Response to: 'The antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region' by Rinaudo-Gaujous *et al*

Assessment of clinically relevant immunogenicity is a much-debated topic. With respect to the neutralising capacity of anti-drug antibodies (ADAs) to tumour necrosis factor (TNF) blockers, we recently demonstrated that the vast majority of antibodies in fact compete with TNF binding.¹ Therefore, we are pleased to find this notion further supported by the letter of Rinaudo-Gaujous *et al*.²

The aim of our study was to quantify to which extent ADAs were neutralising. Using the TNF competition assay, we concluded that >90% (90.2–99.3%, n=34) of all ADAs could neutralise the drug. A strong correlation between ADA titres determined with the antigen binding test (which measures all ADA) and ADA titres determined with the WEHI bioassay (which measures neutralising antibodies) confirmed this conclusion. This neutralising effect of ADA was nicely reproduced by Rinaudo-Gaujous *et al* using an ADA ELISA and the reporter HEK-Dual TNF cell line, although only a qualitative correlation was shown. Furthermore, many studies over the last 10 years have demonstrated a link between antibodies to infliximab and loss of response in various patient groups, including Baert *et al*,³ Bendtzen *et al*,⁴ Pascual-Salcedo *et al*,⁵ Wolbink *et al*⁶ and Bito *et al*.⁷

Together with our conclusion that most ADAs bind infliximab on or close to the TNF binding site and thereby compete with TNF, these results imply that to measure the ADA titre the bioassays that are only sensitive to neutralising ADA will give virtually the same results as the assays that measure binding ADA. Our study found this high neutralising capacity not only for antibodies to infliximab but also for antibodies to adalimumab, certolizumab and golimumab. These results suggest an immunodominant role for the TNF binding site of anti-TNF therapeutic antibodies.

As Rinaudo-Gaujous *et al* pointed out, the neutralising ADA level is an important measurement for drug activity. We would like to stress that by measuring the level of free or active drug also the direct impact of neutralising ADA will be measured since drug bound by neutralising ADA will remain undetected. Several groups have found a correlation between infliximab trough levels and clinical effect.^{8–10} Monitoring primarily the level of infliximab would therefore be sufficient to determine whether the therapy is still effective or not. In case the drug levels are low or non-existent, additionally the ADA titre can be measured to ascertain if this is due to immunogenicity.

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