

Comment on 'Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial' by Tanaka *et al*

We have read with interest the paper of Tanaka *et al*¹ and support the need for a more personalised approach in dosing regimens of tumour necrosis factor (TNF) inhibitors.² They adjusted infliximab dose based on TNF concentrations at baseline, under the assumptions that baseline TNF concentrations can be accurately measured, and that high disease activity (ie, more inflammation) is associated with higher TNF concentrations. However, several factors argue against these assumptions, which we would like to add to the study by Tanaka *et al*. These factors might explain the absence of an association between TNF concentrations and treatment response.

First, the quantification of TNF at baseline is in fact challenging: TNF is an unstable molecule with a short half-life.³ Baseline concentrations in circulation are very low, around the detection limit of most immunoassays, even during active disease. It is doubtful that baseline TNF concentrations can be measured with sufficient accuracy and precision to serve as basis for individualised treatment decisions including the adjustment of infliximab dose.

Second, they suggested that low infliximab trough levels in non-responding patients might be a consequence of excessive TNF production and resultant high TNF plasma concentrations. However, we have recently been able to quantify total circulating TNF during adalimumab and etanercept treatment in rheumatoid arthritis patients.^{4,5} On treatment, we observed an increase in circulating drug-bound TNF, reaching steady-state concentrations around 100–1000 pg/mL. This increase could be explained by a prolonged TNF half-life, due to its tight binding to the TNF inhibitor, which itself has a very long half-life. Nevertheless, steady-state TNF concentrations are still orders of magnitude lower than typical TNF inhibitor trough levels, also for infliximab. No association between TNF captured in circulation and concentrations of adalimumab and etanercept >1 µg/mL was observed.^{4,5} It is therefore unlikely that TNF induces target-mediated clearance of infliximab, explaining the lower infliximab concentrations in patients with high baseline TNF. Instead, we suppose that low infliximab concentrations are mainly the result of antidrug antibody (ADA) formation.⁶ Unfortunately, the association between serum drug concentration and ADA formation has not been addressed in the paper of Tanaka *et al*.

Finally, our recent data indicate that TNF concentrations in circulation are not at all reflective of (underlying) inflammation or disease activity, since steady-state TNF concentrations remained extremely stable for a follow-up of 2 years, irrespective of disease activity. Furthermore, to our surprise, we found a similar increase in circulating TNF in healthy volunteers who received a single dose of an adalimumab biosimilar.⁴ This suggests that the majority of TNF in circulation most likely does not originate from pathological processes.

The aim of the study by Tanaka *et al* to personalise treatment is of significant value. Our recent results give an explanation

why circulating TNF might not be an appropriate biomarker for treatment response, like Tanaka *et al* showed. Instead, the use of therapeutic drug monitoring to optimise the dose in clinical practice is of growing interest and could significantly contribute to personalised treatment.²

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REFERENCES

- 1 Tanaka Y, Oba K, Koike T, *et al*. Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial. *Ann Rheum Dis* 2020;79:94–102.
- 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 van der Poll T, van Deventer SJ, Hack CE, *et al*. Effects on leukocytes after injection of tumor necrosis factor into healthy humans. *Blood* 1992;79:693–8.
- 4 Berkhout LC, l'Ami MJ, Ruwaard J, *et al*. Dynamics of circulating TNF during adalimumab treatment using a drug-tolerant TNF assay. *Sci Transl Med* 2019;11:eaat3356.
- 5 Berkhout LC, l'Ami MJ, Kriekaert CLM, *et al*. The effect of methotrexate on tumour necrosis factor concentrations in etanercept-treated rheumatoid arthritis patients. *Rheumatology*. 2019. doi:10.1093/rheumatology/kez513. [Epub ahead of print: 06 Nov 2019].
- 6 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.