1. **TAXIT study investigates therapeutic drug monitoring in IBD with mixed results**

It is known from post-hoc analyses of RCTs that serum infliximab trough concentrations (TC) correlate with clinical response, remission and mucosal healing in patients with IBD. However, whether pro-actively titrating IFX doses to achieve therapeutic TCs is useful and cost-effective is unknown. TAXIT was a single center prospective study from Belgium which compared the efficacy and cost-effectiveness of TC-based dosing of IFX with standard of care (clinically-based dosing) in a cohort of stable IBD responders on maintenance therapy with infliximab. The primary endpoint was the rate of clinical remission at 1 year after treatment optimization. In the first, “optimization” phase, 263 IBD patients (186 CD and 89 UC) with stable response to therapy had their IFX dose adjusted up or down to achieve a pre-specified TC of 3-7 mcg/mL (76 had their dose increased, 72 decreased and 115 were left unchanged). The 251 patients in whom this was successful were randomized to a “maintenance” phase in which one group continued with IFX dose adjustments based on TC and the other with IFX dosed based on symptoms and CRP (clinical-based group). In the “optimization” phase after dose escalation, the proportion of CD patients in remission increased from 65% to 88% (p=0.02) but did not change in UC patients. Instead, only 4% (3/72) patients lost response and 11% lost remission after the IFX dose was decreased based on TC. During the maintenance phase, there was no additional benefit to continuing TC-based dosing vs. symptoms/CRP based dosing – remission rates of 66-69% in both groups. A slightly higher proportion of patients in the clinical-based group needed rescue therapy compared to TC-based dosing (17% vs. 7%). Significantly more patients in the clinical-based dosing developed undetectable IFX levels and slightly more had positive antibodies compared to TC-based dosing. Interestingly, in the pharmaco-economic evaluation, TC-based dosing was associated with a lower QALY but also slightly lower cost (by about € 300 or $330/patient x year) compared to clinically-based dosing.

**Comments:** Although TAXIT failed its primary endpoint (increased efficacy after 1 year of maintenance therapy), there are several important take-home messages resulting from this study. In particular, it provides a very useful cross-sectional analysis of the pharmacology of IFX (and likely other biologics) in IBD patients thought to be “responders” on clinical grounds: less than half have “optimal” drug levels, 30% have low levels (including 9% - undetectable) and 27% had “supra-therapeutic” levels based on the proposed “ideal” trough concentrations. Thus, even if the study was overall negative, it is the first to demonstrate that dose de-escalation is actually possible and safe in IBD stable responders. The reason the study was negative is likely because it studied a low-risk population (i.e. stable responders) and a study design in which patients were randomized after drug optimization rather than before. This study clearly needs to be replicated prospectively during induction therapy and using an intent-to-treat analysis whereas patients are randomized to pro-active dosing based on trough levels or clinical monitoring (standard of care) alone from the first dose. A study investigating this strategy in patients with secondary loss of response to anti-TNF biologics is currently ongoing (RAPID). Until then, the benefits of optimizing therapy based on therapeutic drug levels remains unclear. Similar studies investigating optimization of injectable anti-TNF drugs such as adalimumab, certolizumab or golimumab are also warranted.

2. 6-TGN concentrations correlate with IFX trough levels in IBD patients on combination therapy

Studies have demonstrated the benefit of combination therapy with IFX and IMM in patients with CD and UC who are naïve to either drug class (SONIC and UC SUCCESS). However, there is controversy as to the optimal dose of IMM for preventing immunogenicity in these patients. Combination therapy has also been associated with an increased risk of side-effects, particularly opportunistic infections and lymphoma. In this cross-sectional single center study, the investigators set to determine the correlation of thiopurine metabolites (6-TGN) with trough IFX and antibody levels (ATI) in a retrospective cohort of 72 IBD patients in stable response on combination therapy. 34 patients on IFX monotherapy served as controls. All pharmacokinetic analyses were performed at a reference lab. An optimal cut-off IFX level of 8.3 mcg/mL was chosen based on the association with mucosal healing. The majority of patients on combo therapy received IFX at a dose of 5 mg/kg q 8 and an azathioprine equivalent dose of 1.8 mg/kg. IFX trough levels were significantly lower in patients on mono-therapy compared to combo therapy. Among patients on combo therapy, there was a positive correlation between IFX levels and 6-TGN concentrations (rho 0.53, p<0.0001) with a cut-off 6-TGN concentration that best predicted an optimal level of IFX (8.3 mcg/mL) of 125 pmol/8x10⁸ RBC. Patients with lower 6-TGN levels also had a significantly higher likelihood of detectable ATI (OR, 13, p<0.01). In multi-variate analysis, 6-TGN levels, the IFX dose/kg x week and age were positively associated with IFX levels. Patients on combo therapy as a group had higher rates of mucosal healing compared to those on monotherapy (OR, 8.2, p<0.001).

Comments: This study provides useful information regarding the optimal dose of IMM for maintaining adequate IFX trough levels in patients who are stable responders. Although the equivalent daily dose of thiopurine is not provided, based on the 6-TGN level this seems to be just over half the therapeutic dose (or ≈ 1.5 mg/kg azathioprine) and it appears to be significantly higher compared to the dose suggested by other retrospective studies. Several limitations have to be taken into account including a significant selection bias. Patients in this study were all doing well on combination therapy but information about drug concentrations in patients who failed medical treatment is not available. The authors did not specify the reason for therapeutic drug level testing in this subgroup of patients. There is no separation of patients with UC and CD and it is also unclear if the data with IFX can be extrapolated to other biologics. Nevertheless, if the results in this paper can be replicated in prospective studies, it will represent a significant progress in the medical management of IBD.


3. CRP, calprotectin and lactoferrin for detecting endoscopic activity in IBD

The “treat to target” strategy in IBD involves optimizing medical therapy until a well-defined goal is achieved. Since symptoms are unreliable, several surrogate objective markers of disease activity have been studied for disease assessment in IBD. The current paper is a review of the diagnostic accuracy of CRP, fecal calprotectin (FC) and lactoferrin (FL) for assessment of endoscopic disease activity in IBD. Investigators have summarized data from 19 studies encompassing just under 2,500 patients, all of them from outside the US. The pooled sensitivity and specificity were 0.49 and 0.92 for CRP, 0.88 and 0.73 for calprotectin and 0.82 and 0.79 for lactoferrin. Fecal calprotectin was more sensitive than CRP in both UC
and CD and was more sensitive in UC than CD. A number of sensitivity analyses showed that the results were robust to a number of non-IBD control iterations. The investigators also found significant heterogeneity between studies in clinical and endoscopic endpoints and cut-off points for each test. On the basis of summary ROC curves, the authors concluded that optimal thresholds for CRP, FC and FL are 5 mg/dL, 50 mcg/g and 7.25 mcg/mL to distinguish between active and inactive endoscopic disease activity. To illustrate the clinical utility of these biomarkers, the authors provide useful Fagan plots for probability estimation of active disease (see below inset a for FC and c for CRP).

Comments: This is a very useful review of the diagnostic accuracy of several biomarkers in IBD using endoscopy as a reference standard. As opposed to CRP which is a ubiquitous inflammatory marker, calprotectin is specific for gut inflammation, as is lactoferrin although the latter is not commonly utilized in practice. As the authors pointed out, the information in this paper lends support for using these tests not only for the initial diagnosis but also for monitoring disease activity and, perhaps disease recurrence after surgery. In particular, the high negative predictive value suggest that these tests can be confidently used to rule out active disease and thus sparing a large number of subjects from getting expensive and invasive diagnostic tests such as colonoscopy and cross-sectional studies. The authors also discuss the limitations of each study in the context of IBD diagnosis. Also, no information is provided in this review about the correlation of biomarkers with the endoscopic disease severity and prediction of response to medical therapy.