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To cite this article: Chi Chiu Mok, Wen Chan Tsai, Der Yuan Chen & James Cheng Chung Wei (2016) Immunogenicity of anti-TNF biologic agents in the treatment of rheumatoid arthritis, Expert Opinion on Biological Therapy, 16:2, 201-211, DOI: 10.1517/14712598.2016.1118457

To link to this article: http://dx.doi.org/10.1517/14712598.2016.1118457
Immunogenicity of anti-TNF biologic agents in the treatment of rheumatoid arthritis

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ABSTRACT

Introduction: The use of biologic disease-modifying anti-rheumatic drugs (DMARDs), including therapeutic antibodies, antibody fragments and protein constructs that target key mediators in the pathophysiology of rheumatoid arthritis (RA), has improved the chance of achieving low disease activity and clinical remission. However, individual patients respond differently to biologic DMARD therapy, particularly the tumor necrosis factor (TNF) inhibitors.

Areas covered: While the variation of clinical response may be related to pharmacogenetic and other unknown factors, immunogenicity associated with some of these agents may contribute in part to a lack of efficacy and immune-mediated side effects. Timely detection of immunogenicity may avoid continued administration of ineffective treatment, and reduce unnecessary risks and costs. Access to and appropriate implementation of clinically validated drug level assays is required.

Expert opinion: There are currently no evidence-based recommendations to guide biologic therapy on the basis of drug level and immunogenicity testing but as more data become available and better tests are developed, a strategy of immunopharmacologic guidance to individualize treatment of RA will emerge. The potential benefits of this approach must be balanced against the costs of monitoring, and further research is required.

1. Introduction

Biologic disease-modifying anti-rheumatic drugs (DMARDs) represent a major breakthrough in the treatment of rheumatoid arthritis (RA). Since the late 1990s, the introduction of a number of agents that target and block key protein messenger molecules (e.g. tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6]) or cells (such as B-lymphocytes) involved in the pathogenesis of RA has made it possible to achieve very low disease activity or even clinical remission, end points that have been adopted as realistic goals in current treatment guidelines.[1–4]

The TNF inhibitors, a T-cell co-stimulation inhibitor (abatacept), a B-cell inhibitor (rituximab) and an IL-6 antagonist (tocilizumab), are the currently available biological agents for the treatment of RA.[3] Globally, the TNF inhibitors tend to be the first agents prescribed when biologic DMARDs are indicated in RA, due to the wealth of evidence, experience and long-term follow-up data.[3,5] Today, five TNF inhibitors are available in the market: infliximab, etanercept, adalimumab, golimumab and certolizumab pegol. In recent years, biosimilar versions of the older branded biologic DMARDs have also become available in some countries. Yisaipu, for example, is an etanercept biosimilar marketed in China,[6] and CT-P13, an infliximab biosimilar, has been marketed in South Korea.[7] Other etanercept and rituximab biosimilars are in clinical trials in other Asian countries.[8]

While there is no evidence from clinical trials that any TNF inhibitor is more effective than any other, a certain proportion of patients do not respond adequately as judged from their clinical response. The reasons for the refractoriness to the TNF inhibitors remain to be elucidated and may be related to pharmacogenetic and many yet unknown factors. One of the potential reasons for the lack or loss of efficacy of the TNF inhibitors over time is the immunogenicity associated with biologic DMARDs.[9–11] This article...
reviews the current understanding of the immunogenicity of biologic agents used in the treatment of RA, and the implications for clinical practice and treatment outcomes in Asian countries.

2. Basic concepts in immunogenicity of biologic DMARDs

Immunogenicity is the ability of a substance to provoke an immune response when recognized by the body as being foreign. Biologic therapies used in RA are engineered molecules such as therapeutic antibodies, antibody fragments or protein constructs. Therapeutic proteins are a common cause of immune reactions; therefore, it is not surprising that biologic DMARDs have the potential to be immunogenic, and can result in the formation of antibodies against the drug, known as antidrug antibodies.[9]

The first therapeutic antibodies developed were of mouse origin and resulted in the production of human antimouse antibodies in 90% of treated patients, substantially limiting their clinical use.[12] Newer treatments are therapeutic antibodies and antibody fragments that are partly human derived – such as the chimeric human–mouse monoclonal antibody (mAb) infliximab – or mAbs such as adalimumab and golimumab, which are mostly human derived. These therapies have lower immunogenicity than the original murine antibodies, but even fully human therapeutic antibodies can produce an immune response.[13]

The mechanisms involved in immunogenicity against biologics are complex, and their manifestations and clinical implications vary among patients; effects can be persistent or transient and are influenced by many factors other than the composition of the drug itself.[9]

3. Factors influencing the development of immunogenicity

The high variation in the prevalence of antidrug antibodies in RA patients using the TNF inhibitors reported in different studies suggests that patient factors may play an important role in immunogenicity and its manifestations. Immunogenicity is also influenced by the underlying disease, the treatment schedule – drug dose, administration route, frequency, continuity – the drug’s physicochemical properties (for example, purity, aggregation) and concomitant medications, in particular where biologics are commonly used in conjunction with traditional DMARDs.[9,11,12,14–33] The observation of immunogenicity may also be related to assay methods (see Section 4.3) and the timing of serum sampling.[14,34,35]

The reported frequency of antidrug antibodies to mAbs varies across different diseases (Table 2), [15,32,36–54] although the wide range is also the result of other factors described above, and the use of concomitant immunomodulators.[30]

4. Immunogenicity of TNF inhibitors and its potential clinical implications

4.1. Differences in the immunogenic regions of mAbs and soluble fusion proteins

The most recent addition to the TNF inhibitor class is certolizumab pegol, a PEGylated Fab fragment of a humanized anti-TNF antibody.[5] Its lack of an Fc region avoids potential Fc-mediated effects such as complement- or antibody-dependent, cell-mediated cytotoxicity; attachment of the PEG moiety to the Fab fragment extends the plasma half-life to approximately 2 weeks.[55] Potential immunogenic sites on the TNF inhibitor molecules are summarized in Table 3.[56]

4.2. Potential impact of immunogenicity on the pharmacokinetics of TNF inhibitors

The neutralizing effect of antidrug antibodies on TNF inhibitors is evident from their inverse relationship with serum drug levels, which was first demonstrated in RA patients receiving intravenous infliximab.[36] Development of antidrug antibodies resulted in low serum drug levels and was associated with treatment failure, need for dose increases, immune-mediated adverse effects and cessation of therapy. Several other studies in patients treated with infliximab or adalimumab have also shown that the development of antidrug antibodies over time correlates with the disappearance of drug from the blood.[35,56]
Factors that may affect the development of immunogenicity to biologic DMARDs.

- Among RA patients treated with adalimumab, 67% of those who develop antidrug antibodies do so within the first 28 weeks of treatment, meaning that 1 of 3 patients will develop antidrug antibodies much later if therapy is continued [14].
- 2 out of 3 infliximab-treated RA patients who develop antidrug antibodies do so within the first 22 weeks of treatment, although additional cases are detected up to week 46 [15]: 14% of patients who develop antidrug antibodies do so >1 year after starting therapy [16].

**Detection methods**

- The use of different assays for antidrug antibodies contributes to variation in the frequency of antibodies reported in different studies [9].

**Drug structure**

- Immunogenicity is markedly reduced with the more humanized mAbs compared to chimeric mAbs [12].
- The greatest structural difference among the TNF inhibitors is between the mAb-based drugs and etanercept, a soluble TNF receptor-Fc Ig fusion protein; although formation of antidrug antibodies is described in the etanercept label, these antibodies are not neutralizing and do not affect clinical efficacy [11, 17–20].

**Mode of administration**

- Subcutaneous (SC) vs. intravenous (IV): The SC route is potentially linked to increased risk of immunogenicity as a result of differences in antigen presentation.
- Abatacept is the only biologic DMARD available for both SC and IV administration; immunogenicity in RA patients is comparably low for both routes [21–23].

- Continuous vs. intermittent use: Intermittent use of biologics may induce a higher frequency of antidrug antibodies than continuous therapy [11].
- In RA patients, the risk of serious infusion reaction to infliximab (thought to be related to immune complex formation between the drug and antidrug antibodies) is higher when patients are retreated after a prolonged interval off treatment [24].
- A non-significant increase in immunogenicity may occur when abatacept therapy is interrupted in patients with RA, but the effect may be reversed when abatacept is reintroduced [21].

**Genetic polymorphism**

- The role of genetic factors in immunogenicity to biologic DMARDs in RA is unclear [9].
- Genetic predisposition is suggested by the fact that patients who show an immune reaction to one TNF inhibitor are more likely to also develop antidrug antibodies to another TNF inhibitor [25, 26].
- Formation of antibodies against adalimumab in RA patients has been associated with IL-10 gene polymorphisms [27].

**Underlying disease**

- Patients with certain autoimmune diseases (e.g., systemic lupus erythematosus [SLE]) are more prone to develop antidrug antibodies. One study shows that 1 of 3 SLE patients develop antibodies to the chimeric mAb rituximab after administration for 1 year, which is associated with poor B-cell depletion [28].

**Disease/ inflammatory activity**

- Patients with high baseline disease activity of RA are more prone to the development of antidrug antibody after being treated with adalimumab. Higher incidence of anti-adalimumab antibody is observed in patients with more longstanding and severe (often with erosion) disease at baseline, and higher disease activity score [29].

**Concomitant immunomodulators**

- Co-administration of methotrexate or azathioprine reduces the immunogenicity of therapeutic antibodies in RA and other chronic inflammatory conditions, although the mechanism is unclear [30, 31].
- In a systematic review, among patients with immune-mediated inflammatory diseases (RA, ankylosing spondylitis, psoriasis and inflammatory bowel disease), the use of methotrexate, azathioprine or mercaptopurine reduces the frequency of antidrug antibodies to TNF inhibitors by 47% and attenuates their impact on clinical response [20].
- In patients with Crohn’s disease treated with infliximab, concomitant azathioprine or methotrexate significantly reduces the incidence of antidrug antibodies and prolongs the duration of response compared with infliximab monotherapy; in the absence of antidrug antibodies, concomitant DMARDs do not influence the duration of response, indicating that the effect is attributable to immunogenic modulation [32].
- In a 3-year longitudinal cohort of 272 RA patients treated with adalimumab, the development of anti-adalimumab antibody correlates inversely with the weekly dose of concomitant methotrexate [33].

| Table 1. Factors that may affect the development of immunogenicity to biologic DMARDs. |
|---------------------------------|---------------------------------|
| **Factor**                     | **Evidence**                    |
| **Timing of serum sampling for antidrug antibody assay** | • Among RA patients treated with adalimumab, 67% of those who develop antidrug antibodies do so within the first 28 weeks of treatment, meaning that 1 of 3 patients will develop antidrug antibodies much later if therapy is continued [14]. |
| **Detection methods** | • The use of different assays for antidrug antibodies contributes to variation in the frequency of antibodies reported in different studies [9]. |
| **Drug structure** | • Immunogenicity is markedly reduced with the more humanized mAbs compared to chimeric mAbs [12]. |
| **Mode of administration** | • Subcutaneous (SC) vs. intravenous (IV): The SC route is potentially linked to increased risk of immunogenicity as a result of differences in antigen presentation. |
| **Continuous vs. intermittent use** | • Intermittent use of biologics may induce a higher frequency of antidrug antibodies than continuous therapy [11]. |
| **Genetic polymorphism** | • The role of genetic factors in immunogenicity to biologic DMARDs in RA is unclear [9]. |
| **Underlying disease** | • Genetic predisposition is suggested by the fact that patients who show an immune reaction to one TNF inhibitor are more likely to also develop antidrug antibodies to another TNF inhibitor [25, 26]. |
| **Disease/ inflammatory activity** | • Patients with certain autoimmune diseases (e.g., systemic lupus erythematosus [SLE]) are more prone to develop antidrug antibodies. One study shows that 1 of 3 SLE patients develop antibodies to the chimeric mAb rituximab after administration for 1 year, which is associated with poor B-cell depletion [28]. |
| **Concomitant immunomodulators** | • Co-administration of methotrexate or azathioprine reduces the immunogenicity of therapeutic antibodies in RA and other chronic inflammatory conditions, although the mechanism is unclear [30, 31]. |
| **Subsequent administration of a drug in the presence of antidrug antibodies can result in the formation of immune complexes, which may affect the ability of the drug to bind to its therapeutic target. These neutralizing antidrug antibodies may also reduce therapeutic efficacy indirectly by reducing the release of the drug from the injection site into the circulation, thereby compromising bioavailability.” [56, 57] For biologics administered by subcutaneous injection, development of antidrug antibodies near the injection site can contribute to local formation of immune complexes. [56] The incidence of antidrug antibodies to the fusion protein etanercept is much lower than that reported with the monoclonal anti-TNF antibodies (6% according to one study [19] in RA and 0% in other studies. [17, 18]). The occurrence of anti-etanercept antibodies does not appear to affect the clinical efficacy (non-neutralizing) of the TNF inhibitor. [19] |
Table 2. Reported frequencies of antidrug antibodies to infliximab and adalimumab in various inflammatory diseases.

<table>
<thead>
<tr>
<th>Inflammatory disease</th>
<th>Percentage of patients with antibodies to infliximab</th>
<th>Percentage of patients with antibodies to adalimumab</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>8–51</td>
<td>12–37</td>
<td>[15,36–42]</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>14–61</td>
<td>0.04–17</td>
<td>[32,43–49]</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis</td>
<td>NA</td>
<td>16</td>
<td>[50]</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>29</td>
<td>31</td>
<td>[51,52]</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>NA</td>
<td>18</td>
<td>[53]</td>
</tr>
<tr>
<td>Psoriasis vulgaris</td>
<td>NA</td>
<td>45</td>
<td>[54]</td>
</tr>
</tbody>
</table>

Adapted with permission from [30]. Published by BioMed Central.
NA: not applicable.
*Overall frequency in each study was taken when developing this table; in some studies, frequency was shown to vary with dose or when infliximab/adalimumab was given in combination with another drug.

The low rate of anti-adalimumab antibodies reported by Hanauer et al. [49] may have been related to the relatively short duration of the study (4 weeks).

Table 3. Summary of immunogenic sites of TNF inhibitors for RA.

| Drug (and year of first approval for use in RA) | Structure | Mode of administration | Mouse epitope on drug | Mouse epitope on drug | Human idiotopes in or on drug binding site to TNF-α | Human allotopes on constant regions of IgG | Nonhuman glycosylations | Neoepitopes on drug aggregates | Splice-region peptide |
|-----------------------------------------------|-----------|------------------------|-----------------------|-----------------------|--------------------------------------------------|--------------------------------------------|----------------------------|------------------------|----------------------|------------------|
| Etanercept (1998)                             | TNF receptor–Fc fusion protein                     | SC                    |                       |                      | ✓                                                | ✓                                          | ✓                                       | ✓                     | ✓                   | ✓                |
| Infliximab (1999)                             | Chimeric human–mouse mAb                           | IV                    | ✓                     | ✓                     | ✓                                                | ✓                                          | ✓                                       | ✓                     | ✓                   | ✓                |
| Adalimumab (2002)                             | Human mAb                                          | SC                    | ✓                     | ✓                     | ✓                                                | ✓                                          | ✓                                       | ✓                     | ✓                   | ✓                |
| Golimumab (2009)                              | Human mAb                                          | SC                    | ✓                     | ✓                     | ✓                                                | ✓                                          | ✓                                       | ✓                     | ✓                   | ✓                |
| Certolizumab pegol (2009)                     | PEGylated recombinant humanized Fab fragment of anti-TNF mAb | SC                    | ✓                     | ✓                     | ✓                                                | ✓                                          | ✓                                       | ✓                     | ✓                   | ✓                |

Adapted with permission from [56].

CDR: Complementarity-determining variable region; Fab: Fragment antigen binding; Fc: Fragment crystallizable region; FR: Framework region; IgG: Immunoglobulin; IV: Intravenous; mAb: Monoclonal antibody; PEG: Polyethylene glycol; RA: Rheumatoid arthritis; SC: Subcutaneous; TNF: Tumor necrosis factor.
Shaded rows indicate mAbs.

4.3. Immunogenicity testing

While immunogenicity may explain some of the differences among the TNF inhibitors, the lack of standardized assays has led to the great variation in the prevalence of antidrug antibodies to these agents. The specificities and sensitivities of available assays differ, making comparisons between studies difficult.[9] Standard enzyme-linked immunosorbent assay (ELISA) techniques are the least specific, and do not distinguish between functionally active and inactive antidrug antibodies.[9,56] Improved methods are two-site (bridging) assays and radioimmunoassay (RIA)-based antigen binding tests.[58] However, the bridging assay does not detect certain types of antidrug antibody that are more prominent after prolonged drug exposure (IgG4).[56] A comparison of various assay methods in RA patients treated with infliximab concluded that RIA- and ELISA-based solid-phase cross-binding tests were inferior to fluid-phase RIA.[59]

The measurement of antibodies against antibodies is further complicated by the presence of the drug itself. Current antibody assays measure unbound antibodies, not those bound in an immune complex; therefore, when both drug and antidrug antibody are present, formation of immune complexes between the two results in lower levels of free antidrug antibody (as well as lower levels of unbound drug) and the test will indicate a falsely low level. Conversely, in the presence of antidrug antibodies, drug concentration measurements may be incorrect.[9] Interpretation of antibody assessments should therefore make reference to the dosing and timing of the drug, and to the corresponding serum drug levels.[9] To minimize interference with antidrug antibody analysis, blood samples should be collected immediately prior to drug administration, when drug levels are at their lowest.[60] Even so, individual trough levels may vary. To overcome such interactions, new methods (reporter gene assays) are being explored that directly measure TNF neutralization and its inhibition by antidrug antibodies.[61] Assays using liquid chromatography with tandem mass spectrometry are also being developed (Wen-Chan Tsai, unpublished observations).
5. Potential clinical consequences of immunogenicity

5.1. Clinical efficacy

Evidence of the consequences of immune responses to biologic DMARDs has grown substantially during the last decade,[34] largely based on experience with infliximab [15,16,36,40] and adalimumab.[14,25,35,37] These studies consistently show that, in patients with RA, immunogenicity is strongly linked to sub-therapeutic serum drug levels and a compromise of clinical response. A 3-year longitudinal study of 407 RA patients showed that etanercept and adalimumab are similar in inducing a good long-term clinical outcome, but for adalimumab these are strongly dependent on the presence of antidrug antibodies.[62] Patients with anti-adalimumab antibodies had the lowest rate of sustained minimal disease activity compared to those without antidrug antibodies or treated with etanercept.[62]

Another study of 147 RA patients treated with infliximab for at least 6 months showed an interesting finding. Among those who achieved low disease activity, one-third of patients had anti-infliximab antibodies, with half of these patients having these antibodies every visit for more than 1 year[63] Thus, monitoring of infliximab trough levels and the presence of anti-infliximab antibodies can assist in the clinical decision of down-titration and discontinuation of infliximab in patients with stable low disease activity state so that drug cost can be minimized.[64]

Data on the long-term consequences of immunogenicity of the anti-TNF biologics in RA are available from open-label extensions of randomized clinical trials and observational registries. For example, in a 3-year follow-up of 272 RA patients treated with adalimumab, development of antidrug antibodies was associated with lower adalimumab concentration and lower likelihood of achieving minimal disease activity or clinical remission.[14] Information regarding immunogenicity of the newer TNF inhibitors such as golimumab and certolizumab is less well reported in the literature.

As it takes time to produce an antibody response to an exogenous protein, drug immunogenicity is not a likely explanation for most primary response failures to the TNF inhibitors; however, it is a major contributor to secondary response failure, which affects up to 50% of patients with good primary responses to TNF inhibitors.[56]

Limited information on immunogenicity is available in clinical trials of TNF inhibitors originating from Asian countries. In the multicenter study of adalimumab monotherapy in RA patients in Japan (CHANGE), approximately one-third of patients treated with adalimumab expressed antidrug antibodies at week 24 and this was associated with poorer clinical response (defined by American College of Rheumatology criteria for 20% improvement) when compared to those without antidrug antibodies.[41] The efficacy and safety of adalimumab monotherapy in Japanese patients was similar to that observed in a similar study at comparable doses in Western patients,[42] except that there was a higher frequency of injection-site reactions in the Japanese study (25% vs. 10%). However, for unknown reasons, mean steady-state serum concentrations of adalimumab in Japanese patients were lower than in the study of Western patients, and the incidence of anti-adalimumab antibodies was higher.[41]

A recent study examined the effect of antidrug antibodies on the clinical efficacy and withdrawal rate of infliximab, adalimumab and etanercept in 58 Chinese patients with rheumatic diseases.[65] The proportion of patients who developed antidrug antibodies was 50, 31 and 0%, respectively. Those with antidrug antibodies had significantly lower serum drug levels and a significantly higher drug withdrawal rate due to lack of efficacy. In patients with RA or psoriatic arthritis, non-response was significantly more frequent in those with antidrug antibodies than in those without (54% vs. 13%; p = 0.01). Treatment significantly improved disease activity score in patients with spondyloarthritis or ankylosing spondylitis who were antidrug antibody-negative, but not in those who were antidrug antibody-positive.[65]

Epidemiologic studies of RA in Asia are scarce,[66] but data on the use of biologics are beginning to emerge from patient registries and national databases. A registry-based study for RA patients in Taiwan revealed that anti-adalimumab antibodies were detected in 27.8 and 36.1% of adalimumab-treated patients after 12-month therapy using ELISA and radioimmunoassay, respectively, but were not detected in any of the etanercept-treated patients. The presence of anti-adalimumab antibodies was associated with lower drug trough levels and lower therapeutic response compared to those without anti-adalimumab antibodies.[35] A registry-based study in Taiwan demonstrated that high-titer (>100 AU) and low-titer (12–100 AU) anti-adalimumab antibodies can be detected in 20 and 63%, respectively, of ankylosing spondylitis patients after 44 weeks of treatment. These antibodies were associated with decreased serum drug levels and reduced clinical efficacy.[67] An observational cohort study of 115 patients with ankylosing spondylitis...
spondylitis treated with adalimumab in the Netherlands and Taiwan found that 27% of patients had detectable anti-adalimumab antibodies at week 24. Mean adalimumab levels were significantly higher in patients without antibodies than in those with antibodies (12.7 vs. 1.2 mg/l; p < 0.001) and there was a significant relationship between adalimumab levels and clinical response (p = 0.02).[68]

5.2. Infusion reaction
Potential adverse effects mediated by antidrug antibody immune complexes include infusion-related hypersensitivity reactions, which have been observed in up to half of RA patients expressing anti-infliximab antibodies [24,30,69] and 20% of infliximab-treated patients across all clinical trials.[70] Such reactions have been linked to the formation of infliximab–anti-infliximab complexes,[71] with higher antibody concentrations associated with a higher risk of infusion reactions.[43] The majority of infusion reactions are mild to moderate, occur during or within 2 hours of the infusion, and can be managed by slowing or interrupting the infusion and administering antihistamines and/or corticosteroids. However, more severe hypersensitivity and anaphylactic reactions have been reported, including laryngeal/pharyngeal edema and severe bronchospasm, and require appropriate emergency treatment. The risk of serious infusion reactions may be higher when patients are retreated after a prolonged interval off treatment; moreover, the reaction may be a delayed one, commonly occurring after initiation of the second infusion.[24] Serious infusion reactions have not been reported with etanercept, although mild to moderate injection-site reactions (erythema, itching, pain, swelling, bleeding and bruising) lasting 3–5 days are the most common adverse event; these generally occur in the first month and then become less frequent.[72] Whether the etiology of this reaction is irritative or immune-mediated is not fully understood.[73]

5.3. Other adverse consequences
Serum sickness and Arthus reactions are local immune complex-mediated type III hypersensitivity reactions that are occasionally associated with immunogenicity of anti-TNF mAb therapy.[74] With infliximab, serum sickness-like reactions have been observed as early as the second dose, and also when therapy is restarted after an extended period off treatment. These reactions are associated with a marked increase in antibodies to infliximab, and are characterized by fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema, and dysphagia.[70]

Immunogenic reactions against biologics have also been associated with thromboembolic events. A cohort study of adalimumab-treated RA patients reported that thromboembolic events were more commonly observed in those who tested positive for the anti-adalimumab antibody.[75] The authors suggested that drug–antidrug immune complexes might induce aggregation and procoagulant microparticle release. However, this observation has to be confirmed by other groups and future studies.

6. ‘Cross-reactivity’ of the antidrug antibodies
A cohort study of 235 patients with RA treated with adalimumab reported that 20% of patients developed anti-adalimumab antibodies.[25] Fifty-two (22%) patients in this cohort were switchers from infliximab to adalimumab. Patients positive for anti-adalimumab antibodies had significantly lower reduction of disease activity score in 28 joints (DAS28) at week 28 compared to those without anti-adalimumab antibodies. It is also interesting that the incidence of anti-adalimumab antibodies was significantly higher in those switchers from infliximab who had developed anti-infliximab antibodies than in those who were TNF inhibitor-naïve (33% vs. 18%; p = 0.04).[25] However, the improvement in DAS28 score was significantly lower in switchers without the anti-infliximab antibodies than in patients naïve to the TNF inhibitors. While further data are needed to confirm this observation, this might suggest that, when treatment failure to an anti-TNF agent is not because of immunogenicity, the chance of a clinical response to a second anti-TNF agent is lower because these patients are likely to be refractory to the drug mechanism of TNF blockade.

7. Retention rate of the TNF inhibitors and switching of anti-TNF therapy
While short-term data suggest that the survival rates of the anti-TNF biologics may be similar, long-term observational data show that etanercept exhibits the best long-term drug survival (60% at 4 years).[76] In the Italian GISEA registry, the 4-year global drug survival of adalimumab, etanercept and infliximab was lower than 50%, but etanercept had the best retention rate. [77] Drug survival was also highest for etanercept in the Danish DANBIO registry.[78] Data on registries are now available in Asia. In the biologic registry maintained by the Hong Kong Society of Rheumatology, it was reported that the 5-year retention rate of the anti-TNF
agents for the treatment of rheumatic diseases was lower with infliximab than with adalimumab and etanercept.[79]

When anti-TNF therapy fails, options include intensifying therapy, switching to another anti-TNF therapy or switching to another class of drug; however, there is no universally accepted approach and without knowing the precise reason for treatment failure it is effectively a trial-and-error strategy.[56] With infliximab, some patients benefit from raising the dose from 3 mg/kg every 8 weeks to 10 mg/kg as often as every 4 weeks when the clinical response wanes over time (secondary treatment failure),[41] because the incidence of anti-infliximab antibodies has been shown to correlate inversely with the dosage of infliximab being administered (7, 21 and 53%, respectively, in patients treated with infliximab 10 mg/kg, 3 mg/kg or 1 mg/kg [39,80]). However, a higher dose of the anti-TNF monoclonals to overcome immunogenicity will result in higher treatment cost incurred.[36,37,81] Conversely, patients who continue on TNF inhibitor therapy during clinical remission may risk developing antidrug antibodies that compromise the efficacy of subsequent courses of treatment. Identification of these patients will allow withdrawal of therapy that would help to reduce drug cost.[64]

Observational data from several national registries and open-label studies suggest that switching TNF inhibitors is a useful strategy in RA patients who fail treatment with a first TNF inhibitor.[11,25,82–84] However, no immunogenicity data are available in these studies; therefore, it is difficult to interpret whether treatment failures were attributable to development of antidrug antibodies and the implications for switching therapy.

A recent study of 292 consecutive RA patients treated with etanercept showed that among those who were switched from infliximab or adalimumab (30%), the presence of antidrug antibodies to the first TNF inhibitor was associated with a better clinical response in terms of improvement in DAS28 score at week 28 after etanercept therapy.[85] Thus, determining immunogenicity can help to identify patient subsets in whom switching to another anti-TNF agent could be beneficial.

8. Conclusions

The immunogenicity of anti-TNF therapies, even those described as fully human, influences their efficacy and safety in patients with RA. Currently, the issue of immunogenicity of the biological DMARDs and the monitoring of drug levels is not yet addressed in the updated 2013 EULAR recommendation.[3] However, regular monitoring of immunopharmacologic status using robust and clinically validated tests may facilitate a better understanding of the treatment response and enable individualization of the most appropriate therapy. Further research is necessary to better establish the relationship between drug levels, antidrug antibodies and clinical efficacy. When clinical efficacy of the biological DMARDs decreases with time or adverse drug reactions emerge, measuring drug level and/or antidrug antibody levels could help to guide dosage adjustments and drug switching. When more data become available and better tests are developed, a strategy of immunopharmacologic guidance may become a standard of care in the future and help improve the cost-effectiveness of the anti-TNF biologics in the treatment of rheumatoid arthritis.

9. Expert opinion

The high cost of most biologic DMARDs precludes their widespread use, particularly in developing regions of Asia. Therefore, it is prudent to recognize intolerance or lack of response to TNF inhibitor therapy early. Given the high individual variability in the pharmacokinetics of the anti-TNF agents, and the difficulty of predicting outcomes by clinical judgment alone, the rationale for therapeutic drug level monitoring of biologics and assessment of antidrug antibody responses is strengthening. However, the value of immunopharmacologic guidance in RA is a topic of ongoing debate. To date, there are no evidence-based recommendations to guide selection or switching of biologic therapies based on drug level and immunogenicity testing after failure of anti-TNF therapy, and the benefits of adopting such an approach would need to be balanced against the availability of reliable and reproducible tests and the costs of monitoring.

In clinical practice, it is likely that plasma drug levels will be useful in the monitoring of anti-TNF therapy. Sub-therapeutic plasma drug levels may be due to poor treatment adherence, pharmacogenetic reasons or the development of neutralizing antibody against the anti-TNF agent. If further testing confirms the presence of antidrug antibodies, increasing the dose may improve response; however, the practice of intensifying therapy to restore lost efficacy is not always successful and the cost may be prohibitive. Furthermore, immunogenicity may change over time and patients may either become tolerant to treatment or continue to produce further antibodies.
Therapeutic algorithms based on expert opinion suggest utilizing pharmacokinetic and immunogenic testing to guide anti-TNF treatment.[10,11,20,35,56] We propose a practical clinical algorithm for the monitoring of drug level and immunogenicity of the anti-TNF agents (Figure 1), based on our own opinions. As antidrug antibody tests can produce false-negative results if conducted too early after initiation of the TNF inhibitors, it is better to measure drug level and antidrug antibody level at baseline, and ideally every 6 months, or whenever clinical efficacy wanes.

**Figure 1.** Proposed treatment algorithm for RA patients who stop responding to treatment with TNF inhibitor therapy. ADAb: Antidrug antibodies; mAb: Monoclonal antibody; RA: Rheumatoid arthritis; TNF: Tumor necrosis factor.

Financial and competing interests disclosure

Medical writing support was provided by Susanne Gilbert at ACUMED, an Ashfield Company, and was funded by Pfizer Inc. WC Tsai has received consultation fees from Abbvie, Chugai, Eisai, Janssen, Novartis and Pfizer. JCC Wei has received research grants or consultation fees from Abbvie, Bristol-Myers Squibb, Celgene, Chugai, Eisai, Janssen, Novartis, Pfizer, Sanofi-Aventis, TSH Taiwan and UCB Pharma. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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