

REVIEW ARTICLE

Treatment failure with antagonists of TNF- α : mechanisms and implications for the care of patients

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ABSTRACT. The use of TNF- α antagonists has substantially improved the care of many patients with inflammatory and autoimmune diseases. However, approximately one third of such patients fail to respond well to treatment, regardless of the antagonist used or of the underlying disease. The mechanisms underlying these failures are analyzed in this review, and proposals made concerning how best to adapt therapeutic decisions in these instances.

Keywords: TNF- α , monoclonal antibodies, biotherapies, rheumatoid arthritis, Crohn's disease, ankylosing spondylitis

The first antagonist of tumor necrosis factor alpha (TNF- α) used in therapeutics was infliximab, following reports of its effects in rheumatoid arthritis (RA) in 1994 [1], and in Crohn's disease (CD) in 1997 [2]. Since then, the field of inflammatory disease treatment with TNF- α antagonists has grown enormously, both as regards the numbers of antagonists available and the diversity of disorders treated. In 2010, there are five TNF- α antagonists approved for the treatment of several inflammatory and auto-immune diseases, as summarized in *table 1*. Three of these antagonists are: anti-TNF- α monoclonal antibodies (mAbs), which are either chimeric (infliximab) or human (adalimumab, golimumab). The other two are certolizumab, a single, humanized anti-TNF- α Fab' conjugated with polyethylene glycol (PEG) and without the Fc domain, and etanercept, a soluble TNF receptor, composed of a protein fusion between the extracellular domain of hTNFR2 and the Fc domain of a human IgG1 (therefore joining two hTNFR2 to one Fc domain). In addition to the already approved indications of treatment, TNF- α antagonists are currently being evaluated with encouraging results in various, additional clinical conditions, including systemic angiitis (Wegener's granuloma and Horton's disease), dermatomyositis, polymyositis, severe uveitis and Behcet's syndrome, Still's disease, and amyloidosis. Unlike the antibody-based antagonists, the soluble receptor, etanercept, is not effective against Crohn's disease. This may be because, as a soluble receptor, it has only limited action on events mediated by membrane TNF- α [3]. This phenomenon presumably also accounts for the incidence of tuberculosis reactivation being lower in etanercept-treated patients than in mAb-treated patients [4]. TNF- α antagonists are not used as first-line treatment. This is partly because they

are expensive: in the range of 12,000 to 18,000 euros per patient and per year. Nevertheless, it is estimated that 40,000 to 60,000 patients in France are treated with TNF α antagonists, and in 2008, the total worldwide sales of TNF- α antagonists reached \$16.4 billion.

These numbers underline the effectiveness of TNF- α antagonists for the treatment of inflammatory and autoimmune disorders. Nevertheless, TNF- α antagonist therapy is not successful in all cases. Some patients suffer from either adverse events or intolerance, although the frequencies of these events have declined following introduction of preventive actions, particularly screening and treatment of latent tuberculosis. These adverse events and intolerance will not be addressed here. Other patients show no improvement under this treatment. About 30% of patients fall into this group for all these antagonists, regardless of the underlying disease. Such treatment inefficacy can be either primary (diagnosed three to six months after the beginning of treatment), or secondary (loss of response after a phase of transitional improvement).

Following such treatment failure, physicians can propose increasing either the dose or the frequency of administration of the drug, changing to another TNF- α antagonist (switch), changing to another, approved biotherapy for the disease, or a combination with another immunosuppressive drug; alternatively, the physician may recommend returning to classical care of the disease, such as surgical amputation of the inflammatory gut. There are currently no formal guidelines for cases of treatment failures with TNF- α antagonists. Surprisingly, in routine care there has been no investigation of individual patients, and the decision of the physician is left to their "personal experience", without any clear understanding of the cause of treatment failure. However, clinical trials

Table 1
TNF- α antagonists approved for the treatment of inflammatory/auto-immune diseases

Generic name (trade name)	Format	Diseases
Infliximab (Remicade [®])	Chimeric IgG1	RA, CD, psoriatic arthritis and plaque psoriasis, UC, AS
Adalimumab (Humira [®])	Human IgG1	RA, JIA, CD, psoriatic arthritis and plaque psoriasis, AS
Etanercept (Enbrel [®])	TNFR2 ECD - IgG1 Fc fusion protein	RA, JIA, psoriatic arthritis and plaque psoriasis, AS
Certolizumab Pegol (Cimzia [®])	Humanized Fab' conjugated with PEG	RA, CD
Golimumab (Simponi [®])	Human IgG1	RA, psoriatic arthritis and AS

RA: rheumatoid arthritis; CD: Crohn's disease; UC: ulcerative colitis; JIA: juvenile idiopathic arthritis; AS: ankylosing spondylitis; ECD: extracellular domain; PEG: polyethylene glycol.

indicate that there are two main causes of treatment failure. The first is an insufficient concentration of the drug in body fluids, which may or may not be related to an immune response against the drug, and the second cause is a true resistance of the disease to TNF- α antagonists. It might be expected that these two mechanisms should lead to different therapeutic approaches. In this article, we will review in more detail, the various mechanisms leading to the failure of treatment with TNF antagonists, and discuss how appropriate investigations could help orientate practice so as to personalize therapeutic decisions according to the features of each patient.

RELATIONSHIP BETWEEN RESPONSE TO TREATMENT AND SERUM CONCENTRATION OF TNF- α ANTAGONISTS

Circulating concentrations of TNF- α antagonist have been evaluated in several studies involving patients treated with infliximab, adalimumab and etanercept. Most of these studies report a direct relationship between response to treatment and concentration of the antagonist.

Trough serum concentrations of infliximab were determined after 54 weeks of treatment, in 428 subjects with active rheumatoid arthritis (RA) and enrolled in a multi-center, randomized, double-blind, placebo-controlled trial (ATTRACT) evaluating four treatment regimens [5]. The values obtained were compared to clinical improvement, measured using the ACR (American College of Rheumatology) response criteria, the reduction from baseline of serum C-reactive protein level, and the progression of radiographic joint damage. As anticipated, infliximab concentrations were related to the dose administered and schedule: the concentrations were lower in patients receiving 3 mg/kg every eight weeks than 10 mg/kg every four weeks, and were intermediate in the two groups with intermediate doses/frequency of administration. There was also a clear relationship between the trough infliximab concentration and the clinical response as assessed by each of the three clinical measures used. An infliximab concentration of 1 mg/L appeared to be a threshold under which the rate of response was significantly lower. These findings have been confirmed by three other studies, which also show that infliximab concentrations after six weeks of treatment for RA predict the response within the following year [6-8]. In the START study evaluating infliximab dose escalation according to

clinical response, patients requiring escalation had lower pre-infusion concentrations of infliximab [9]. In RA patients treated with adalimumab, the highest rate of good response was observed in patients with the highest serum concentrations of adalimumab. This concentration was above 3 mg/L in most patients with a good response [10]. The therapeutic range for etanercept in RA appears to be between 0.5 and 4 mg/L [11, 12]. There is, as yet, no evidence for a lower rate of response in RA patients with low circulating concentrations of etanercept.

The relationship between the response to treatment and the serum concentration of TNF- α antagonists has been also addressed in patients with inflammatory disorders other than RA. For Crohn's disease (CD) treated with infliximab, the rate of clinical remission was higher for patients with a detectable trough serum concentration of infliximab than for patients in whom serum infliximab was undetectable [13]. In patients with psoriasis and initially responding to infliximab treatment, secondary failure was associated with a drop in serum infliximab concentrations, relative to that in patients with a persisting response [14]. In patients suffering from ankylosing spondylitis (AS), a first retrospective study involving 38 patients showed that the circulating concentration of infliximab was lower in non-responders [15]. However, this finding was not confirmed in a larger, double-blind, multicentric study [16]. TNF- α antagonist concentrations were also similar in responder and non-responder AS patients treated with etanercept [15]. These two studies suggest that, in contrast to other inflammatory diseases, the drug concentration may not be the sole determinant of success or failure in AS.

IMMUNIZATION, A MECHANISM LEADING TO LOW SERUM CONCENTRATIONS OF TNF- α ANTAGONISTS

Anti-TNF- α mAbs and etanercept are immunogenic and lead to the production of anti-drug antibodies (ADA) in 1% to 55% of patients, according to different studies. It is difficult to compare the immunogenicity of the different antagonists, as no head-to-head comparison has been done, and because immunogenicity may depend on the administration schedule of the antagonist, its association with other immuno-suppressive drugs and the underlying inflammatory disease. Also, assays detecting ADA may differ in their sensitivity, and the appearance of ADA increases with time [8]. Even patients treated with

humanized or human antibodies may develop ADA, especially if not associated with an immunosuppressant [17]. It has been suggested that etanercept is less immunogenic than anti-TNF- α mAbs [12].

Many studies have concluded that immunization is a major cause of treatment failure in patients receiving TNF- α antagonists, and that it makes a substantial contribution to circulating concentrations of the antagonist being insufficient.

In RA patients treated with infliximab, high levels of ADA have been correlated with undetectable serum infliximab and subsequent escape of the disease [6-8]. Patients requiring infliximab dose escalation due to treatment inefficacy had higher frequencies and levels of ADA [18]. Similar findings have been reported for adalimumab-treated RA patients [10]; however, this study indicated that the ADA titer, rather than their simple presence, is important for treatment failure, as only high levels of anti-adalimumab antibodies predicted treatment failure. In psoriasis patients treated with infliximab and initially responding to treatment, the response was maintained in only 39% with ADA, but in more than 80% without ADA [14]. Therefore, the emergence of ADA predisposes the patient to treatment failure, but durable success is possible even in immunized patients. In CD patients treated with infliximab, ADA are associated with long-term inefficacy [19] and with low infliximab concentrations [20], but the relationship between these two markers and ADA is only significant for ADA concentrations above 8 μ g/mL. In patients failing to respond to infliximab and switched to adalimumab, a sustained response to adalimumab was associated with higher adalimumab concentrations and the absence of ADA [21]. A single study reported no influence of ADA on the response to infliximab in CD patients [22]. Therefore, most studies in RA, psoriasis and CD indicate that the development of ADA significantly contributes to treatment failure, by reducing circulating concentrations of the TNF- α antagonist. In non-responders with anti-infliximab antibodies, the formation of immune complexes *in vivo* between infliximab and ADA has been demonstrated by the infusion of radiolabelled infliximab; these complexes are rapidly taken up by the liver and the spleen [23]. Interestingly, several studies have indicated the TNF- α antagonist concentration may decline several weeks before detection of ADA [8, 20]. Presumably, immune complexes composed of ADA and TNF- α antagonists are rapidly cleared from the circulation by macrophages, accounting for the early fall in the TNF- α antagonist half-life. This would also result in ADA not being detected unless or until they are produced in large amounts. Note that the presence of a TNF- α antagonist in the serum may interfere with assays used to detect ADA. In patients with ADA and treatment failure, increasing the TNF- α antagonist dose is one therapeutic option. Rescue, with recovery of efficacy, increased circulating levels of the antagonist and disappearance of ADA is possible. It is unknown whether these two latter events and recovery of efficacy are related, although this seems likely. However, it should be noted again that the presence of a TNF- α antagonist in the serum may prevent detection of ADA in most assays.

It was initially proposed that ADA may prevent response to treatment by mechanisms other than accelerated clearance, such as anti-idiotypic immunization preventing recognition of TNF- α by the antagonist. However, there is at the population level, a strong relationship between the drop in the antagonist concentration and treatment failure in patients with ADA. It is yet unclear whether alternative mechanisms play a significant role in treatment failure, especially in the few non-responder patients with ADA, but with circulating concentrations of the antagonist within the normal range.

IS IMMUNIZATION THE ONLY MECHANISM CAUSING LOW SERUM CONCENTRATIONS OF TNF- α ANTAGONISTS?

Concentrations of TNF- α antagonists are frequently low in the absence of detectable ADA. This raises the question whether immunization is the only, or even the main, cause of an insufficient concentration of the drug. Low concentrations of the antagonist may precede detection of ADA by many weeks or even months. This has led to the suggestion that low concentrations of TNF- α antagonists may, by themselves, favor immunization against the drug. Although it is not possible to rule out this hypothesis formally, combined clearance of the antagonist and of ADA, as well as interference in assays, appear more likely to account for this finding. On the other hand, there are many cases in which no immunization is detected during the follow-up of patients with initially low levels of antagonist. This is best exemplified in the study of Bendtzen [8]. In a large group of RA patients, they found a correlation between infliximab concentration at week 6 of treatment and the presence of ADA at month 6. However, a significant fraction of patients with initially low infliximab concentrations, remained without ADA. Note also that a large, inter-individual heterogeneity of infliximab serum concentrations has been reported as early as two weeks after the first infusion [5, 16], which appears to be too early to be explained by immunization. Finally, rates of immunization have significantly decreased with improved strategies, such as use of human antibodies, associations with other immunosuppressive drugs and continuous treatments. Despite this, large, inter-individual heterogeneity in serum antagonist concentrations persists. Possibly, the pharmacology of TNF- α antagonists may differ between individuals, independently of any immunization. In a cohort of 274 subjects with AS and treated with infliximab, Xu *et al.* described interindividual variability for clearance and volume of distribution of 34.1% and 17.5%, respectively [24]. In addition to ADA status, white blood cell counts influenced clearance of infliximab, whereas body surface area and sex influenced the volume of distribution. Gender indeed, influences the half-life of TNF- α antagonists, with shorter half-lives in women [25-28]. Whether these parameters influence only infliximab pharmacokinetics or also affect other anti-TNF- α antibodies, and possibly soluble receptors, remains an open question. However, it suggests that the recommended doses of TNF- α antagonists, derived from rates of response in pivotal clinical

studies, may not be optimal for every patient. An insufficient dose and serum concentration, may expose patients to failure, whereas excessive concentrations may favor adverse events, and particularly infections, which are dose-dependent.

In summary, insufficient circulating concentrations of TNF- α antagonists are presumably explained in most cases by the development of immunization. However, this may not be the only mechanism: pharmacokinetic heterogeneity may also contribute to this phenomenon, and thus to treatment failure.

ARE PATIENTS WITH INFLAMMATORY DISEASES EQUALLY SENSITIVE TO TNF- α NEUTRALIZATION?

The relationship between low circulating concentrations of infliximab, presence of ADA and treatment failure has been established since the first studies in RA; the same has subsequently been found for other TNF- α antagonists and several other inflammatory disorders. However, a critical analysis of published data reveals that, in addition to this undoubted reason for treatment failure, there are significant numbers of patients failing to respond despite trough serum concentrations within or even above the therapeutic range (1-10 mg/L for infliximab). For example, 24% of RA patients with trough infliximab concentrations above 10 mg/L display no clinical improvement [5], and the percentage is ~30% in RA patients treated with adalimumab [10]. Both studies demonstrated a huge overlap of antagonist concentrations between responders and non-responders. This demonstrates that, although at the population level the antagonist concentration is a critical indicator of the response, there is large, inter-individual heterogeneity regarding the circulating concentration required to control disease activity. Similar findings have been reported for CD [21].

There is another approach to finding evidence that sensitivity to TNF neutralization differs between individual patients with inflammatory disorders: assessing the outcome after a first TNF- α antagonist has failed and a second is introduced. Clinical experience shows that many patients are rescued, by switching from one antagonist to another. This is consistent with the notion that an insufficient concentration of the antagonist in the first phase of treatment accounted for failure, and that this does not predict failure after switching (because the mechanism of failure initially presumably does not apply to the second drug). Indeed, in a recent study, RA patients previously treated with infliximab and who developed ADA and treatment failure, were switched to adalimumab: the rate of success was good and did not differ from that for naive patients, despite the observation that they developed antibodies against adalimumab more frequently [29].

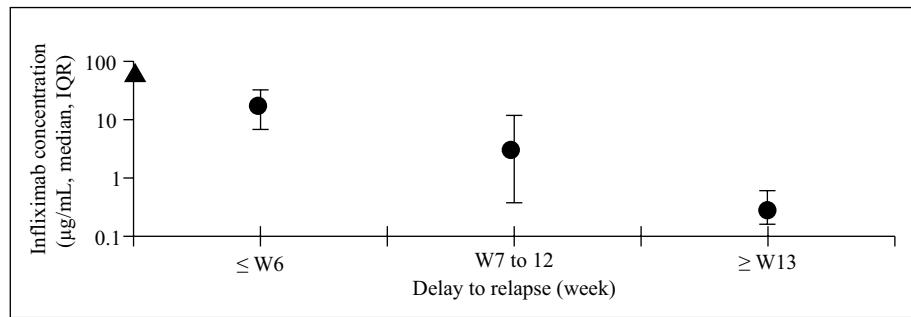
Detailed analysis of large cohorts of patients however, shows that treatment failure with a first TNF- α antagonist predisposes to treatment failure with a second. This has been demonstrated by Hyrich *et al.* in an elegant study [30]. They evaluated a cohort of 6,739 RA patients starting treatment with a TNF- α antagonist. Fifteen months

later, 503 and 353 patients were switched to a second TNF- α antagonist, because of either inefficacy or intolerance. Follow-up of this cohort showed that the risk of a second discontinuation for inefficacy was higher for patients switched because of inefficacy than for either naive patients or for patients switched due to intolerance. This indicates that a fraction of patients failed to respond to a first course of treatment with a TNF antagonist because their disease was poorly sensitive to TNF neutralization. Similarly, Bartelds *et al.* studied RA patients switching from infliximab to adalimumab: treatment failures with the second antagonist were more frequent among patients who had no ADA against the first antagonist than among those who did [10]. This is consistent with patients with no ADA, and therefore adalimumab concentrations within the therapeutic range, suffering from a disease that was poorly TNF- α -dependent. Therefore, these findings reveal forms of RA resistant to TNF- α neutralization in patients with a treatment failure not explained by insufficient concentrations of the drugs and/or immunization. Sensitivity to TNF- α antagonists may differ depending on the stage of evolution of the disease. Moreover, RA, and, more generally inflammatory, disorders, are presumably heterogeneous in their mechanisms, which may not be equally sensitive to TNF- α neutralization.

Inter-individual heterogeneity in the sensitivity to TNF- α neutralization is even more apposite for AS than for RA. The two largest studies performed failed to demonstrate any relationship between response and the circulating concentration of the antagonist, either in patients continuously treated with infliximab [16] or with etanercept [12]. In the infliximab study, an original trial design for one of the two treatment groups allowed the minimal concentration of infliximab required to control AS activity to be determined. In this group of 65 patients, treatment was stopped after the first three infliximab infusions, until relapse occurred. The infliximab concentration at time of relapse was then recorded. As expected, the infliximab concentration at relapse correlated inversely to the time since the last infusion. More importantly, this study showed that approximately one third of patients were not controlled at any time despite a median infliximab concentration of > 15 mg/L, whereas approximately one third relapsed only when median infliximab concentration dropped below 0.3 mg/L (figure 1). Therefore, in the case of AS, the inter-individual heterogeneity in the sensitivity to TNF neutralization massively outweighs inter-individual heterogeneity of TNF- α antagonist concentration, which is also observed, as an explanation of treatment failure.

CONCLUSION

Altogether, these reports indicate that at least two types of phenomenon contribute to treatment failure in patients treated with TNF antagonists. The first is the large inter-individual heterogeneity in circulating levels of the drug, leading, in many patients, to insufficient concentrations of the antagonist, and is often associated with an immunization against it. The second is a variable sensitivity of

**Figure 1**

Patients with AS (n = 65) received infusions of infliximab (5 mg/kg) on weeks 0, 2 and 6. They were then followed until relapse of AS symptoms. Circulating concentrations of infliximab were determined at the moment of relapse. Results show infliximab concentrations according to the delay between the last infusion and relapse. Twenty four, 22 and 19 patients relapsed before six weeks, between seven and 12 weeks or after 13 weeks after the last infusion, respectively.

the inflammatory disease to TNF neutralization. In the case of RA, CD and possibly psoriasis, the first of these two factors is the major contributor to explain treatment failures, whereas for AS, it is the second. However, both causes can be involved in each disease.

Therefore, the cause of failure differs between patients: it is unsound that the physician's decision between increasing dose/frequency, switching to another anti-TNF, or definitive withdrawal of TNF- α antagonists, with or without a switch to another biotherapy, should be based solely on "experience", without even minimal analysis of the cause of failure. Current routine practice is indeed the absence of monitoring of drug concentration or immunization in patients with treatment failure. It is likely that for patients with low concentrations of TNF- α antagonists, increasing the dose/frequency of the antagonist or switching to another TNF- α antagonist would be satisfactory, as recently suggested in preliminary studies by Bartelds *et al.* for RA and Afif *et al.* for CD [10, 31]. By contrast, treatment failures despite concentrations of antagonist within (or even above) the therapeutic range, with or without ADA, presumably reflect forms of the disease less dependent on TNF- α , and therefore less sensitive to TNF- α neutralization. These disorders may correspond either to forms of the disease at a different stage of evolution or different diseases with a shared clinical presentation. For example, analysis at treatment initiation of factors predictive of failure in RA patients highlighted a negative impact of age, disease duration and extent of joint destruction. This suggests that patients suffering from advanced disease may be less inflammatory, and therefore less sensitive to TNF- α neutralization. It would be valuable to conduct clinical trials similar to those reported by Bartelds *et al.* and Afif *et al.* [10, 31], evaluating prospectively and in larger numbers of patients, the impact of drug and ADA monitoring on the therapeutic strategy used for patients failing to respond to TNF- α antagonists. Until relevant results are obtained, it appears reasonable to propose such monitoring in these patients, to help orientate a physician's decision, to document the nature of the underlying disease and to establish cohorts of patients with optimal evaluation of treatment failure mechanism and subsequent follow-up. Unfortunately, monitoring antagonist and ADA concentrations has been difficult, making any such work more complex. Assays

are now available for routine use, and their prescription for patients failing to respond to TNF- α antagonists should be recommended. However, assays available for routine practice may not all be equal. Better evaluation of their performance and a standardization of their use are still needed.

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