Response to: '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*' by Berkhout *et al*

We would like to thank Berkhout *et al* for their comments on the absence of an association between serum TNF concentrations and treatment response to infliximab in our paper.¹

First, reliability of the obtained results on the serum levels of TNF in the study should be firmly confirmed, because the quality control of the assessments was stringently managed by the laboratory company who assessed the serum.^{2,3} However, as they mentioned, it remains unclear how serum levels of any cytokines reflect their tissue levels produced in inflamed tissues. There was a limitation in the context.

Second, serum levels of infliximab did not differ among the programmed treatment groups with low, intermediate and high levels of serum TNF at the baseline in the study, as shown in the online supplementary table 1.² Similar results were also seen in the RISING study.⁴ However, because antidrug antibodies (ADA) were detected in some patients though very limited number, the assumption that low concentration of infliximab might be results of ADA formation cannot be excluded.

Third, we agree that serum levels of TNF may not adequately reflect inflammation and disease activity. The critical point of the study was that we could not escalate the dose until week 14 according to the approved usage by the government² and that it might reduce the efficacy of the programmed treatment strategy since the very start time may be the most important period to achieve a clinical remission by fine tuning the dose. However, recent progress in assessments of proteins using electrochemiluminescence and other methods would warrant improvement of the estimation of serum protein levels. Otherwise, are any surrogate markers better than TNF required for the treat-to-target instead of TNF itself?

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REFERENCES

- Berkhout LC, l'Ami MJ, Wolbink GJ, *et al*. 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*. *Ann Rheum Dis* 2019. doi:10.1136/annrheumdis-2019-216557. [Epub ahead of print: 19 Nov 2019].
- 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* 2019. doi:10.1136/annrheumdis-2019-216169. [Epub ahead of print: 19 Oct 2019].
- Oba K, Horie N, Sato N, *et al*. Remission induction by raising the dose of remicade in RA (RRRR) study: rationale and study protocol for a randomized controlled trial comparing for sustained clinical remission after discontinuation of infliximab in patients with rheumatoid arthritis. *Contemp Clin Trials Commun* 2017;8:49–54.
- 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.