

Utility of measuring free vs. total anti-Infliximab antibodies in assessing clinical response to Infliximab in patients with inflammatory bowel disease

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Introduction

Therapeutic drug monitoring (TDM) of Infliximab (IFX) has been in use in our centre since 2012 and has become increasingly widespread in the UK with the availability of several CE marked assays. TDM of IFX is useful in optimisation of therapy in patients with inflammatory bowel disease (IBD). The detection of antibodies against Infliximab can guide clinical decision making with regard to dose escalation, immunomodulation or drug switching / withdrawal. However the utility of measuring free versus total (IFX-complex + free) anti-Infliximab antibody (ADAb) remains debatable, further complicated by lack of assay standardisation.

Aim

The aim of this study was to assess the relationship between free/total ADAb, drug levels and clinical/biochemical markers of disease activity.

Method

A prospective evaluation of trough drug levels and ADAb was performed using our local Theradiag LISA-TRACKER assay (LT, France) in 79 IBD patients between January-May 2014. Samples were also analysed by Immundiagnostik ELISA (IM, Germany) for ADAb. LT utilises a specific bridging ELISA to quantitatively measure free ADAb (Figure 2) whereas IM utilises a dissociation step to enable detection of total ADAb (Figure 3) generating semi-quantitative results derived from a cut-off control. Faecal calprotectin (FCAL >59 ug/g), C-reactive protein (CRP >5 mg/L) and Harvey Bradshaw Index (HBI >5) were used as markers of disease activity.

ADAb Assays

Figure 1 – Key.

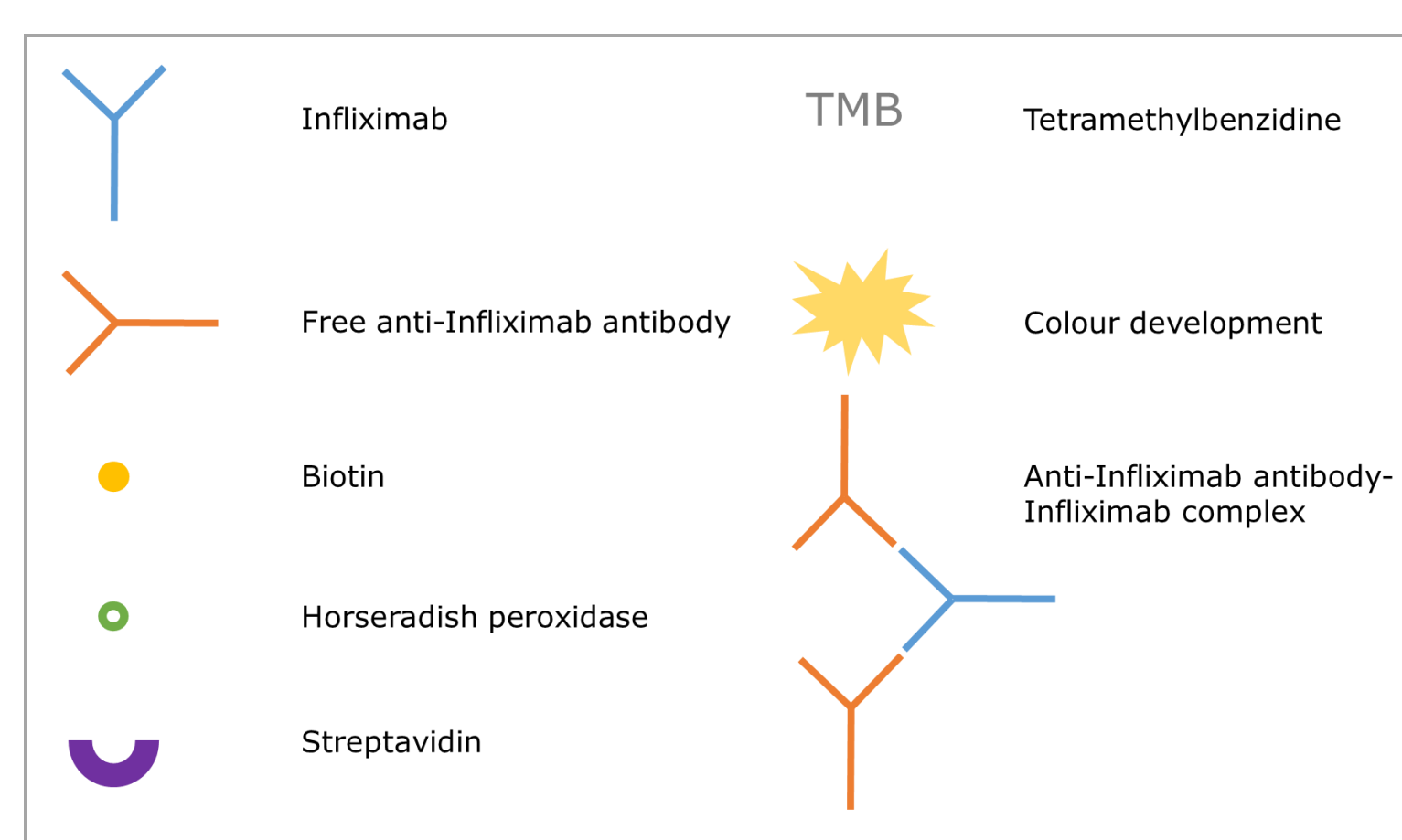


Figure 2 – Theradiag LISA-TRACKER "Free" ADAb assay.

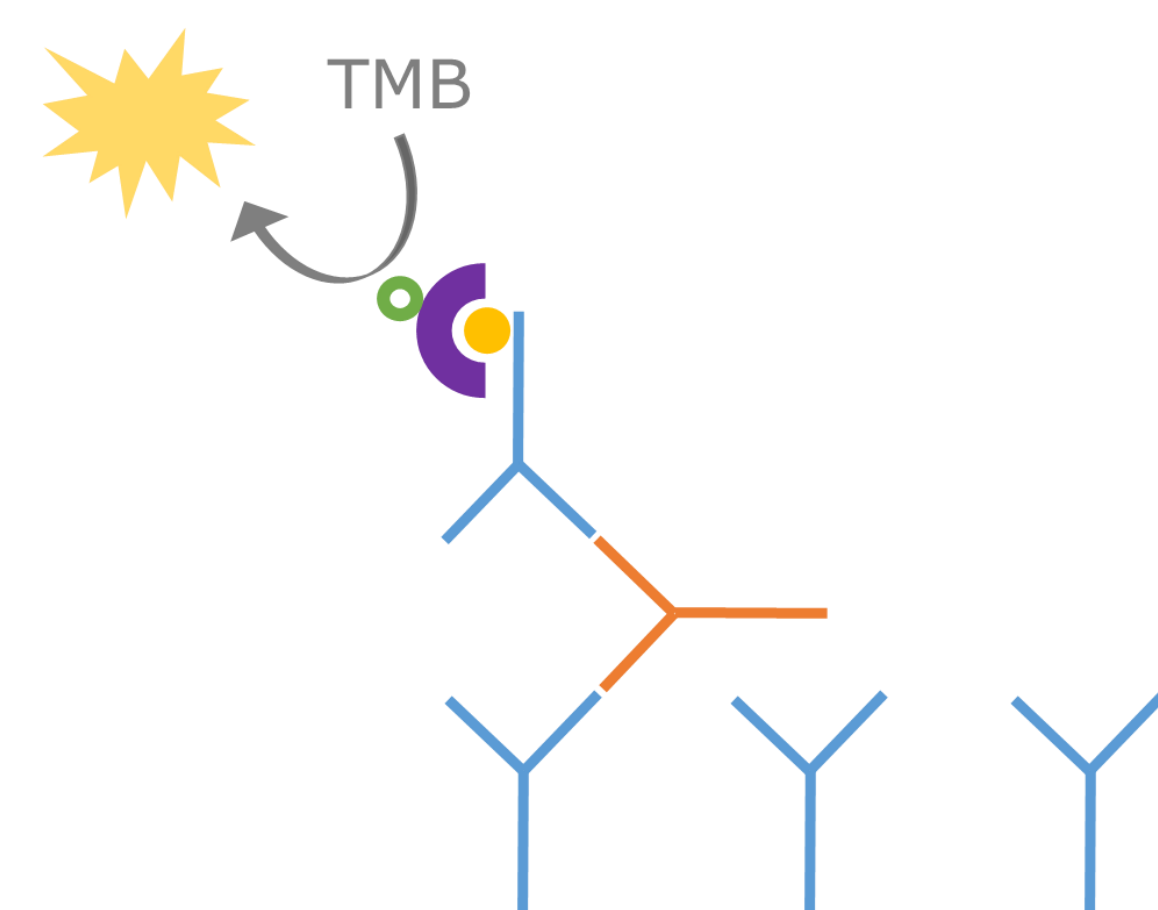
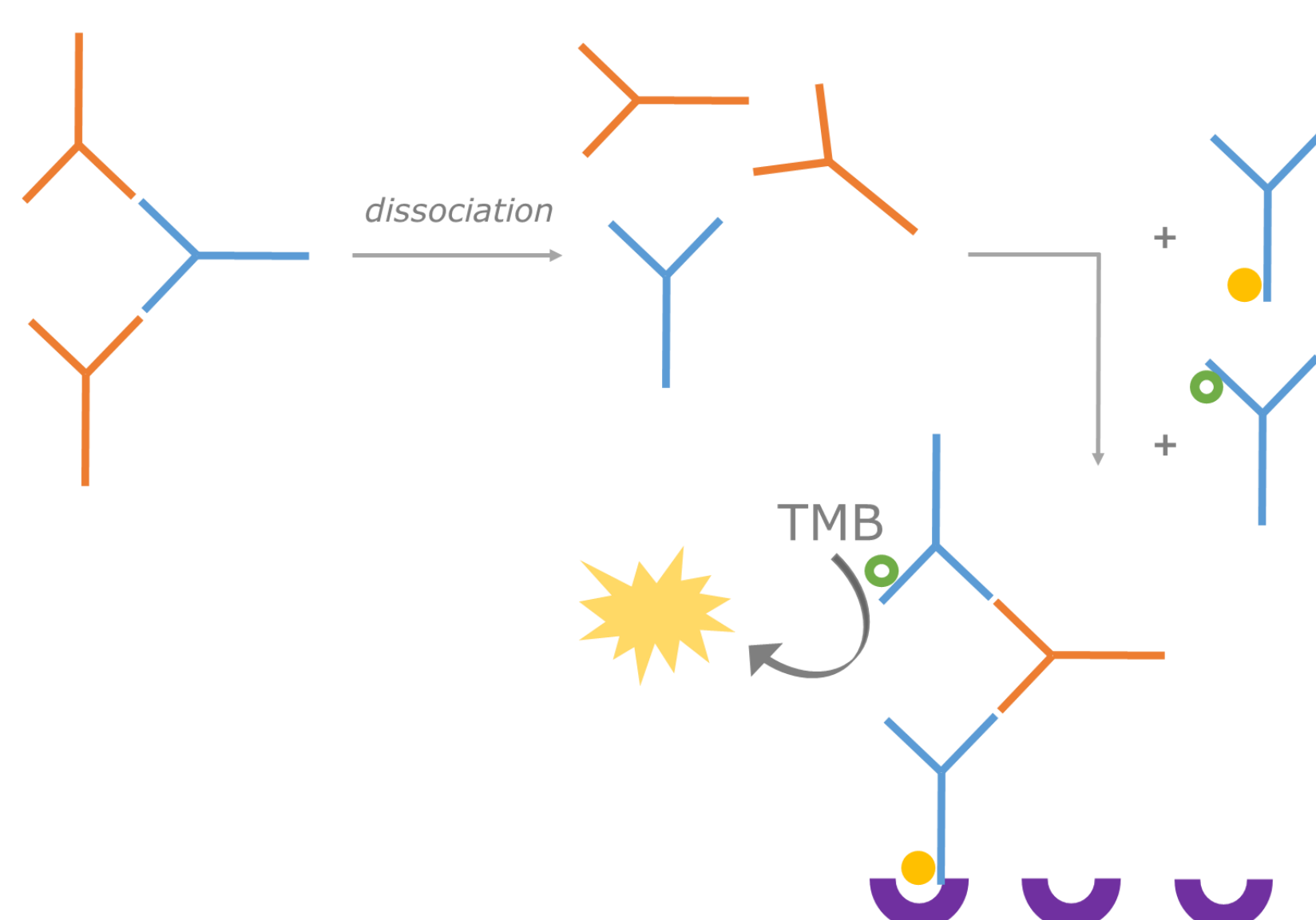


Figure 3 – Immundiagnostik "Total" ADAb assay.



Results

ADAb Detection

3/79 patients had detectable free ADAb using the LT assay with one of these patients testing negative using IM total ADAb assay.

17/79 patients tested total ADAb positive but free ADAb negative.

Drug Levels

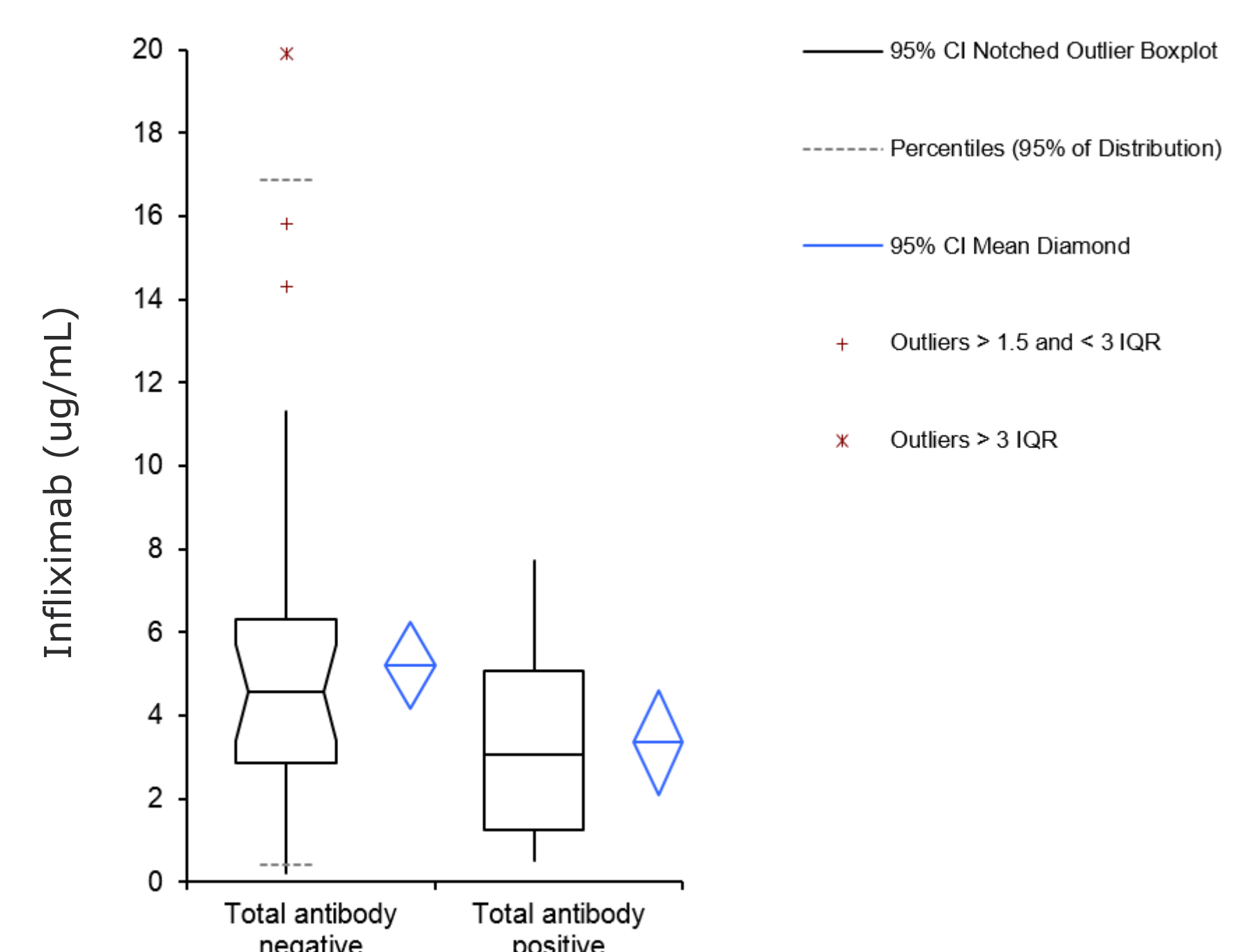
All patients positive for free ADAb had subtherapeutic levels of drug (<1.0 ug/mL).

On average, drug levels were 1.9 ug/mL lower in patients with detectable total ADAb (Figure 4) though this association did not reach statistical significance (p=0.07).

11/19 patients tested positive for total ADAb despite therapeutic drug levels (>2.0 ug/mL). Only 3/17 patients who tested total ADAb positive but free ADAb negative had subtherapeutic levels of drug.

3/79 patients had sub-therapeutic drug levels with negative free and total-ADAb.

Figure 4 – Infliximab concentrations relative to total ADAb status.



Markers of Disease Activity

All patients with detectable free ADAb showed evidence of active disease (FCAL > 59ug/g).

The clinical phenotype of patients with positive total ADAb was variable (Table 1) with no clear correlation between total ADAb status and clinical outcomes (all p values >0.2).

Table 1 – Total ADAb status and clinical outcome.

Total ADAb + / Free ADAb - (n=17)	Number	%
HBI <5	13	76
CRP <5 mg/L	12	71
FCAL <60 ug/g	7	41

Conclusion

Positive free ADAb with subtherapeutic IFX drug levels correlated well with clinical and biochemical markers of disease activity. Though there was a weak association between total ADAb status and IFX drug levels, this didn't translate into different clinical outcomes. As such, further work is required to establish the significance and utility of total ADAb in clinical decision making.