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Letter: infliximab induction regimens in steroid-refractory acute severe colitis - a propensity score analysis

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Dear Editors,

We read with great interest the article by Sebastian *et al.*[1] comparing colectomy rates in patients with acute severe ulcerative colitis (ASUC) receiving standard and accelerated infliximab dosing regimens. While an accelerated infliximab dosing strategy is often employed, there is limited evidence to support such practice with no controlled data currently

available. In particular no significant difference in early or late colectomy rates has been found between accelerated and standard regimens in two recent systematic reviews.[2,3]

Clinicians' perception of disease severity often drives the selection of standard versus accelerated therapy. Sebastian *et al.* are to be commended for their use of propensity scoring analysis in their study as a means of addressing provider bias.[1] Whilst the unmatched comparison found no difference in colectomy rates between the two groups, after propensity matching the index admission and Day 30 colectomy rates were lower in the accelerated group; suggesting benefit from this strategy in the short-term. However, long-term colectomy rates were not significantly different between accelerated and standard regimens, similar to the findings of a retrospective study by Gibson *et al.*[4] The lack of long-term benefit from an accelerated strategy raises the possibility that either the maintenance regimen employed was insufficient or that regardless of the induction regimen employed an accelerated regimen may be postponing the inevitable.[5] Nevertheless an argument in favour of accelerated induction is that it may convert an emergent colectomy into an elective colectomy thereby potentially reducing the associated morbidity and mortality.

It is important to acknowledge the heterogeneity in the definitions of the dosing regimens described in this study. The accelerated dosing arm included patients who received two doses of 5mg/kg infliximab with a maximum 7-day gap between the two doses as well as patients who received an initial 10mg/kg dose prior to a second dose within 2 weeks.[1] While these regimens reflect real-life practice, the strategies are pharmacokinetically distinct and makes analysis challenging. Accelerated infliximab clearance is associated with treatment failure[6] and thus it is important to understand whether the initial dosing strategy can influence the pharmacokinetic behaviour and indeed, the clinical outcome.

Although the propensity matching strategy used by Sebastian *et al.*[1] takes into account *known* confounders to reduce the effect of provider bias, the retrospective design of the study does not allow controlling for *unknown* confounders. This reinforces the need for a controlled trial of infliximab dosing regimens in ASUC which is currently underway via the PREDICT UC study which we hope will minimise the risk of imbalance of known and unknown confounders between groups. (Clinicaltrials.gov NCT02770040)

Future studies in ASUC should aim to identify clinical, endoscopic, biochemical and immunological predictors of response. Insights into patient preferences, patient-reported outcomes and quality of life are equally important. Only after all these factors are considered can we hope to find the optimal strategy which will pave the way towards precision medicine in ASUC.

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