Biologic therapies for the treatment of chronic autoimmune inflammatory diseases such as RA, SpA, PsA, psoriasis (PSO) and IBD have enhanced both outcomes and patients’ expectations. The most frequently used biologics in rheumatology are anti-TNFs. As all biologics are proteins produced by living organisms (bacteria, yeast or mammalian cells), they have the potential to act as antigens and stimulate an immunological response. This ability to induce a specific cell or humoral immune response is termed immunogenicity.

While anti-TNFs are effective in many patients (response rate is typically 60-70% across these diseases), a substantial proportion do not respond adequately; the lack of effectiveness may be primary (usually determined by inadequate response by 12-16 weeks of treatment) or secondary (loss of effectiveness after an initial response, typically occurring 6 months after start of treatment), or due to side effects. One explanation increasingly used for secondary failure of anti-TNF therapy is the formation of antibodies against the drug [antidrug antibodies (ADAb)] [1]. The development of ADAb may influence serum drug concentrations and function by two possible mechanisms: first, by increasing drug clearance through formation of immune complexes between drug and antibody (neutralizing, non-neutralizing or both), thus reducing the drug’s half-life; and second, by decreasing the activity and effectiveness of the drug through binding to that part of the molecule responsible for binding to TNF and hence blocking the interaction [2]. Another (indirect) effect of ADAb is to cause allergic or hypersensitivity reactions and other adverse events, which can reduce tolerance and drug retention. This effect has been shown by meta-analysis of the association of ADAb with reduced safety in seropositive immune-mediated inflammatory diseases compared with seronegative patients [3].

However, the presence of neutralizing and non-neutralizing ADAb does not necessarily correlate simply with reduced therapeutic effect, but it rather depends on the balance between the concentration of the drug and ADAb levels [1]. The factors that influence ADAb formation can be patient related (e.g. IL-10 polymorphism), disease related [e.g. higher observed occurrence of ADAb formation in RA (0.72–87%) compared with PSO (6–45%)] [4–6] or treatment related (e.g. immunogenicity—highest with chimeric human-murine antibodies and lowest for fusion protein, the route of administration, dose, treatment schedule and concomitant use of DMARDs) [2].

In addition, the duration of biologic treatment, timing of serum sample collection and the method of ADAb detection are also important factors to consider [7]. The spectrum of results of ADAb occurrence in patients treated with biologics is very diverse depending on the method used to detect them. The most commonly used method to detect ADAb, ELISAs (direct and indirect), may favour the detection of IgM antibodies at the expense of monovalent IgG4 antibodies, which may have a greater potential for neutralization [1]. Radioimmunoassay has the ability to detect IgG4 antibodies, which are more prone to drug or RF interference, and has been used successfully in more recent prospective studies, but it is more expensive and requires the use of radioisotopes [1]. Interpreting assays are further complicated by the presence of the drug in serum containing ADAb, which can induce the formation of drug-antibody complexes that, in vivo, may lead to increased clearance of both the drug and ADAb and, in vitro, decreased detection of both. Therefore, timing the measurement from administration of biologic may influence detection of ADAb. Unfortunately, standardization between assays, to produce a trustworthy comparison between ADAb formation and their potential relationship with effectiveness and safety of the treatment is not currently possible [1].

A meta-analysis of 17 studies measuring ADAb in RA, SpA, PSO and IBD has shown that detectable ADAb reduced the drug response rate by 68% overall (RR = 0.32, 95% CI 0.22, 0.48), with significant between-study heterogeneity [8]. The formation of ADAb decreases the clinical response in RA but, paradoxically, not in SpA or IBD: RA patients with ADAb had poorer clinical responses for up to 6 months [odds ratio (OR) = 0.03; 95% CI 0.01, 0.21], and for between 6 and 12 months (OR = 0.03; 95% CI 0.00, 0.30). What is more, the occurrence of ADAb not only increases the risk of discontinuation of biologics in RA patients for a number of reasons, but also increases the risk of hypersensitivity reaction in all autoimmune diseases. Concomitant treatment with anti-TNF and DMARDs such as MTX or AZA limits ADAb formation (OR = 0.32; 95% CI 0.25, 0.42) [1, 3].

How can we best utilize this knowledge? Should we measure serum drug and ADAb levels during treatment?
of all patients with anti-TNFs? Just in those with inadequate response? Or should we follow our clinical experience and intuition? Attempts have been made to compare different treatment approaches in patients on anti-TNFs. Garcés et al. [9] compared the effectiveness of immunogenicity-based versus empirical-based switches in a cohort of 105 patients with established RA. One year after the therapeutic decision, patients with therapeutic decisions concordant with the proposed immunogenicity-based algorithm had a higher probability of achieving a response (OR = 7.91, \( P < 0.001 \), 95% CI 3.27, 19.13) and low disease activity (OR = 9.77, \( P < 0.001 \), 95% CI 4.69, 20.37) compared with patients who had had discordant decisions [9]. Vincent et al. [1] proposed an algorithm for treating RA patients who do not respond to anti-TNFs, using measurement of ADAb and concentration of the drug (Fig. 1).

Measurement of ADAb and drug concentration are not in routine clinical practice at present. Despite evidence accruing that supports measurement of one or both parameters before making a clinical decision, the lack of standardized detection methods and cut-off values for defining the presence of ADAb and defining the therapeutic range of concentration for each anti-TNF drug, as well as the cost of those tests, are preventing their uptake in the clinic.

Is it essential to conduct further research on improving the methodology of evaluating the concentration of the drug and ADAb? Or should we look for a different biomarker for response? We have recently shown that higher IFN-response gene expression in RA neutrophils correlates with a good response to anti-TNF therapy [10], but more work is required to evaluate this as a robust biomarker.

There is still a pressing need, both clinically and financially, to develop a stratified medicines approach for biological therapy in inflammatory arthritis. The identification of ADAb, with some biologics, that correlate with clinical effectiveness is an interesting development. However, we call for caution when interpreting results from these assays and for the application of good clinical acumen, as always.

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