Top-down in the long-term in Crohn's disease

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Anti-TNF therapy has revolutionised management of Crohn's disease (CD) and has helped shift the goals of therapy from reactive symptom management to proactive disease modification. The landmark SONIC study showed that in antimetabolite (thiopurine or methotrexate) and anti-TNF naïve patients, combination infliximab/azathioprine therapy resulted in higher rates of steroid-free clinical remission and mucosal healing at 26 weeks[1]. However, a seminal question remains whether the optimal long-term management strategy for CD is 'top-down' (early combined immunosuppression) or 'step-up' (initial corticosteroids, escalating to immunosuppressants and biologics if/when required). There are short term data but long-term data comparing the two strategies are lacking.

Enthusiasm for an early aggressive approach is founded in the concept of a 'therapeutic window' in which biology and disease course may be altered[2]. Conversely, early therapy may not alter long-term outcomes and disease course may return to baseline when the drug is withdrawn. The seminal randomised control trial (RCT) on this question was published in the *Lancet* in 2008 - this study aimed to test the hypothesis that combination immunosuppression with antimetabolite and

infliximab ('top-down') was superior than conventional 'step-up' therapy in early CD[3]. The top-down group received three doses of infliximab (weeks 0, 2 and 6) and then continued with antimetabolite monotherapy. As was practice when the study was designed, additional infliximab infusions were provided only in the case of clinical deterioration. The step-up group received two tapering courses of corticosteroid, followed by antimetabolite and then infliximab as required. Steroid-free clinical remission was found to be higher in the early combined group at weeks 14, 26 and 52 but did not persist beyond a year. A follow-up study of 35% of participants found that mucosal healing was superior in the top-down group (71% vs. 30%, p=0.36)[4].

In this issue of *JCC*, the same authors report on long-term outcomes of 119 of the 133 recruited into the original RCT using a retrospective review of medical records over eight years after the initial two-year trial (**REF**). Over this follow up period, treatment decisions were left to the discretion of their individual physician. In this study, Hoekman *et al* found no difference in clinical remission rates between the top-down vs. step-up cohorts when they were compared over defined time periods (i.e. semesters) during follow-up. These findings may represent a true lack of difference between the two groups, or alternatively be a reflection of the episodic infliximab therapy in the initial study design (potentially masking a more sustained clinical benefit if scheduled maintenance therapy had been used).

The authors report on various secondary end-points some of uncertain clinical and/or statistical significance. Hospitalization, endoscopic remission, surgery or new fistulas were no different between the two groups, although corticosteroid use was higher in

the step-up cohort. There was a lower chance of ever requiring anti-TNF in the follow up period in the top-down group although this finding is not directly relevant in the era of maintenance therapy. It does, however, provide an interesting observation that ongoing therapy may not be required for all patients and raises an important clinical challenge regarding timing and identification of patients for de-escalation of therapy: a complex area with no clear answers at present[5].

In this study, there was no difference between the two groups in terms of serious infections or malignancy. This is possibly a reflection of the relatively small number of patients in the study, given that combination therapy is thought to increase the risk of serious infections compared to monotherapy, and thiopurine use is associated with increased risk of lymphoproliferative disorders and non-metastatic skin cancer[6]. The risk of overtreatment using a top-down approach is real: in the original RCT, antimetabolite use was by definition 100% in the top-down group vs. 76% in the step-up group at week 104. This suggests steroids were sufficient to induce sustained remission in over 20% of patients without further need for escalation of therapy. Here is an obvious example of a group which may be over treated in the top-down approach.

This study provides some valuable long-term insights, in particular, that top-down treatment is probably not necessary for all patients. Although top down therapy may induce early mucosal healing more frequently than a conventional step-up approach, the question remains: could this be achieved with timely ‘accelerated’ escalation on the basis of clinical symptoms and biomarkers, which has recently been found to be superior to escalation based on clinical symptoms alone in the CALM study[7].

The main limitations of this study (acknowledged by the authors) are the retrospective study design, lack of statistical power and possible type I error with multiple testing. However, probably the most important limitation in terms of translation to clinical practice is the dramatic change in the clinical landscape since the study was designed in the late 1990s including the shift from episodic to scheduled maintenance therapy for anti-TNF, therapeutic drug monitoring, incorporation of anti-TNF antibodies into clinical management, the advent of cheaper biosimilars and the availability of other biologics (e.g vedolizumab and ustekinumab). These changes will influence or challenge the concept of whether the first decision for the clinician should be top-down vs. step-up; or rather, "who benefits from early anti-TNF"?

IBD clinicians yearn for a time when biomarkers will allow for treatment decisions in a 'personalised' or 'precision' medicine approach[8]. This ideally should provide some guidance as to who will benefit from more intensive early therapy. So far, however we are left with relatively poor clinical phenotypic indicators to identify high risk patients. There are many current studies that will examine different therapeutic strategies from various angles and there will be undoubted progress towards a more molecular approach for precision medicine in IBD. Until then, we advocate for an 'accelerated step-up' approach to therapy in early CD with tight control of inflammatory activity using adjusted therapy based on frequent monitoring.

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