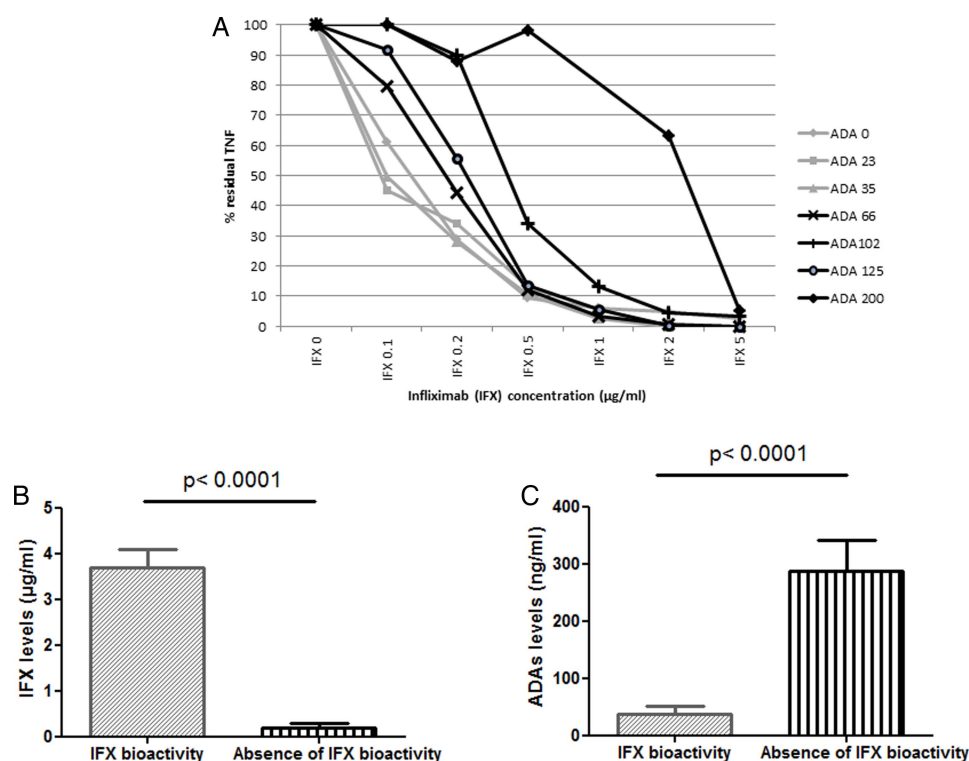


The antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region

We read with a great interest the report by Van Schie *et al*¹ which highlighted that the antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region. The results described in this report confirm very clearly the results that we obtained recently.

This study adds to the one we performed, which shows the neutralising capacity of antidrug antibodies (ADAs) against infliximab (IFX) in patients with inflammatory bowel disease (IBD) treated by IFX. We assessed ADAs' biological activity by a functional assay using a reporter HEK-Dual TNF cell line developed for TNF detection (InvivoGen). Briefly, sera of patients with IBD were first incubated with various amounts of IFX (from 0.1 µg/mL to 5 µg/mL), then with recombinant tumour necrosis factor (TNF) (10 ng/mL, R&D Systems), and then deposited in wells with HEK-Dual TNF cells. In parallel, ADA levels were measured by ELISA assay (Lisa Tracker, Theradiag). For ADA levels higher than 50 ng/mL in ELISA, activation of HEK-Dual TNF cells was observed for higher concentrations of IFX (figure 1A). A good correlation was noticed between ADA levels in ELISA and activation of HEK-Dual TNF cells estimating residual TNF in the mixt of sera with IFX and exogenous TNF, demonstrating the capacity of ADAs to block IFX bioactivity (figure 1A). Using the same assay, IFX activity was secondarily evaluated in 119 sera from 44 patients with IBD treated with IFX. Presence of detectable IFX in ELISA was a good surrogate marker of its bioactivity in patients with IBD (figure 1B). Moreover, in the presence of ADAs in ELISA, no biological IFX was detected in these sera with our functional assay (figure 1C). To sum up, both assays were similar for IFX and ADAs detection in patients with IBD, proving their respective bioactivity.

Figure 1 Evaluation of ADAs and IFX bioactivity in patients with IBD treated with IFX using a functional test. (A) Neutralising capacity of ADAs in patients with IBD (ADAs concentration expressed in µg/mL). Residual TNF represents the quantity of recombinant TNF added not blocked by IFX. (B) Relation between IFX levels in ELISA and its bioactivity (C) Correlation between ADAs level and IFX bioactivity. ADAs, antidrug antibodies; IBD, inflammatory bowel disease; IFX, infliximab.



The results obtained in this report are consistent with clinical data already published. In fact, several studies have reported an association between ADA production and reduced levels of TNF blockers.²⁻⁴ This association can be partially explained by an increased drug clearance secondarily to the formation of immune complexes between ADAs and anti-TNF.⁵ Clinically, the presence of ADAs is associated with a significantly higher risk of loss of clinical response to IFX,^{6,7} reinforcing ADAs importance in terms of interference with drug action.

In conclusion, ADAs interest is increasing as many clinical and physiological studies have shown their importance in drug activity. As the majority of ADAs are neutralising, their monitoring during TNF blocker treatment seems to be highly relevant. More algorithms must be developed^{8,9} regarding drug characteristics and the assay used for drug and ADA determination.

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