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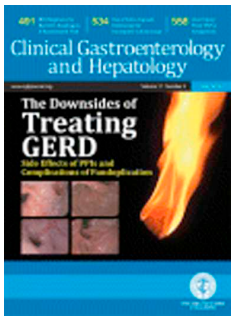

Reactive versus proactive therapeutic drug monitoring in IBD patients treated with infliximab: A self-fulfilling prophecy

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TITLE PAGE

Title: Reactive versus proactive therapeutic drug monitoring in IBD patients treated with infliximab: A self-fulfilling prophecy.

Short "running" title: Therapeutic drug monitoring in IBD

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Abbreviations: IBD inflammatory bowel disease

TDM therapeutic drug monitoring

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Dear Editor,

We read the article by Papamichael *et al*. with interest.[1] This was a retrospective cohort study comparing the long-term outcomes of inflammatory bowel disease (IBD) patients treated with infliximab. The authors concluded that proactive therapeutic drug monitoring (TDM) was associated with better clinical outcomes including greater drug durability, less need for IBD-related surgery or hospitalization, and a lower risk of developing antibodies to infliximab than those in whom TDM was reactive. However, there are some issues with the study design that we would like to draw attention to.

Reactive TDM was performed only in patients who presented with symptoms consistent with current disease activity, or those who had experienced a prior infusion reaction. Thus, the apparent association of proactive TDM with improved clinical disease outcomes is likely to be largely related to the disparity in disease activity between patients in the proactive and reactive TDM groups at study entry. Although the authors acknowledge this as a limitation, they did not provide data on disease activity at the time of first institution of TDM.

In addition, the proportion of patients receiving escalated dosing of infliximab at the time of inclusion in the study was significantly higher in the reactive TDM group (51% vs. 35%; P = 0.009), again suggesting a significant difference in inflammatory activity between the two groups. Furthermore, at the time of allocation to proactive versus reactive TDM, antibodies to infliximab were present in a significantly higher proportion of patients in the reactive versus the proactive groups (28% versus 5%), which is likely to explain the increased risk of subsequent infusion reaction seen in this group of patients, as has been described previously.[2]

The TAXIT study was a randomized controlled trial assessing the impact of TDM in infliximab treated IBD patients.[3] In this study, infliximab responders with optimized

infliximab trough levels were randomized to a dosing regimen based only on physician's assessment of clinical disease activity, or a group where dosing was based on TDM. There was no difference in clinical and biological remission between the two groups after 12 months of therapy, but the proportion of patients flaring during the maintenance phase of the study was lower in those with TDM-based infliximab dosing. These findings indicate that Papamichael *et al.* are likely to have overestimated the superiority of proactive over reactive TDM on clinical outcomes in IBD.

Optimization of anti-TNF therapy may be associated with improved outcomes in IBD,[4] and further studies investigating how better to personalize these treatments are welcome.[5] Proactive TDM is the logical approach to the long-term management of patients treated with infliximab but, on the basis of the findings of the current study, its superiority over reactive TDM cannot be ascertained.

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