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MINIREVIEWS

Adalimumab and pharmacokinetics: Impact on the clinical prescription for inflammatory bowel disease

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Abstract

Anti-tumor necrosis factor (TNF) drugs are widely prescribed for inflammatory disease. A loss of response to adalimumab is frequent and the pharmacokinetics of anti-TNF therapy have important implications for patient management. Individual factors such as albumin, body weight, and disease severity based on the C-reactive protein level influence drug metabolism. Adalimumab trough levels are associated with clinical remission. On the other hand, the detection of antibodies is associated with clinical relapse. Immunosuppressive therapy could reduce antibody formation although the clinical impact is not proven. New algorithms are available to provide personalized treatment and adapt the dosage. More data are needed on dose de-escalation.

Key words: Pharmacokinetics; Adalimumab; Crohn's disease

Core tip: We have reviewed all the recent data about the factors that influence Adalimumab pharmacokinetics and the impact for the clinicians in the assessment of inflammatory disease. We looked at the inter patient variability, the drug clearance, antibodies detection, the effect of concomitant use of immunosuppressive.

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INTRODUCTION

Crohn's disease (CD) is a chronic disease due to immune dysregulation of the commensal enteric flora in genetically susceptible individuals. There is overproduction of the tumor necrosis factor (TNF) alpha by monocytes

Table 1 Factors influencing Adalimumab response

Sub-cutanous absorption	Age/sex
	Body weight
	Injection site
Disease activity	CRP
Nutritional condition	Albumin

CRP: C-reaction protein.

macrophages and T cells[1-3].

Therapeutic monoclonal antibodies targeting the tumor necrosis alpha pathway for the treatment of immune disease have been shown to be effective. Adalimumab is a recombinant fully human subcutaneously delivered immunoglobulin G1 monoclonal antibody. It has binding properties and affinities for the soluble and transmembrane form of TNF alpha[4]. Anti-TNF drugs have been approved for use in moderate to severe CD when corticosteroids and/or immunomodulators have failed[5].

Twenty-five percent to 30% of patients show no or limited response to these treatments and treatment becomes ineffective during maintenance therapy in 50% of responders[2,6]. Dose escalation is often necessary to maintain a clinical response[7,8]. In addition, the aim of treatment has changed from sustained corticoid free remission to mucosal healing[9]. Little is known about the exposure - response relationship and the factors affecting it. These factors must be clarified to improve the therapeutic efficacy of these drugs. In addition, the pharmacology of anti-TNF drugs depends on the structure of the antibody as well as the properties of the target antigen[2,10]. All of these data suggest that individualize therapy and dosing are necessary[11].

This review will present the most recent data on the factors influencing Adalimumab pharmacokinetics and their clinical impact in the assessment of inflammatory bowel disease.

Pharmacokinetic variability

Maintaining effective concentrations of anti-TNF drugs is not easy and deciding on the appropriate dose depends mainly on clinical symptoms or biological data. Pharmacokinetic data have recently been shown to help with this decision[2].

There seems to be different types of non-responders with several pathogenic mechanisms causing non-response. It is unclear why certain non-responders to one anti-TNF respond to another one while others require a different drug.

One potential explanation for the lack of response to TNF is incomplete suppression of TNF activity[4]. Suboptimal exposure may be due to underdosing, rapid drug clearance and/or the development of anti-drug antibodies.

Inter-patient variability

The effective dose of each individual must be identified to adjust the doses of anti-TNF during the course of drug absorption. For example, subcutaneous absorption varies among patients due to lymphatic drainage, a smaller volume of the drug than with intravenous administration and the risk of immunogenicity associated with a skin reaction[4]. Subcutaneous absorption is slow, incomplete and variable. It takes between 2 to 8 d to reach maximum plasma concentrations. Fifty percent to 100% of the administered dose is absorbed, depending on age, body weight and injection site[2]. Low albumin as well as high body mass index (BMI) and male sex increase drug clearance as shown with Infliximab[12-14]. Adalimumab concentrations were also negatively associated with C-reaction protein (CRP) and correlated to disease severity (Table 1)[15,16]. Disease type has also been shown to influence drug response because patients with ulcerative colitis seemed to have faster clearance than CD patients. One hypothesis is that the overall inflammatory burden in patients with ulcerative colitis is higher with a greater area of mucosal lesions and a greater loss of medication in the intestinal lumen. These data must be confirmed[4].

While inter-individual levels vary, intra-patient adalimumab levels are relatively stable over time (28 wk of follow-up)[16].

Clearance

Because of their high molecular weight, monoclonal antibodies do not undergo renal elimination or metabolism by hepatocytes[4,12].

The primary route of IgG clearance is the intracellular proteolytic catabolism *via* the reticuloendothelial system with receptor mediated endocytosis. This is a saturable route of clearance[2,4].

ANTIDRUG ANTIBODIES

The drug provokes antibody formation. An inactive drug antibody complex (neutralizing antibody), may result in decreased efficacy. The drug antibody complex can also be cleared, providing an alternative clearance pathway for therapeutic protein[17,18].

Drug and antibody dosing can be performed. In clinical practice, Maser *et al*[19] first described the correlation between detectable infliximab trough levels and improved clinical outcomes in CD patients. Results were similar for rheumatoid arthritis[20]. Baert *et al*[21] first reported that patients with anti-infliximab antibodies lost the response to therapy faster than those without. Low infliximab trough levels and high antibodies were significantly more prevalent in patients with a loss of response. Most of the time, the detection of antibodies preceded the clinical loss of response by 2 mo.

Numerous studies have confirmed the positive correlation between adalimumab levels and efficacy and the negative correlation between adalimumab antibodies (ADA) and clinical response[11,22,23].

ADA levels vary from 2.6% to 46% and have increased with the development recent methods measuring free and bound ADA[3,15,22,24-27]. The risk of developing antibodies against a second anti-TNF is increased in patients who

develop antibodies against a first anti-TNF agent and in this case, they usually appear during the first year[28-31].

The notion of transient antibodies has emerged, defined as antibodies that disappear for 2 consecutive infusions. These antibodies, which appear after a median of 13.5 mo, represent 23% of antibodies[15]. Paul *et al*[32] studied 13 patients treated with adalimumab without concomitant therapy. Five patients had transient antibodies with no impact on clinical outcome.

Factors influencing antibody formation have been identified: Low early serum adalimumab concentrations have been shown to increase the future risk of antibody formation[15]. These concentrations have predictive value and could help as a guide to optimize treatment before symptoms develop. Higher post induction concentrations decrease the risk of antibody formation[13,15].

The level of antibodies rather than a simple positive/negative status is also important and the cut off is not known. For Yanai *et al*[33] ADA > 4 g/mL is predictive of failure with a 90% specificity while it is 10 ng/mL for Roblin *et al*[34]. All these factors influence efficacy as well as safety due to hypersensitivity reactions.

However, ADA are not the only mechanism because a loss of response was observed in up to 50% of patients while anti-ADA were detected in 10%-15% of the cases[4].

ADALIMUMAB AND ANTI-ADALIMUMAB ANTIBODY DETECTION

Different methods were developed to measure adalimumab and ADA with some limitations for ADA depending on the detection of non-neutralizing antibodies and of free and/or bound ADA. So the method used influences the interpretation of results.

Enzyme-linked immunosorbent assay (ELISA) is the most common test for measuring adalimumab levels and for ADA detection in patient serum. For drug measurement, TNF coated on the assay plate is exposed to patient serum and the presence of adalimumab is revealed by a labelled polyclonal anti-immunoglobulin (Figure 1). All anti-TNF drugs can be detected in this assay and give a signal which explains why adalimumab can be detectable with this test even if the patient is treated with another anti-TNF.

For ADA detection, the therapeutic antibody [Fab or F(ab)2 fragment] is coated on the assay plate and exposed to patient serum and the presence of ADA is revealed by a labelled therapeutic antibody (Figure 2). However, ELISA has the following limitations: Rheumatoid factors, heterophilic antibodies, both may interfere in antibody detection, ELISA may fail to detect IgG4 antibody which may dominate after prolonged immunization and anti-TNF may aggregate on plastic surfaces giving false positive results. More important ELISA is drug-sensitive and only detects free ADA. ADA cannot be detected in presence of the drug as they are complex with a risk of false negative results. Thus, certain investigators state that ADA results are inconclusive if drug levels are elevated in sera testing negative for ADA because of the presence of antibody-drug complex[35].

Different methods have been developed to overcome this problem. Separate drug-antibody complexes by acid dissociation (pH shifting) were proposed and certain authors found that 20% more ADA could be detected. Indeed the level of ADA is underestimated as they are detected only if the concentration of antibody exceeds that of the drug in the serum[36]. In a variant of this assay, the pH shift anti-idiotype antigen-binding test (PIA) was developed in which rabbit anti-idiotype Fab is added to inhibit re-formation of ADA-drug complexes (PIA)[37]. However by this process, incomplete dissociation, re-formation of complexes or even irreversible destruction of ADA binding epitopes may occur. In another test, the drug was used as a capture antibody and anti-lambda antibody was used as a detecting antibody[38].

Fluid assays were also developed to measure drugs and ADA. In the PIA, immunoglobulins from patient sera were aggregated on a protein (Sepharose) and the presence of ADA was revealed by radiolabelled anti-TNF or F(ab)2 (to avoid rheumatoid factor interference). In the homogeneous mobility-shift assay (HMSA), a fluorescent labelled anti-TNF was used to capture free and bound ADA were separated by size exclusion high performance liquid chromatography (unclear)[39]. However, as complexes could be artificially split during chromatography, non-neutralizing ADA *in vivo* could be detectable by PIA or HMSA with no real clinical relevance.

The last assay was the cell based reporter gene assay (RGA)[40]. This is a functional test based on the detection of TNF activity. It is less sensitive than ELISA and HMSA but highly specific for the clinical response because it detects anti-TNF activity and neutralizing anti-drug antibodies alone thus mimicking the effect of ADA *in vivo*. Steenholdt *et al*[41] recently showed that unlike HMSA and PIA which gives false positives, the results of ELISA and RGA were correlated.

The clinical relevance of low concentrations of ADA that are not detectable in drug sensitive assays has not be clarified and ELISA is actually the most commonly used test because it is easy to perform, less expensive and correlated to the cell assay detecting neutralizing ADA. However, a blood sample should be taken before the next injection and testing should not be performed on blood obtained close to when the drug is administer to be sure to measure ADA without drug interference.

CONCOMITANT USE OF IMMUNOSUPPRESSIVE

Theoretically the effect of concomitant use of immunosuppressive therapy is to reduce antibody formation, to increase the anti-TNF alpha drug in serum and to decrease drug clearance for better clinical outcomes[1].

Two studies have shown that combination therapy minimizes the immunogenicity for Infliximab and Adali-

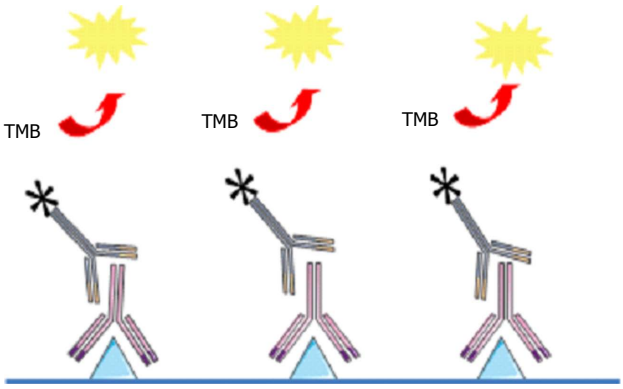

Figure 1 Adalimumab detection. TMB: 3,3',5,5'-Tetramethylbenzidine.

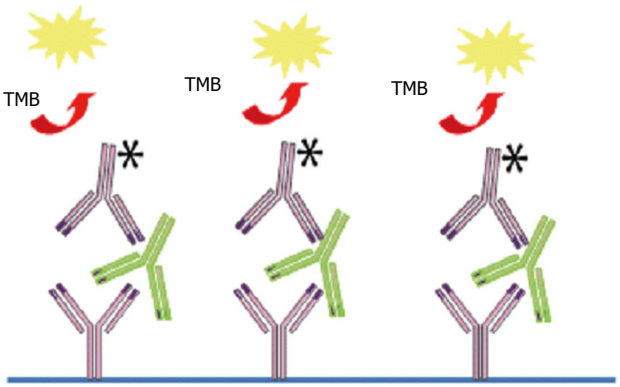

Figure 2 Anti-adalimumab antibodies detection. TMB: 3,3',5,5'-Tetramethylbenzidine.

mumab[42,43]. In Classic 2, 2.6% (n = 7) of 269 patients developed antibodies to Adalimumab and none of the patients with concomitant immunosuppressive therapy had antibodies. Among the 7 patients with antibodies, 43% were in remission 24% and 29% at week 56. A recent study by Baert *et al*[15] confirmed that concomitant use of immunosuppressive therapy prevented antibody formation. In a retrospective analysis of 148 patients, a low serum adalimumab concentration in monotherapy was found to increase the risk of antibody formation. On the contrary, a high post induction drug concentration decreased the risk of antibody formation[15].

However, in their meta-analysis Paul *et al*[3] and Mazor *et al*[22] found that concomitant immunosuppressive therapy did not influence adalimumab levels. In a retrospective study among 217 patients treated with adalimumab, van Schaik *et al*[43] found no beneficial effect of immunosuppressive co-medication for antibody formation. The limit of the study is that they did not evaluate clinical response.

A cut off value for adalimumab levels ranged from 4.8 to 5.9 g/mL whatever the method of measurement for a clinical benefit[3].

However it is important to emphasize that the cut off value depends on the dosing method which is often different in published studies. In addition most of the assays were not compared.

Clinical utility of therapeutic drug monitoring

Long lasting remission of CD can be optimized by maintaining adequate drug levels and preventing antibody formation. Defining predictors of response to anti-TNF alpha and indications for dose escalation will help clinicians choose the best therapy for the appropriate IBD patients with to maximize efficacy and minimize toxicity.

Dose escalation to weekly therapy was needed in 16 (4%) of patients during the 1st year of adalimumab therapy in a prospective study of 201 patients[44]. CRP at week 12 was predictive of clinical efficacy. Azathioprine decreased the probability of dose escalation in this study. In the CHARM trial of 260 patients, 27.3% changed to weekly dosing during the first year and an additional 13.1% changed to weekly dosing during the second year. In another study, 168 patients were followed-up for a median of 20.4 mo. All failed to response to infliximab. Sixty-seven percent responded to Adalimumab at week 12, 65% had to step up to 40 mg per week and 71% responded to the dose escalation. Discontinuation was related to low adalimumab levels and the presence of antibodies[24].

Dose escalation is effective for managing secondary loss of response in CD. One study followed-up 92 patients for 170 wk who achieved a primary response. Eighty percent had clinical response after dose escalation and 56% experienced tertiary loss of response[45]. For ulcerative colitis the rate of escalation was 38.4% for early non responders. At week 52, 25% were in remission[46]. A high body mass index (BMI) and non-response to infliximab were predictive for a dose escalation[7]. There are no pharmacologic data in these studies.

Pharmacokinetics can help select patients who will benefit from dose escalation. A study on mucosal healing has confirmed the association between trough adalimumab levels, clinical remission and mucosal healing[47].

Roblin *et al*[47] explored the clinical utility of therapeutic drug monitoring of Adalimumab in a prospective observational study. The cut off for adalimumab blood levels was 4.9 g/mL. They demonstrated that patients with low blood levels and no antibodies had a better response than patients with antibodies whatever the blood level of drug. The presence of antibodies was related to nonresponse to adalimumab.

The induction phase of treatment also influences antibody formation: Baert *et al*[15] showed that low early drug concentration after induction influenced the risk of antibody formation. These findings show the predictive value of measuring serum adalimumab concentrations early to guide treatment optimization before antibody formation and symptom occurrence. Patients with more severe inflammation require higher than average drug doses to obtain the necessary degree of drug exposure and optimum results.

The reason for discontinuation of infliximab was a clear clinical predictor of response to adalimumab. Among the primary non-responders to infliximab, short-term response to adalimumab was 36% compared to

83% in those who discontinued infliximab for other reasons. There is a clear relationship between serum drug concentrations, clinical effect and long term efficacy.

Mucosal healing has emerged as a major therapeutic goal in IBD. Roblin *et al*[47] studied the association between therapeutic drug monitoring of ADA and mucosal healing among 40 patients. They have shown that therapeutic drug monitoring of ADA was associated with clinical remission in IBD patients and the negative impact of immunogenicity. Median ADA trough levels were significantly higher in patients who achieved mucosal healing. The optimal cut-off value of ADA trough levels for predicting mucosal healing was generally similar to that observed for clinical remission.

Few studies have explored anti-TNF dosage reduction[48]. Baert *et al*[49] recently explored reduction in IFX dosage. For adalimumab, dose de-escacalation to every 2 wk after successful escalation was possible in 63% of patients. There are no pharmacokinetics data in this study.

One study evaluated Adalimumab doses in 6 patients treated after surgery for CD. Adalimumab trough levels in patients with clinical or endoscopic levels were lower than in those in clinical remission after a 2 years of follow-up[50]. More studies are needed to confirm these data.

CONCLUSION

Anti-TNF drugs are extensively prescribed for inflammatory diseases. Loss of response to adalimumab is frequent and the pharmacokinetics of anti-TNF therapy has important implications for patient management. The pharmacology of adalimumab is not completely understood in particular drug clearance. Individual factors such as albumin, body weight and CRP level also influence drug metabolism. Recent data have shown that there is a clinical benefit to the drug and antibody dosage for patient management. Adalimumab levels are associated with clinical remission. On the other hand, the detection of antibodies is associated with treatment failure. There is also a non-anti-TNF pathway in some patients with treatment failure and another therapeutic should then be proposed. New algorithms are available to provide personal treatment and dose adaptations. More data are needed for dose de-escalation. Monitoring drug levels and optimization of treatment without clinical relapse has not been confirmed in clinical practice.

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