

EDITORIAL

Are we ready for therapeutic drug monitoring of biologic therapeutics?

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See related research by Ducourau *et al.*, <http://arthritis-research.com/content/13/3/R105>

Abstract

In the previous issue of *Arthritis Research & Therapy*, Ducourau and colleagues report that they retrospectively detected anti-infliximab antibodies in 21% of patients with rheumatic diseases. Patients with anti-infliximab antibodies had lower serum drug concentrations. These findings contribute to the existing evidence of immunogenicity of biologicals and its clinical relevance. We argue for therapeutic drug monitoring to optimize treatment response.

Therapeutic drug monitoring seems to be an important new aspect in the treatment of patients with rheumatic diseases. This is argued by Ducourau and colleagues [1] in the previous issue of *Arthritis Research & Therapy*. In a retrospective study of 17 patients with rheumatoid arthritis and 91 patients with spondyloarthritis, the authors measured trough serum infliximab levels and antibodies toward infliximab at each visit. Antibodies against infliximab were detected in 21 patients (19%), and the median detection time was 3.7 months. In the larger group of patients with spondyloarthritis, infliximab levels were only 1.6 mg/L in those with antibodies and 15.8 mg/L in those without antibodies ($P < 0.001$), and the same pattern was found in the smaller rheumatoid arthritis group. In addition, patients with antibodies used methotrexate less often and infusion reactions occurred more often in the antibody-positive patients (52% versus 1%). We believe that this is an adequately performed but retrospective study that does not show exciting new data but that does confirm the clinical relevance of measuring serum levels and anti-drug antibodies in patients treated with biologicals.

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Immunogenicity, the ability to provoke an immune response against a foreign protein, results in suboptimal drug levels and is one of the reasons for a lack of clinical response. In patients with an immunogenic reaction against a biological, drug levels are less likely to be in the therapeutic range and the treatment effect is far from optimal, especially when there is no drug present in the serum [1,2].

In the last decade, evidence of the detrimental effect of this immunogenicity has risen significantly [2-5]. It has been documented that the presence of anti-drug antibodies is associated with drug levels below the therapeutic range, or even with absent drug levels, and thus with poor clinical outcome. In addition, anti-drug antibodies have been associated with adverse events; for example, in infliximab-treated patients, infusion reactions, which can be serious and life-threatening, occur more often in patients who have developed anti-infliximab antibodies [3]. Recently, an increased risk of thromboembolic events in patients with an immunogenic reaction against biologicals was also suggested [6].

The extent to which these effects of immunogenicity occur relies on several aspects related to the patient, the drug, and detection: the dose, frequency, and administration route of the drug; the timing of the serum sampling; and the complexity of measuring anti-drug antibodies. Different assays for the measurement of anti-drug antibodies are available, but these assays have their own advantages and disadvantages [7]. Measuring serum drug concentrations is less complex but preferably should be done in trough samples.

The use of concomitant medication such as methotrexate, azathioprine, and prednisone influences the formation of anti-drug antibodies [8]. The incidence of anti-drug antibodies is lower in patients taking concomitant immunosuppressive medication, and, as a result, more patients have drug levels in the therapeutic range and a better treatment response.

Given the variation in pharmacokinetics and its clinical relevance observed in patients treated with immunogenic drugs (generally with high costs), it is remarkable that

serum drug levels are not measured routinely in these patients. Additionally, in patients with drug levels below the therapeutic range, the detection of antibody formation could reveal the reason for these low drug levels.

Although the effects of immunogenicity have become widely studied for infliximab and adalimumab, comparable studies for other biologicals are lacking. In contrast, reported frequencies of antibodies to etanercept are lower and these antibodies might not be directed to the tumor necrosis factor-binding side but to the hinge region of the molecule and therefore are non-neutralizing [9,10]. Nevertheless, to verify whether drug levels are in the therapeutic range, it seems important to measure at least serum drug concentrations in patients using biologicals. Recently, it was shown that patients with the lowest trough etanercept concentrations are more often non-responders but that patients with the highest etanercept levels are more often responders [11].

In conclusion, immunogenicity certainly does play a role in the treatment of biological therapeutics. Apart from the issue of an elevated risk of side effects, the finding of antibodies against a biological and low or absent drug levels is important and clinically relevant since it is related to a low or even absent biological response. Although measurements of antibodies and trough serum drug concentrations are not widely available (particularly for the new biological therapeutics) and additional research questions need to be resolved, the evidence that these measurements are clinically relevant for individual patients is gradually and consistently growing. In our opinion, the time has come to start therapeutic drug monitoring in patients with biological therapies.

Competing interests

CLMK declares that she has no competing interests. WFL has received speaker honoraria from Abbott (Abbott Park, IL, USA), Merck (Darmstadt, Germany), and Roche (Basel, Switzerland).

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References

1. Ducourau E, Mulleman D, Paintaud G, Chu Miow Lin D, Lauféron F, Ternant D, Watier H, Goupille P: **Antibodies toward infliximab are associated with low infliximab concentration at treatment initiation and poor infliximab maintenance in rheumatic diseases.** *Arthritis Res Ther* 2011, **13**:R105.
2. Bartelds GM, Krieckaert CL, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JW, Dijkmans BA, Aarden L, Wolbink GJ: **Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up.** *JAMA* 2011, **305**:1460-1468.
3. Baert F, Noman M, Vermeire S, van Assche G, D'Haens G, Carbonez A, Rutgeerts P: **Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease.** *N Engl J Med* 2003, **348**:601-608.
4. Karmiris K, Paintaund G, Noman M, Magdelaine-Beuzelin C, Ferrante M, Degenne D, Claes K, Coopman T, Van Schuerbeek N, Van Assche G, Vermeire S, Rutgeerts P: **Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease.** *Gastroenterology* 2009, **137**:1628-1640.
5. Pascual-Salcedo D, Plasencia C, Ramiro S, Nuño L, Bonilla G, Nagore D, Ruiz Del Agua A, Martínez A, Aarden L, Martín-Mola E, Balsa A: **Influence of immunogenicity on the efficacy of long-term treatment with infliximab in rheumatoid arthritis.** *Rheumatology (Oxford)* 2011, **50**:1445-1452.
6. Korswagen LA, Bartelds GM, Krieckaert CL, Turkstra F, Nurmohamed MT, van Schaardenburg D, Wijbrandts CA, Tak PP, Lems WF, Dijkmans BA, van Vugt RM, Wolbink GJ: **Venous and arterial thromboembolic events in adalimumab-treated patients with antiadalimumab antibodies: a case series and cohort study.** *Arthritis Rheum* 2011, **63**:877-883.
7. Wolbink GJ, Aarden LA, Dijkmans BA: **Dealing with immunogenicity of biologicals: assessment and clinical relevance.** *Curr Opin Rheumatol* 2009, **21**:211-215.
8. Krieckaert CL, Bartelds GM, Lems WF, Wolbink GJ: **The effect of immunomodulators on the immunogenicity of TNF-blocking therapeutic monoclonal antibodies: a review.** *Arthritis Res Ther* 2010, **12**:217.
9. Dore RK, Mathews S, Schechtman J, Surbeck W, Mandel D, Patel A, Zhou L, Peloso P: **The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis.** *Clin Exp Rheumatol* 2007, **25**:40-46.
10. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, Jackson CG, Lange M, Burge DJ: **A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.** *N Engl J Med* 1999, **340**:253-259.
11. Jamnitski A, Hart M, Nurmohamed MT, Krieckaert C, Dijkmans BA, Aarden L, Voskuyl AE, Wolbink GJ: **Patients non-responding to etanercept obtain lower etanercept concentrations compared to responding patients [abstract].** *Ann Rheum Dis* 2011, **70** (Suppl 3):119.

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