

Review

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Immunogenicity of biologic agents in rheumatoid arthritis patients: lessons for clinical practice

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Abstract

Anti-drug antibodies (ADABs) develop in up to a third of patients treated with biologic agents, with such immunogenicity being one of the main reasons for the loss of efficacy observed in an important proportion of patients treated with such agents. The appearance of ADABs has consequences in terms of efficacy and tolerance of the biodrug: the development of ADABs is associated with a poorer clinical response and with an increased risk of adverse effects. Formation of ADABs has been observed with all biologic DMARDs, but anti-TNF agent mAbs appear to be the largest contributors, independent of humanization of the antibody. ADAB identification is technically difficult and not standardized, partly explaining important variations between published studies. A variety of factors can influence the risk of ADAB appearance, some of which are linked to the treatment strategy, such as the combination with synthetic DMARDs or the rhythm of administration of the biodrug, whereas other factors are dependent on the patient, such as the level of inflammation at onset or body weight. The detection of these antibodies and/or the dosage of the biologic agent itself could have consequences for the bedside practice of clinicians and should be well understood. This review of the literature proposes an overview of the data published on the subject to help clinicians manage the biodrugs according to these new concepts.

Key words: immunogenicity, biologic agents, biodrug, anti-TNF, infliximab, adalimumab, etanercept, anti-drug antibody, methotrexate, rheumatoid arthritis.

Rheumatology key messages

- Immunization to therapeutic biologic agents is common in RA patients, especially with anti-TNF mAbs.
- Antidrug antibodies appearance correlates with low serum concentration of the biodrug and loss of efficacy in RA patients.
- The combination of methotrexate and biologic agents decreases the risk of antidrug antibody production in RA patients.

Introduction

Biologic agents, especially TNF inhibitors, have been a major advancement in the management of RA. However, not all patients respond well to these treatments: it has been estimated in registries that ~20–30% of RA patients fail to respond to the first TNF inhibitor and that >20% of patients who initially respond experience a loss of efficacy

within the first 2 years of treatment [1–3]. Interestingly, it has long been shown that in cases in which there is loss of efficacy, clinical response could be restored by switching from the first TNF inhibitor to another, demonstrating that the problem was not the TNF target and suggesting that loss of efficacy could be related to immunogenicity [4, 5]. Indeed, biologic agents are large molecules that are potentially immunogenic, with such immunogenicity being attested by the development of anti-drug antibodies (ADABs). Furthermore, immunogenicity has been observed previously with many therapeutic proteins, such as erythropoietins, insulins, interferons, haemophilic factors, Gaucher or Fabry substitute enzymes and polyvalent IVIGs [6].

Although the literature on ADABs against biodrugs for RA is mainly recent, Elliot *et al.* [7] noticed very early that,

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while at that time infusion of infliximab (formerly cA2) was not systematically performed every 8 weeks but at the time of disease relapse, repeated injections of infliximab led to a progressive decrease of the time to relapse after drug infusion. Elliot *et al.* [7] suggested, as far back as 1994, that this could be the consequence of the immunogenicity of infliximab, presumably due to the chimeric nature of this molecule. This initial observation was the reason for the design of the ATTRACT study, which evaluated three ascending doses of infliximab, alone or in combination with MTX to decrease the immunogenicity of the biologic agent. In that historical study, Maini *et al.* [8] showed an inverse relationship between administered doses and ADA production and a preventive effect of the combination with MTX: anti-infliximab antibodies were observed in, respectively, 53%, 21% and 7% of patients receiving 1, 3 and 10 mg/kg of infliximab alone, vs 15%, 7 and 0% of patients receiving the same infliximab regimens in combination with MTX. That study suggested the potential role of immunogenicity in response failure to biologic therapies in RA.

In this review, we dissect the most recent data from the literature and propose a course of action for daily practice regarding immunogenicity of the biologics. To perform this review, we searched original articles and reviews in PubMed until June 2014 with the following terms: (infliximab or etanercept or adalimumab or golimumab or certolizumab or abatacept or rituximab or tocilizumab) and (immunogenicity or anti-drug antibodies). All papers were read in full text version, and the PubMed search was completed based on the references of the identified papers.

Mechanisms of immunogenicity against biologic agents

For therapeutic mAbs, ADABs may be directed against two sites: the Fab fragment or the Fc fragment (for the latter, mainly the junction between Fc and Fab). The assays developed with only one of these two portions of the antibody have shown that, in the case of infliximab, adalimumab, golimumab and certolizumab, most ADABs are directed against the Fab fragment, and have a neutralizing capacity (i.e. preventing the fixation of the antibody to TNF molecules) [9]. Such immunization could be attributed to an anti-idiotypic reactivity [10], which is a normal reaction of the immune system to the appearance of any novel antibody [11]. This could explain the unexpected finding that humanization did not really influence the immune reactivity to a therapeutic antibody.

By contrast, ADABs directed against the Fc fragment or junction portion (anti-hinge) did not affect neutralizing ability. However, such ADABs form complexes with the drug and increase its clearance.

Two types of ADAB to fusion molecules have been described: one type directed against the receptor, the other against the Fc fragment or junction. ADABs developed against etanercept are not neutralizing [12]. For abatacept, some ADABs have an anti-CTLA-4

reactivity and exhibit a neutralizing activity; others are directed against the Fc or hinge portion [13]. However, it is important to remember that, whether neutralizing or not, ADABs are capable of decreasing the drug availability and thus its activity.

Clinical consequences of ADABs against biologic agents

ADABs are associated with a decrease in biologic agent efficacy

Several studies have shown a clear relationship between disease activity and the presence of antibodies against infliximab or adalimumab. In a cohort of 69 RA patients treated with infliximab ($n=35$) or adalimumab ($n=34$), Radstake *et al.* [14] showed that the clinical response correlated with the levels of ADABs against both TNF inhibitors: 14 of 15 (93%) good responders to infliximab at 6 months had no detectable anti-infliximab antibodies, while 3 of 6 (50%) moderate responders had low levels and all non-responders had medium or high levels of anti-infliximab antibodies. All patients with anti-adalimumab antibodies were non-responders to adalimumab at 6 months. In a Dutch cohort of 235 RA patients treated with adalimumab, Bartelds *et al.* [15] were able to detect the presence of anti-adalimumab antibodies in the serum of 46 (17%) patients at 28 weeks of treatment. The Δ DAS28 of these patients was [mean (s.d.)] 0.6 (1.3), compared with 1.8 (1.4) in patients without such antibodies ($P < 0.0001$). Additionally, they noticed in this cohort that patients previously treated with infliximab who presented anti-infliximab antibodies developed anti-adalimumab antibodies more often than patients previously naive for TNF blockers [15]. A meta-analysis performed on 12 observational prospective cohort studies evaluated that the development of ADABs reduced the anti-TNF response rate (RR) by 68% (RR=0.32, 95% CI 0.22, 0.48) [16].

ADABs also strongly influence the maintenance rates of a good clinical response to both infliximab and adalimumab. Patients who presented detectable ADABs to infliximab required higher doses of the drug and/or shorter intervals between infusions to achieve or maintain a good clinical response [17, 18]. In the Dutch cohort of 272 RA patients treated with adalimumab, Bartelds *et al.* [19] showed that the presence of anti-adalimumab antibodies was associated with a lower proportion of patients with sustained low disease activity (DAS28 < 3.2) and sustained remission (DAS28 < 2.6) at 3 years. After adjustment for the confounding variables (MTX dosage, ESR and CRP), patients with anti-adalimumab antibodies less often achieved sustained low disease activity [hazard ratio (HR) 3.6; 95% CI 1.8, 7.2; $P < 0.001$] or remission (HR 7.1; 95% CI 2.1, 23.4; $P < 0.001$). Anti-adalimumab antibodies also correlated with adalimumab withdrawn for treatment failure (HR 3.0; 95% CI 1.6, 5.5; $P < 0.001$) [19]. Similar observations have been made by others with infliximab [20–22]. The association between ADABs and clinical response was not found for etanercept,

abatacept, certolizumab or tocilizumab [13, 16, 23, 24]. However, the low prevalence of the appearance of ADABs associated with these agents makes it difficult to establish reliable correlations.

ADABs contribute to adverse events associated with biologic agents

The formation of ADABs not only affects the efficacy of biologic agents but also increases the risk of some adverse events, especially infusion reactions. Pascual-Salcedo *et al.* [21] showed that the serum concentration of anti-infliximab antibodies was significantly higher in patients who developed infusion reactions to infliximab than in patients without infusion-related reactions. Interestingly, the concentration of ADABs following infusion reaction fell dramatically before returning to previous values during the next weeks. In the DANBIO registry, patients with detectable ADABs at 6 weeks had an increased risk of treatment withdrawal for adverse reaction during the first year of follow-up than patients without anti-infliximab antibodies (HR 5.06, 95% CI 2.36, 10.84; $P < 0.0001$), and all infusion reactions were observed in patients with detectable ADABs [17 (14%) vs 0 (0%), $P < 0.001$] [22].

ADABs are inversely correlated with biologic agent serum concentration

A close relationship has been noticed between treatment serum concentrations of the drug (concentration measured just before the following injection, or c-trough) and the detection of ADABs. In a series of 106 RA patients from the South Swedish Arthritis Treatment Group receiving infliximab 3mg/kg, it was observed that low or undetectable trough concentrations of infliximab were associated with the presence of anti-infliximab antibodies [25]. In a series of 218 RA patients from the DANBIO registry who underwent infliximab treatment, patients with detectable anti-infliximab antibodies had lower infliximab trough levels compared with those without detectable anti-infliximab antibodies [22].

In the cohort of Bartelds *et al.* [26], at 28 weeks of treatment, the adalimumab trough level varied from undetectable concentrations to 28 mg/l, and the mean trough level was significantly higher in patients without anti-adalimumab antibodies than in patients with detectable antibodies, in a dose-dependent manner. An association was also observed between the adalimumab trough concentration and the quality of the EULAR response to treatment. We will see later what could explain this inverse relationship between c-trough level of the biologic agent and serum concentration of ADABs.

Immunogenicity of the main biologic agents

Many different assays have been developed to measure ADAB serum concentrations, some by biologic agent manufacturers, others by academics. These different assays have led to important variations between studies in the

evaluation of the prevalence of ADABs. Another source of discrepancy is the delay between treatment onset and the time of ADAB evaluation. For instance, the prevalence of ADABs against infliximab has been evaluated as 13% at 1.5 months, 30% at 3 months and 44% at 6 months by Bendtzen *et al.* [27] through to 33% at 1.5 months, 67% at 3 months and 78% at 6 months by Krintel *et al.* [22] with another method of detection. These results demonstrate that, in cases of immunogenicity, the levels of detectable ADABs increase rapidly over time (a point that will be discussed further) and that two different assays may lead to important differences in results [28]. For adalimumab, the proportion of ADAB-positive patients ranged from <1% [29] to 87% [30], but was most often ~20% [31].

It has been suggested that fusion molecules may be less immunogenic than mAbs because only a small proportion of patients (2–5%) developed ADABs to etanercept [32–34], and only 1–3% of patients treated with abatacept developed ADABs (equally with s.c. or i.v. formulations) [13, 35, 36], without any correlation with the clinical response for either product. However, it is important to notice that RF has been suspected to interfere with the detection of ADABs directed against the Fc fragment or hinge portion, the very same portion targeted by fusion molecule ADABs directed against the fusion molecule [37]. However, there is no indication that more ADABs to etanercept and abatacept are detectable in PsA or AS patients than in RA patients. Furthermore, low rates of ADABs have been observed with other antibodies: ADABs to golimumab have been detected in ~6% of patients [38, 39]; detection of ADABs to certolizumab ranged from 5% to 8%, with no evidence regarding clinical parameters [40, 41]; only 0.6% of patients developed anti-tocilizumab antibodies in pivotal trials [42], while 3.5% of patients who received tocilizumab subcutaneously developed antibodies to the agent vs 0% of patients treated intravenously in a trial comparing both formulations of the drug [43], with no correlation between anti-tocilizumab antibodies, adverse events or inefficacy of the drug. Finally, antibodies against rituximab were identified in 3–4% of RA patients [44] and were associated with an infusion reaction in one patient [45].

Thus, three conclusions can be drawn from these studies. First, the identification of ADABs is technically difficult, and there are significant variations between the various assays developed to detect ADABs for each biologic agent. Second, there are important differences in the ability of the different biologic DMARDs to induce an immune response: it seems that infliximab and adalimumab are more prone than others to induce ADABs. It is noteworthy to consider that most academic studies have been performed with these two mAbs, while most studies conducted with the other biologics (antibodies or fusion molecules) have been driven by the corresponding companies. Third, humanization of biologic agents does not appear to be a key point in preventing ADAB formation, as the proportion of patients who develop ADABs to adalimumab, a fully human mAb, is comparable to those who develop ADABs to infliximab, a chimeric antibody with a murine Fab fragment.

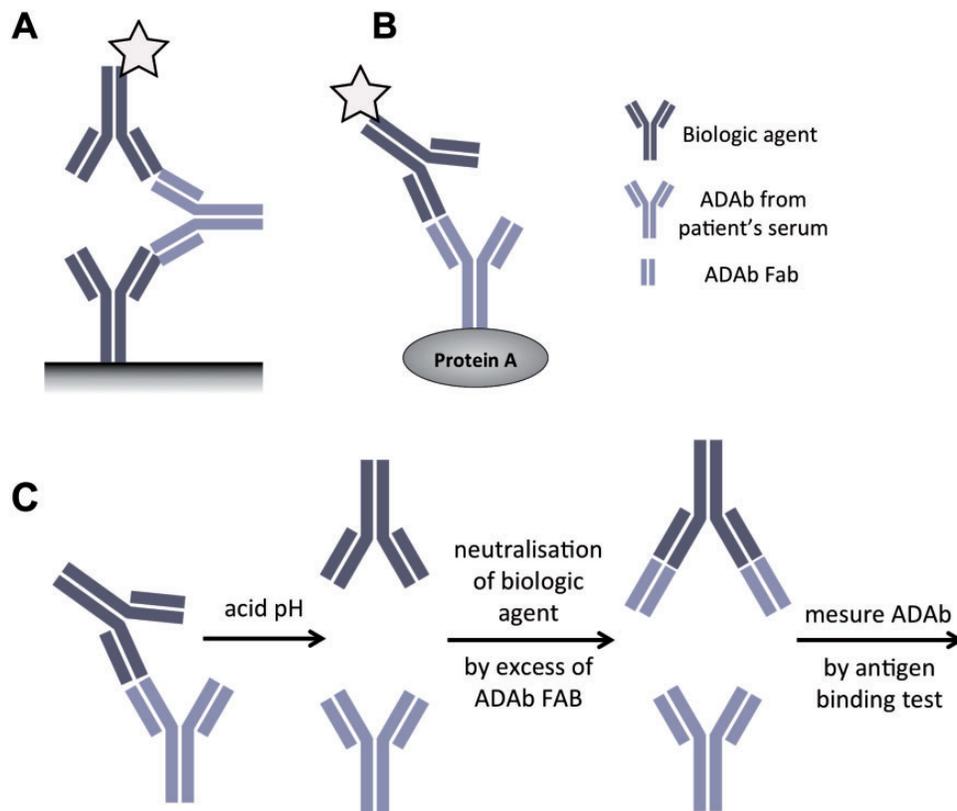
Detection of ADABs

Two techniques are mainly used to detect ADABs: (i) a classical sandwich ELISA, in which the therapeutic antibody, coated on the assay plate, is exposed to patient serum, and the presence of ADABs is revealed by a labelled therapeutic antibody (Fig. 1A); and (ii) an antigen binding test where immunoglobulins from patient serum are aggregated on a protein (Sepharose) and the presence of ADABs is revealed by a labelled therapeutic antibody (Fig. 1B). Both techniques are only able to detect free ADABs, and fail to detect ADABs complexed to the biodrug. As shown in Fig. 2, regarding the immunogenicity of a therapeutic biologic agent, three closely related components are present in the serum: the therapeutic agent itself, the free ADAB and the biodrug-ADAB aggregates. Only free drug and free ADAB concentration are usually measured. Thus, in cases of immunogenicity, a greater amount of drug compared

with ADABs leads to sufficient drug trough concentrations to maintain clinical efficacy, with no detectable ADABs as they are fully complexed to the drug; conversely, a low amount of drug compared with ADABs results in an undetectable concentration of the drug, loss of clinical efficacy and detectable levels of ADABs.

The pH-shift anti-idiotype antigen-binding test (PIA) is another method that has been recently proposed to measure both complexed and free ADABs [46, 47]. In this assay, the ADAB-drug complex is dissociated by lowering the pH before performing a classical antigen-binding test (ABT). This PIA test was compared with the dosage of adalimumab and detection of free ADABs by a classic ABT in a cohort of 99 RA patients with a mean follow-up of 3 years. During this period, ADABs were detected at least once by PIA in 54% of the patients, vs 29% by ABT, and the detection by PIA occurred significantly earlier than by ABT. Interestingly, sustained remission

Fig. 1 Three techniques are used to detect anti-drug antibodies



(A) Sandwich ELISA: the therapeutic antibody, coated on the assay plate, is exposed to patient serum, and the presence of ADABs (light grey) is revealed by a labelled therapeutic antibody. This technique detects only free ADABs. **(B)** Antigen binding test: immunoglobulins from patient serum are aggregated on a protein, and the presence of ADABs is revealed by a labelled therapeutic antibody. This technique detects only free ADABs. **(C)** pH-shift anti-idiotype antigen binding test: The ADABs complexed to the biologic drug are first dissociated by lowering the pH. An excess of Fab ADABs is added to prevent new binding of the drug to ADABs. ADABs are then measured by an antigen binding test. This is the only test that can detect total ADABs from a patient's serum, i.e. both complexed and free ADABs. ADABs: anti-drug antibodies.

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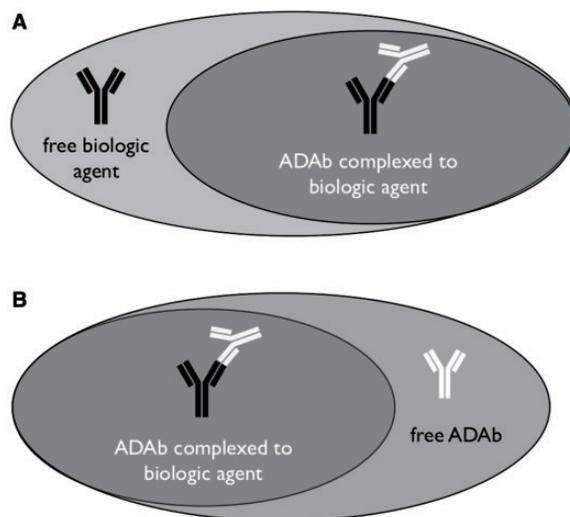
(DAS28 < 2.6) was observed in similar proportions of patients positive or negative for ADABs detected by PIA, while no sustained remission was observed in patients positive for free ADABs detected by ABT. Patients with ADABs detected by PIA were more likely to have low adalimumab trough levels than patients without such ADABs, while patients with ADABs detected by ABT had very low or undetectable adalimumab trough levels. A modelling of the relationship between serum concentrations of adalimumab, ADABs detected by PIA and ADABs detected by ABT was performed as shown in Fig. 3. This study indicates clearly that immunogenicity can be observed even in good responders, that this immunogenicity is associated with decreased trough levels of the drug and that the detection of free ADABs correlates with very low trough levels of the drug and loss of clinical efficacy.

Factors influencing immunogenicity of biologic agents

Inflammation and danger signals

In a cohort of 105 RA patients, Wolbink *et al.* [48] showed that serum infliximab trough levels at 14 weeks were

Fig. 2 The three related components are present in the serum after administration of a biologic agent



First: the therapeutic agent itself, namely the free biologic agent in the left circle in (A) corresponding to the trough concentration of the drug. Second: the free ADABs, in the right circle in (B). Third, the biodrug-ADAB complexes, as shown in the central circle in (A and B); such complexes are undetectable with the usual methods of dosage. In the case of a relative excess of drug compared with ADABs, the biologic agent can be detected in the serum, but ADABs, although present, are not detectable and are instead complexed to a part of the circulating biologic agent. Conversely, in the case of a low level of the biologic agent relative to the ADAB level, free ADABs are detectable, but the biologic agent that is fully complexed to ADABs is not. ADABs: anti-drug antibodies.

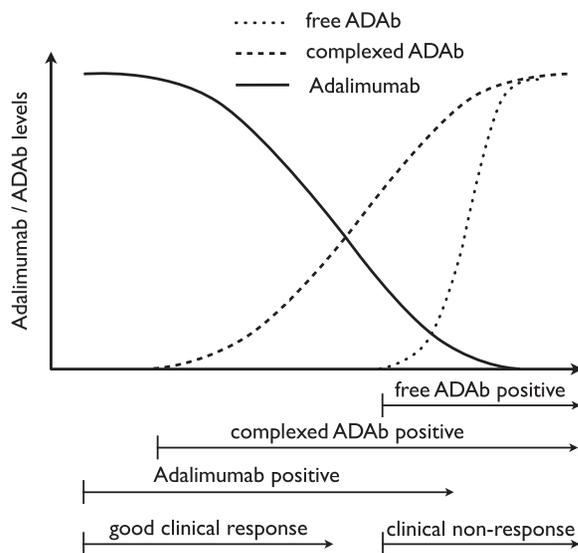
correlated with clinical response to treatment but also negatively correlated with initial CRP levels. Similarly, in a series of 106 RA patients treated with infliximab, Bendtzen *et al.* [27] showed that the serum trough concentration after the first two infusions was clearly influenced by the CRP level at baseline. Clearly, a high disease activity at baseline, with an elevated CRP level and DAS score, was associated with a low infliximab trough concentration after the first two infusions, and this low trough concentration was indicative of an increased risk of ADABs to infliximab at 6 months. These observations could suggest that the high amount of TNF targets at baseline (reflected by the CRP level) consumed a large proportion of anti-TNF agent and is responsible for low trough levels of the drug, thereby promoting the occurrence of ADABs.

On their cohort of 272 RA patients treated with adalimumab, Bartelds *et al.* showed that, among the 28% of patients who developed detectable ADABs, these antibodies occur early in most of the cases, that is, within the first 28 weeks of treatment for two-thirds (67%) of the patients [19, 49] (Fig. 4). Interestingly, this period of treatment introduction corresponds to the period when inflammation is the most prominent and, thus, when the amount of TNF targets is the highest. This could induce low serum concentration of the TNF inhibitor and favour immunogenicity. This highly inflammatory period could also be characterized by high levels of DANGER signals [damage-associated molecular pattern molecules (DAMPs) i.e. HSPs, S100 proteins, reactive oxygen species, microbial DNA, K⁺ efflux] that activate the immune system and could promote the immunogenicity phenomenon. This hypothesis has been explored and confirmed in the haemophilia A field, where the most problematic treatment issue is the development of antibodies against factor VIII. These antibodies occurred mostly within the first 20 days of exposure, and Kurnik *et al.* [50, 51] showed that when the treatment is delivered as a prophylaxis, that is, before any bleeding, it largely reduced the appearance rate of ADABs.

Combination therapy with MTX

Since the first observation by Maini *et al.* [8], other studies have shown that co-administration of MTX reduces the risk of ADAB production against anti-TNF agents, even for non-chimeric agents such as adalimumab [19]. Moreover, Krieckaert *et al.* [49] demonstrated that MTX reduces the immunogenicity of adalimumab in a dose-dependent manner (Fig. 4). In that study, it seemed that a MTX weekly dose of 10 mg was the minimal dose to limit ADAB production in RA patients. A meta-analysis confirmed that the use of immunosuppressive agents, mainly MTX, reduced the proportion of patients treated by infliximab or adalimumab having detectable ADABs by ~41% (RR 0.59, 95% CI 0.50, 0.70) [16]. The mechanism by which MTX influences ADAB production remains elusive: does MTX just limit inflammation and TNF levels, thereby increasing anti-TNF trough concentration, or does MTX have a direct effect on anti-TNF pharmacokinetics?

Fig. 3 Serum concentration of adalimumab, free ADAbs and complexed ADAbs



This model shows a close relationship between the development of ADAbs and decreased serum concentrations of the biologic agent. While there is still enough drug in the blood, all ADAbs are complexed to the drug and are thus undetectable by the usual ELISA and antigen binding tests. It is only when the concentration of the drug is very low that free ADAbs appear and are detectable by these assays. ADAbs: anti-drug antibodies. Adapted from van Schouwenburg PA, Krieckaert CL, Rispens T, Aarden L, Wolbink GJ, Wouters D Long-term measurement of anti-adalimumab using pH-shift-anti-idiotype antigen binding test shows predictive value and transient antibody formation. *Ann Rheum Dis* 2013;72:1680–1686, ©2013, with permission from BMJ Publishing Group Ltd.

Combination therapy with CSs

The influence of steroids is more controversial, the majority of publications showing no effect of concomitant prednisolone use on ADAbs level [17, 27]. A recent meta-analysis confirmed the lack of significant impact of combined treatment with oral CSs and the biologic DMARD on the development of ADAbs [52]. These observations seem in accordance with the fact that the suppressive activity of CSs is predominantly restricted to cell-mediated immunity, with a marginal inhibitory effect on humoral immunity [53].

Serum concentrations of biologic agents

We have previously seen that low serum concentrations of the biologic agent at treatment initiation were associated with the development of ADAbs. In patients who experienced a loss of response and ADAbs development to infliximab 3 mg/kg, adjustment to infliximab 5 mg/kg was followed by the restoration of the clinical response and a decrease in ADAbs levels, while further lowering infliximab to 3 mg/kg led to DAS28 and ADAbs increases [21]. Similar

observations were made by others with adalimumab [26]. Thus, it seems that the maintenance of a constant trough level of the biologic agent is the best guarantee of disease control and the best method for preventing ADAbs development. It is noteworthy that, for these two anti-TNF antibodies, a similar threshold of drug c-trough of between 5 and 10 mg/l was observed to prevent immunogenicity. This is in agreement with the discontinuity theory of the immune response, in which a novel but persistent antigen induces an initial immune response, followed by tolerance if the antigen persists at constant levels, while an intermittent appearance of an antigen promotes a persistent immune response, such as vaccine and vaccine recall [54] (Fig. 5).

In patients on long-term treatment, temporary withdrawal of treatment may occur because of infectious events, surgery or prolonged remission. Such interruptions could favour immunogenicity. In patients treated with abatacept, it has been observed that patients who discontinued their treatment had a higher incidence of immunogenicity than patients who did not discontinue (7.4% vs 2.6%, respectively) [35].

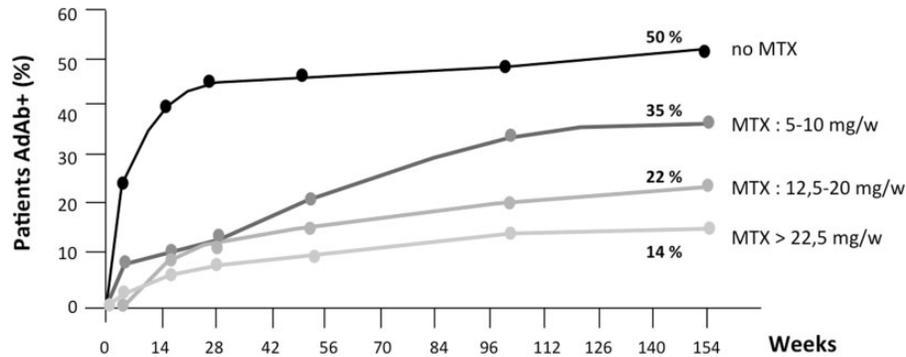
Obesity

Obesity has been associated with a poorer response to several anti-TNF agents [55]. Interestingly, this is even true for infliximab, although the dosage of this agent is adjusted to body weight. However, to our knowledge, obesity has been associated with neither low serum concentrations of the drug or or higher rates of immunogenicity. The influence of all these factors is summarized in Fig. 6.

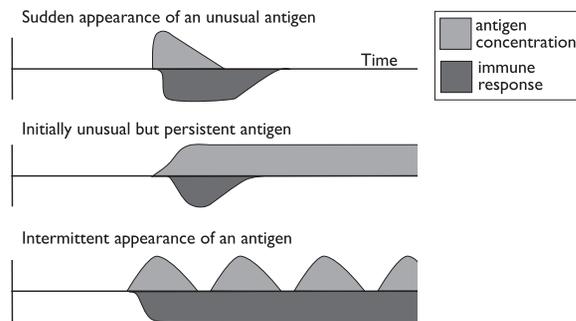
Biologic agent immunogenicity in other disorders

Similar observations have been reported in Crohn's disease. ADAbs have been reported in 10–20% of patients treated with anti-TNF antibodies. The presence of ADAbs is correlated with low levels of the anti-TNF antibody in the serum, both being associated with a higher risk of poor clinical response [56]. Maintained anti-TNF treatment is associated with reduced ADAbs formation compared with episodic treatment, as are concomitant immunomodulators (6-mercaptopurine, AZA or MTX) [57, 58].

In AS, Kneepkens *et al.* [59] showed in an observational cohort study that 31% of patients treated with adalimumab developed ADAbs during a 24-week period of treatment. Consistent with data obtained in RA patients, adalimumab trough levels were higher in ADAbs-negative patients, a significant association was observed between this concentration and clinical response, and a similar threshold of 5 mg/l was observed to prevent immunogenicity. As in RA patients, another study showed that immunization to a first anti-TNF agent determined the response to a second agent [60]. Could potential immunogenicity be an argument for the co-prescription of MTX, even in axial AS? It seems that, in AS, combined

Fig. 4 Percentage of patients developing anti-adalimumab antibodies per baseline MTX dose group

No MTX (black line), low-dose MTX (dark grey line), intermediate-dose MTX (middle grey line) or high-dose MTX (light grey line) was administered concomitantly with adalimumab to RA patients. The frequency of anti-drug antibody (AdAb)-positive patients is shown (according to Krieckaert *et al.* [49]): in most cases, ADABs appear in the first month of treatment, and the combination of MTX (up to 10 mg/week) with adalimumab prevents ADAB production. ADABs: anti-drug antibodies. Adapted from Krieckaert CL, Nurmohamed MT, Wolbink GJ. Methotrexate reduces immunogenicity in adalimumab treated rheumatoid arthritis patients in a dose dependent manner. *Ann Rheum Dis* 2012;71:1914-1915 with permission from BMJ Publishing Group Ltd.

Fig. 5 The discontinuity theory of the immune response

When a novel antigen appears, it leads to an immune response, but persistent antigen induces an initial immune response followed by tolerance if the antigen persists at constant levels. Conversely, an intermittent appearance of an antigen promotes a persistent immune response that is similar to that seen in vaccination and vaccine recall. Adapted by permission from Macmillan Publishers Ltd: *Nature Reviews Immunology* (Pradeu T, Jaeger S, Vivier E. The speed of change: towards a discontinuity theory of immunity? *Nat Rev Immunol* 2013;13:764-769) ©2013.

treatment with MTX and infliximab did not prevent ADAB production [61].

In psoriasis, ADABs have been detected more frequently in patients treated with adalimumab or infliximab than in patients treated with etanercept or ustekinumab [16, 62]. A correlation was observed between the persistence of psoriasis activity (measured by the Psoriasis Area and Severity Index), low serum trough concentration of infliximab and adalimumab and the presence of ADABs (no demonstration for etanercept and

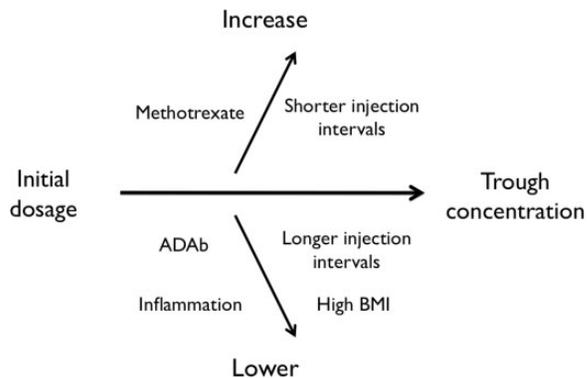
ustekinumab) [63, 64]. Concomitant MTX therapy was negatively associated with the presence of ADABs.

Biologic agent monitoring in daily practice

Several authors proposed that ADAB monitoring could help clinicians understand the reason for biologic treatment failure [12, 25, 27, 65]. Considering, on one hand, the close relationship between the trough serum concentration of biologic DMARD and the development of ADAB, and on the other hand the difficulties encountered in ADAB detection, it seems that the drug trough concentration could be the most useful test. A therapeutic strategy based on serum trough concentration of the biologic agent has been proposed by Mulleman *et al.* [66]. In the case of lack or loss of efficacy of a biologic agent, the dosage of the drug could give the most important information: if the serum level is sufficient, it means that the choice of the target is not appropriate and the practitioner will have to switch to another class of biologic agent; if the serum trough level is low, the result is indicative of either an insufficient dose, or an immunization to the drug; therefore, the practitioner will have two possibilities, either to continue using the same drug, but with increased dosage or a change in the frequency of administration, or to switch to another biologic, keeping the same target.

Conclusion

ADABs are detected in up to one-third of patients receiving biologic agents, especially anti-TNF mAbs; they are associated with low trough drug levels and loss of clinical efficacy. ADABs occur early, most often in the first 28 weeks after treatment onset, and combination with MTX decreases the risk of ADAB production. There is no

Fig. 6 Factors influencing the efficacy of biologic agents

A variety of factors impact on serum trough concentration of biologic agents. Some, such as obesity or inflammation status, depend on the patient, while others are linked to the treatment strategy, such as immunomodulator co-prescription and biologic agent dosage or intervals. Low trough concentrations are thought to play a role in the development of ADAbs. ADAbs: anti-drug antibodies.

demonstration that other conventional synthetic DMARDs, such as LEF and SSZ, may have such protective effects.

Is immunogenicity the final explanation of the loss of efficacy of biologic agents? Probably not: although the development of ADAbs to adalimumab is frequent compared with ADAbs against etanercept, there is only a weak difference in the maintenance rate of these two treatments in RA patients [2, 67]. Moreover, in the Swiss RA registry, only 42% of patients with acquired infliximab resistance had either low infliximab or high anti-infliximab antibody levels.

However, drug immunogenicity is at least a part of this explanation and should be considered in clinical practice. Serum drug trough concentration seems to be the most relevant marker to guide a clinician's decision.

The improvement of our knowledge of biodrug immunogenicity should also influence future management strategies for the biologic agents. If the maintenance of a sufficient trough level of the biologic agent is the best way to maintain disease control and to prevent ADAbs development, we will have to reconsider the approach of spacing or withdrawing biologic agent injections when patients enter remission; tapering the dosage could be a better way to maintain a minimal trough level of the drug.

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