopurine or methotrexate), all 5 patients had gradually decreasing levels of ADAs and restored clinical response. A later study by Yarur *et al*[44] showed that 6-thioguanine (6-TG) levels > 125 pmol/8 × 10^8 RBCs correlated with more optimal levels of infliximab, and 6-TG levels lower than this threshold were associated with presence of antidrug antibodies. These studies did not include patients on adalimumab.

Though a distinct cutoff for antidrug antibody levels was not delineated in these studies, they do suggest that the addition of an immunomodulator is a viable strategy when ADAs form. This strategy has not yet been widely added to treatment algorithms, presumably pending the availability of additional supportive data.

PRACTICAL EXPERIENCE

We describe a retrospective case series of patients on anti-TNF therapy that were found to have low-level antidrug antibodies and underwent escalation of drug therapy or addition of an immunomodulator, with subsequent follow-up drug levels obtained. These patients were receiving care at the University of California-Irvine in the 36-mo period from November 2013 to October 2016.

A total of twelve patients on either infliximab or adalimumab were included in the case series - eight patients with CD and four patients with ulcerative colitis. Median patient age was 43.5 years, ranging from 21 to 71 years. Disease activity in all patients was moderate to severe. Disease extent in Crohn's patients disease included ileal, colonic, and ileocolonic disease, with some patients having stricturing or perianal disease. Disease extent in UC patients included either left-sided disease or pancolitis. The median duration of disease (from the time of diagnosis) was 8 years, ranging from 1 to 30 years. Four patients had previously been on an alternate anti-TNF drug. Four patients were being treated concurrently with immunomodulator at the time of initial evaluation. Of note, all patients had been advised to take a concurrent immunomodulator at the time of anti-TNF initiation but eight of the twelve patients had previously declined due to concern for adverse effects.

Of the twelve patients, seven were being treated with infliximab and five with adalimumab at the time of the study. Median duration of treatment on the respective anti-TNF was 18.5 mo, ranging from 4 to > 120 mo. Drug and antibody levels were checked using an ECLIA or HMSA. Reference values were defined as had been previously determined for the respective assays. Indication for checking drug and antibody levels included presence of symptoms and/or active disease noted on endoscopy. All patients had some subjective or objective evidence of active disease at the time that drug level testing was performed. In our experience, most patients either had the test covered by insurance or paid up to about $250 after subsidization from drug company assistance programs, though the list price for drug level testing is as high as $2500.

The median drug levels prior to alteration of therapy were 4.1 mcg/mL and 3.0 mcg/mL for infliximab and adalimumab, respectively. The median antidrug antibody level for infliximab was 5.5 U/mL using HMSA (negative < 3.1 U/mL). The median antidrug antibody level for adalimumab was 3.1 U/mL for patients tested using HMSA (negative < 1.7 U/mL), and was 52 ng/mL for patients tested using ECLIA (negative < 25 ng/mL). The twelve patients were determined to have a low level of antidrug antibody present, which was determined at the clinical discretion of the treating physician.

After presence of low-level antibodies was noted, eleven patients underwent dose escalation of the anti-TNF drug in the form of either increase in drug frequency or dosage, and one patient had an immunomodulator (methotrexate) added. Addition of an immunomodulator was discussed with all of the patients who were not already treated with one, but most patients declined due to concern for side effects. Those who were already on immunomodulator therapy were continued on dual therapy.

Follow-up drug level testing demonstrated resolution of anti-drug antibodies in eight patients (75%). These patients were found to have increase in drug level: Median levels drug levels increased to 20.2 mcg/mL and 7.9 mcg/mL for infliximab and adalimumab, respectively. These patients were also noted to have improvement in disease activity in the form of decreased inflammatory markers and/or symptomatic improvement. The remaining four patients did not have resolution of anti-drug antibodies after dose escalation and were therefore switched to an alternate IBD therapy. Of note, the four patients who did not have resolution of ADAs carried a diagnosis of CD, though given the small study size, it is unclear whether this is significant (Tables 2 and 3).

CONCLUSION

Though IBD treatment continues to evolve, biologic therapies still remain limited in number; therefore it may be prudent to exhaust a drug therapy before switching to an alternate drug. Therapeutic drug monitoring allows for measurement of drug levels and drug antibodies, and has become instrumental in optimizing anti-TNF drug therapy. In the case of active disease, when drug levels are low, dose escalation of the anti-TNF is recommended; when drug levels are high, therapy may need to be changed. Management of antidrug antibodies is an evolving area of interest, as immunogenicity one of the most common reasons for changing drug therapy. Antidrug antibodies have been demonstrated in multiple studies to be associated with decreased drug levels, loss of response to the drug, and active disease. Strategies to prevent antibody formation include maintenance dosing and concurrent use of an immunomodulator. A small amount of data exists about the possibility of overcoming antidrug antibodies, as reviewed above. Several studies have

Table 2 A total of twelve patients on either infliximab or adalimumab were included in the case serie

Patient	Age (yr)	Sex	Diagnosis	Montreal classification	Duration of disease (yr)	Previous anti-TNF therapy?	Immunomodulator therapy?
1	24	M	CD	A2L3B1	5	Y	Previous - MTX
2	46	M	UC	E3	10	N	Previous - 6MP
3	71	M	CD	A3L1B2	4	N	Previous - 6MP
4	31	F	CD	A2L1B2	9	Y	Current - 6MP
5	46	F	CD	A2L3B2p	5	N	None
6	41	M	UC	E2	18	N	Current - AZA
7	53	F	UC	E2	24	Y	Previous - MTX
8	21	M	UC	E3	1	N	Current - MTX
9	67	M	CD	A3L2B1	3	N	None
10	26	M	CD	A1L2B1	11	N	None
11	49	F	CD	A2L3B2	30	N	None
12	25	M	CD	A2L1B2	7	Y	Current - MTX

Montreal classification CD: Age at Diagnosis (A1: Less than 16 years; A2: Between 17 and 40 years; A3: Over 40 years). Location (L1: Ileal; L2: Colonic; L3: Ileocolonic; L4: Isolated upper digestive tract). Behavior (B1: Non-stricturing, non-penetrating; B2: Structuring; B3: Penetrating; p: Perianal). Montreal classification UC: Location (E1: Proctitis; E2: Left-sided; E3: Extensive or pancolitis). M: Male; F: Female; CD: Crohn's disease; UC: Ulcerative colitis; MTX: Methotrexate; 6-MP: 6-mercaptopurine; AZA: Azathioprine; TNF: Tumor necrosis factor.

Table 3 Adjustment therapy at the time of the study

Pt	Dx	Anti-TNF drug	On immuno-modulator?[1]	Reason for TDM	Predrug level	Pre-Ab level	Adjustment in therapy	Post-drug level	Post-Ab level	Resolved ADAs?	Did patient have improvement?
1	CD	ADA	N	Endoscopic disease	3.0 μg/mL	38 ng/mL	Frequency	10 μg/mL	< 25 ng/mL	Y	Symptom improvement; fecal calprotectin
2	UC	ADA	N	Flare symptoms	< 1.6 μg/mL	4.6 U/mL	Dose/ frequency	13.7 μg/mL	< 1.7 U/mL	Y	Symptom improvement; decreased CRP
3	CD	ADA	N	Flare symptoms	3.3 μg/mL	2.6 U/mL	Frequency	5.8 μg/mL	0	Y	Symptom improvement
4	CD	ADA	Y - 6MP	Flare symptoms, Endoscopic disease	2.6 μg/mL	66 ng/mL	Frequency	4.8 μg/mL	< 25 ng/mL	Y	Symptom improvement
5	CD	IFX	N	Flare symptoms	4.1 μg/mL	4.5 U/mL	Dose/ frequency	23.4 μg/mL	< 3.1 U/mL	Y	Symptom improvement; CRP
6	UC	IFX	Y - AZA	Flare symptoms	1.1 μg/mL	8.2 U/mL	Dose	16.9 μg/mL	< 3.1 U/mL	Y	Symptom improvement
7	UC	IFX	N	Flare symptoms; Endoscopic disease	10.4 μg/mL	5.0 U/mL	Added immuno-modulator (MTX)	11.3 μg/mL	0	Y	Symptom improvement; ESR
8	UC	IFX	Y - MTX	Flare symptoms	0	5.5 U/mL	Dose	26.8 μg/mL	0	Y	ESR/CRP
9	CD	IFX	N	Flare symptoms	23.1 μg/mL	8.6 U/mL	Dose	< 1 μg/mL	88.6 U/mL	N	-
10	CD	IFX	N	Endoscopic disease	< 1.0 μg/mL	3.7 U/mL	Frequency	< 0.4 μg/mL	34 ng/mL	N	-
11	CD	ADA	N	Flare symptoms	5.6 μg/mL	3.1 U/mL	Frequency	4.6 μg/mL	113 ng/mL	N	-
12	CD	IFX	Y - MTX	Flare symptoms	< 1 μg/mL	8.2 U/mL	Frequency	8.2 μg/mL	9.0 U/mL	N	-

[1]Refers to concurrent immunomodulator therapy. Pt: Patient; Dx: Diagnosis; TDM: Therapeutic drug monitoring; Ab: Antibody; ADA: Antidrug antibody; CD: Crohn's disease; UC: Ulcerative colitis; ADA: Adalimumab; IFX: Infliximab; AZA: Azathioprine; 6MP: 6-mercaptopurine; MTX: Methotrexate; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

described resolution of ADAs with therapy modification in the form of dose escalation and/or addition of an immunomodulator. Based on this strategy, recent algorithms for management of secondary loss of response now advocate that patients with low drug levels and low level ADAs undergo adjustment of therapy using these two strategies.

Our case series illustrates application of these strategies, with drug levels obtained before and after the adjustment in therapy. In 75% of cases, we were able to achieve resolution of anti-drug antibodies, confirmed with therapeutic drug monitoring, with either escalation of anti-TNF therapy or addition of an immunomodulator. These patients were noted to have improvement in their

disease activity, based on subjective and/or objective measures. With regard to the possibility of de-escalation of anti-TNF dosing or discontinuation of the anti-TNF, the authors of this study generally did not pursue this if patients are tolerating the therapy without adverse effects, due to concern for formation of recurrent drug antibodies.

Based on this literature and our own experience as described, we believe that in certain patients, low-level anti-TNF drug antibodies can be overcome by dose escalation and/or addition of an immunomodulator, and can allow for clinical improvement in disease status. As the efficacy of subsequent anti-TNF drugs generally diminishes in comparison to the initial anti-TNF drug[41], drug manipulation to overcome low-level antibodies may be a valuable strategy to preserve the use of anti-TNFs in IBD; therapeutic drug monitoring is an instrumental tool to assess success or failure of this approach.

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