

Adalimumab concentration-based tapering strategy: as good as the recommended dosage

Denis Mulleman,¹ Alejandro Balsa²

Drug monitoring consists of observing, recording or detecting the effects of a substance administered to an individual. Therapeutic drug monitoring (TDM) aims at improving patient care based on drug concentration measurement in order to adjust the dose or time interval individually.¹ TDM is based on the assumption of a definable relation between dose and plasma/blood drug concentration and between concentration and therapeutic effects.

In *ARD*, l'Ami *et al* conducted an open-label randomised trial comparing an increasing dosing interval of adalimumab from 2 to 3 weeks with a standard-dose conservative strategy in patients with rheumatoid arthritis (RA) with an adalimumab trough concentration >8 mg/L.² The authors concluded that the dose tapering strategy was not inferior to the conservative strategy over 26 weeks. This important contribution is a step towards implementation of TDM in clinical practice. Prior to this work, the same group found that a drug concentration between 5 and 8 mg/L was associated with a good clinical response and strongly suggested that no additional improvement could be expected by increasing the dose (ie, by reducing the time interval) in patients with trough concentration >8 mg/L.³ A similar range has been described for adalimumab in psoriatic arthritis, which validates these findings.⁴ In the economic context, this tapering strategy can be seen as an opportunity to alleviate the burden for society.

However, in the l'Ami *et al's* study, the target sample size was not reached, which somehow minimises the strength of the conclusion and raises the question of acceptability by patients to participate in the study. Indeed, some patients could have feared a flare or, more probably, because

they wanted to taper the dose, did not want to be allocated to the conservative arm. Whatever this limitation, tapering adalimumab seems to perform as good as the recommended dose in patients with RA with serum drug concentration above the recommended range, who represent more than one-third of the patients in the authors' experience.²

There are three principal arguments to support TDM of a tumour necrosis factor inhibitor (TNFi) in rheumatic diseases (table 1). The first is the variability in drug concentration among patients, which has been largely observed with all biologicals, and with adalimumab concentration ranging from undetectable to 28 mg/L in clinical practice.⁵ The second is the observation of a relation between drug concentration and clinical response, but only in responding patients, as this association is lacking in primary non-responders. For adalimumab, clinical improvement was greater for patients with a trough concentration between 5 and 8 mg/L than below this range.³ The third is the fact that low dosage/concentration may result in decreased efficacy and in increased risk of immunisation^{6,7} and high dosage/concentration may increase the risk of side effects.^{8,10}

There are three requirements for rheumatologists to implement TDM in clinical practice (table 1). First, we need a reliable method to quantify the drug and anti-drug antibodies (ADA).¹¹ Second, we need to establish guidelines or algorithms, supported by the best clinical evidence possible, to define therapeutic options in different clinical situations, such as prediction of response, biological failure or

tapering,¹² and finally, we need to follow personalised medicine, to define for each patient the optimal dosing schedule by using pharmacokinetic-pharmacodynamic (PK-PD) modelling, either what it is called proactive TDM, the dosing schedule at initiation is based on the patients' characteristics (disease activity in particular) and the reactive TDM in which the dosing schedule is adjusted upon clinical response and drug concentration.¹³

Because TDM of a TNFi is based on serum trough concentrations, we need to understand the PK of biopharmaceuticals. Biopharmaceuticals are large proteins that need to be administered parenterally. Because of their high molecular mass and hydrophilicity, their volume of distribution is low (3–4 L).¹⁴ These proteins do not undergo renal elimination or metabolism by hepatic enzymes, and proteolytic catabolism within the cells of the reticuloendothelial system (RES) is the primary route of elimination.¹⁵ Recycling of proteins with Fc domains is mediated by the Brambell receptor (FcRn), which plays a critical role in protecting IgG antibodies against catabolic activities.¹⁶ Elimination is also driven by binding to its antigenic target and irreversible binding by ADAs, when a patient develops immunogenicity.

Factors that may affect the PK and hence PD of biopharmaceuticals are complex, but the two most important are the development of ADAs and antigenic burden (disease activity). Other factors are concomitant immunosuppressive therapy, like methotrexate; disease severity, which may also increase non-immune elimination through RES-mediated mechanisms; disease type, such as inflammatory bowel disease, responsible for loss of the drug into faeces; and finally, patient-related factors such as body mass index and gender.¹⁴

One of the most important factors that affect the efficacy of biologicals is their potential for the development of ADA. ADAs bind to the biological agent, preventing it from binding to its target and forming immune complexes that accelerate the clearance of the drug.¹⁷ Clinically

Table 1 Arguments for therapeutic drug monitoring of a tumour necrosis factor inhibitor in rheumatic diseases and requirements

Rationale	Requirement
Pharmacokinetic interindividual variability	Valid assay for drug concentration measurement and anti-drug antibody detection
Dose–concentration relationship	Algorithm based on clinical and biological assessment
Risk of adverse events, outside the target concentration range*	Personalised dosing-schedule modelling tool, to achieve the target concentration and response

*Immunogenicity with low concentrations and infection with high concentrations.

¹Department of Rheumatology, Université François-Rabelais de Tours, CNRS, UMR 7292, Tours, France

²Department of Rheumatology, Health Research Institute (IdiPAZ), Hospital Universitario La Paz, Madrid, Spain

Correspondence to Dr Alejandro Balsa, Department of Rheumatology, Health Research Institute (IdiPAZ), Hospital Universitario La Paz, Madrid 28046, Spain; alejandro.balsa@salud.madrid.org

relevant ADAs are those that are present at high titers, since they bind to all or most of the circulating drug producing a significant reduction in serum drug concentrations.¹⁸ However, in most patients ADA titers increase slowly, and before they are present in sufficient amounts to completely block therapeutic drugs, there is a period of several months during which patients may present low drug concentrations in serum, or only absent in the last days of the cycle, with a satisfactory or slightly worse clinical condition, which is gradually lost as the amount of ADA increases and completely blocks the drug during most of the treatment period.¹⁹

Disease activity is an important factor affecting the PK-PD. A high inflammatory burden expressed by high expression of TNF in the inflamed tissue will lead to tissue retention of the TNFi, thereby increasing drug concentration in the joint and reducing it in the blood, with less available drug.^{14–20} Hence, patients with high disease activity may require greater amounts of drug to neutralise this high amount of TNF than those with moderate or low disease activity, so disease activity is a key factor in determining the target tissue concentration to achieve a clinical response.²¹ This phenomenon, called the antigenic sink,¹⁴ is a dynamic process because the drug reduces inflammation with consequently less TNF production, less binding to TNFi, thereby leading to increased drug concentration in the blood.²² Accordingly, an inverse correlation is found between peripheral blood TNFi concentration and disease activity in all inflammatory diseases.²³

Biopharmaceuticals need to be available in sufficient quantity in blood and target tissues to exert their effect; however, the optimal drug concentration range for therapeutic efficacy may differ depending on the disease activity, high for very active disease or even very low when the disease is in remission or with low disease activity.²¹ Because the correlation between drug blood concentration and outcome is stronger than between the dose and outcome, measuring drug concentrations in terms of a disease activity state allows clinicians to understand the reasons for the failure or the efficacy of the treatment, and allows for optimising the therapeutic dosage regimen and thus improving the response.

The different clinical situations in which TDM can be useful have been recently reviewed, and dose tapering may be considered in some instances.^{24–25} The lingering question is still when can the clinician consider dose tapering or dose

intensification? Some authors have tried to decrease the dose in patients with low disease activity regardless of the concentrations, showing this strategy to be feasible in most patients, although with loss of response in some cases. The question is, while tapering, can we avoid the occurrence of flares? The study by l'Ami *et al* shows that dose tapering is efficient when selecting patients based on their drug concentration.

Rheumatologists have been primarily concerned with patients with refractory disease or adverse events, which requires a rapid therapeutic decision. Patients in remission or with good response have not drawn much attention so far. With the article by l'Ami *et al*, rheumatologists should now realise that some of their patients have high serum drug concentration when receiving the recommended dose and that dose reduction is feasible, and also has a major implication for rheumatologists and society, because TDM may reduce costs while maintaining the clinical response. A striking observation is that some proposed algorithms have focused on only patients with poor response. Recently, the Monitoring of Antibodies Group in Europe proposed a generalised therapeutic algorithm for biopharmaceutical treatment of inflammatory diseases that considers non-responders and responders.¹²

The unanswered question which remains is the clinical utility of TDM; in other words, what does TDM add in comparison to the experience-based decision? The article by l'Ami *et al* provides some new and important insights into the potential benefit of TDM, in the situation of low disease activity/remission, but still there are some unresolved questions. Is this strategy cost-effective in patients in remission with serum through concentrations within the optimum adalimumab range of 5–8 mg/mL? Some arguments favour TDM of TNFi agents in RA.²⁴ However, the strength of studies is insufficient to support TDM in clinical practice.^{26,28} Still, no large prospective study comparing TDM versus usual care has been published. The present article favours TDM of a TNFi in RA. Prior to this, some authors found that dose reduction of adalimumab was feasible, particularly with high trough concentration.²⁹ Finally, we remind that the decision is based on both clinical opinion and biological information. In addition, although this is the first randomised trial of TDM of a TNFi, we need to reconfirm this finding in further works before implementing TDM of biopharmaceuticals in clinical practice of RA.

Acknowledgements We thank Laura Smales (BioMedEditing, Toronto, Canada) for improving the English language and editing the manuscript and Philippe Goupille and Chamaida Plasencia for advice.

Contributors AB and DM drafted and approved the final manuscript.

Funding The authors participate in the Consortium 'Monitoring of monoclonal Antibodies Group in Europe' (MAGE) for inflammatory diseases. The MAGE Consortium is supported by LE STUDIUM Loire Valley Institute for advanced studies (<http://www.lestudium-ias.com/>).

Competing interests AB has received unrestricted grants from Pfizer, Roche and AbbVie and speaker fees from Pfizer, AbbVie, MSD, BMS, UCB, Novartis, Sandoz, Celltrion and Roche, and has acted as a consultant for Pfizer, Sandoz, Nordic, AbbVie, Roche, BMS, UCB and MSD. DM participated on behalf of his institution in clinical trials sponsored by AbbVie, Roche, BMS, Pfizer, UCB and MSD; his hospital received a grant for research from AbbVie in 2004 and from Nordic Pharma in 2012; he has acted as a consultant and given lectures on behalf of his institution for MSD, Novartis, UCB and Pfizer; he has been invited to attend international congresses by MSD, Roche, BMS, AbbVie and Janssen-Cilag.

Provenance and peer review Commissioned; externally peer reviewed.

Data sharing statement Requested editorial about TDM of anti-TNF drugs in RA.



OPEN ACCESS

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.



To cite Mulleman D, Balsa A. *Ann Rheum Dis* 2018;**77**:473–475.



► <http://dx.doi.org/10.1136/annrheumdis-2017-211781>

Ann Rheum Dis 2018;**77**:473–475.
doi:10.1136/annrheumdis-2017-212376

REFERENCES

- 1 Paintaud G, Passot C, Ternant D, *et al*. Rationale for therapeutic drug monitoring of biopharmaceuticals in inflammatory diseases. *Ther Drug Monit* 2017;**39**:339–43.
- 2 l'Ami MJ, Kriekaert CL, Nurmohamed MT, *et al*. Successful reduction of overexposure in patients with rheumatoid arthritis with high serum adalimumab concentrations: an open-label, non-

- inferiority, randomised clinical trial. *Ann Rheum Dis* 2018;77:484–7.
- 3 Pouw MF, Krieckaert CL, Nurmohamed MT, *et al.* Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Ann Rheum Dis* 2015;74:513–8.
 - 4 Vogelzang EH, Kneepkens EL, Nurmohamed MT, *et al.* Anti-adalimumab antibodies and adalimumab concentrations in psoriatic arthritis; an association with disease activity at 28 and 52 weeks of follow-up. *Ann Rheum Dis* 2014;73:2178–82.
 - 5 Bartelds GM, Wijbrandts CA, Nurmohamed MT, *et al.* Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 2007;66:921–6.
 - 6 Ducourau E, Mulleman D, Paintaud G, *et al.* 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.
 - 7 Bendtzen K, Geborek P, Svenson M, *et al.* Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. *Arthritis Rheum* 2006;54:3782–9.
 - 8 Bejan-Angoulvant T, Ternant D, Daoued F, *et al.* Brief report: relationship between serum infliximab concentrations and risk of infections in patients treated for Spondyloarthritis. *Arthritis Rheumatol* 2017;69:108–13.
 - 9 Bongartz T, Sutton AJ, Sweeting MJ, *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275–85.
 - 10 Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009;68:1136–45.
 - 11 Darrouzain F, Bian S, Desvignes C, *et al.* Immunoassays for Measuring Serum Concentrations of Monoclonal Antibodies and Anti-biopharmaceutical Antibodies in Patients. *Ther Drug Monit* 2017;39:316–21.
 - 12 Dreesen E, Bossuyt P, Mulleman D, *et al.* Practical recommendations for the use of therapeutic drug monitoring of biopharmaceuticals in inflammatory diseases. *Clin Pharmacol* 2017;9:101–11.
 - 13 Passot C, Pouw MF, Mulleman D, *et al.* Therapeutic drug monitoring of biopharmaceuticals may benefit from pharmacokinetic and pharmacokinetic-pharmacodynamic modeling. *Ther Drug Monit* 2017;39:322–6.
 - 14 Ordás I, Mould DR, Feagan BG, *et al.* Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther* 2012;91:635–46.
 - 15 Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2008;84:548–58.
 - 16 Telleman P, Junghans RP. The role of the Brambell receptor (FcRB) in liver: protection of endocytosed immunoglobulin G (IgG) from catabolism in hepatocytes rather than transport of IgG to bile. *Immunology* 2000;100:245–51.
 - 17 van Schouwenburg PA, Rispen T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol* 2013;9:164–72.
 - 18 Strand V, Balsa A, Al-Saleh J, *et al.* Immunogenicity of biologics in chronic inflammatory diseases: A systematic review. *BioDrugs* 2017;31:299–316.
 - 19 Plasencia C, Pascual-Salcedo D, Alcocer P, *et al.* The timing of serum infliximab loss, or the appearance of antibodies to infliximab (ATI), is related with the clinical activity in ATI-positive patients with rheumatoid arthritis treated with infliximab. *Ann Rheum Dis* 2013;72:1888–90.
 - 20 Ben-Horin S, Chowers Y. Tailoring anti-TNF therapy in IBD: drug levels and disease activity. *Nat Rev Gastroenterol Hepatol* 2014;11:243–55.
 - 21 Ducourau E, Ternant D, Lequerré T, *et al.* Towards an individualised target concentration of adalimumab in rheumatoid arthritis. *Ann Rheum Dis* 2014;73:1428–9.
 - 22 Takeuchi T, Miyasaka N, Tatsuki Y, *et al.* Baseline tumour necrosis factor alpha levels predict the necessity for dose escalation of infliximab therapy in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011;70:1208–15.
 - 23 Wolbink GJ, Vis M, Lems W, *et al.* Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:711–5.
 - 24 Medina F, Plasencia C, Goupille P, *et al.* Current Practice for Therapeutic Drug Monitoring of Biopharmaceuticals in Rheumatoid Arthritis. *Ther Drug Monit* 2017;39:364–9.
 - 25 Van Herwaarden N, Van Den Bemt BJF, Wientjes MHM, *et al.* Clinical utility of therapeutic drug monitoring in biological disease modifying anti-rheumatic drug treatment of rheumatic disorders: a systematic narrative review. *Expert Opin Drug Metab Toxicol* 2017;13:843–57.
 - 26 Garcès S, Antunes M, Benito-Garcia E, *et al.* A preliminary algorithm introducing immunogenicity assessment in the management of patients with RA receiving tumour necrosis factor inhibitor therapies. *Ann Rheum Dis* 2014;73:1138–43.
 - 27 Krieckaert CL, Nair SC, Nurmohamed MT, *et al.* Personalised treatment using serum drug levels of adalimumab in patients with rheumatoid arthritis: an evaluation of costs and effects. *Ann Rheum Dis* 2015;74:361–8.
 - 28 Mulleman D, Méric JC, Paintaud G, *et al.* Centre National de la Recherche Scientifique UMR 6239 GICC. Infliximab concentration monitoring improves the control of disease activity in rheumatoid arthritis. *Arthritis Res Ther* 2009;11:R178.
 - 29 Chen DY, Chen YM, Hsieh TY, *et al.* Drug trough levels predict therapeutic responses to dose reduction of adalimumab for rheumatoid arthritis patients during 24 weeks of follow-up. *Rheumatology* 2016;55:143–8.