**Infliximab at Diagnosis - Moving towards Personalisation in Paediatric Inflammatory Bowel Disease**

*Commentary on*

*First-line treatment with infliximab versus conventional treatment in children with newly diagnosed moderate-to-severe Crohn’s disease: an open-label multicentre randomised controlled trial*

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The optimal strategy for induction of remission in paediatric Crohn’s disease, and in particular the timing of introduction of monoclonal antibody therapy, remains controversial. This has long-term implications in a condition where short term benefit, including impact on growth, must be balanced against the potential need for treatment escalation and risks associated with therapy. This is not helped by the fact the condition is heterogenous in type, distribution, and severity. International guidance currently recommends that children presenting with moderate to severe luminal disease are commenced on exclusive enteral nutrition (EEN), oral corticosteroids, intravenous corticosteroids or anti-TNF therapy, with widespread use of exclusive enteral nutrition as first line [1].

In their ground-breaking article, Jongsma *et al* describe the use of anti-TNF therapy for induction of remission , and compare this to ‘conventional’ therapy in an open label randomised control trial [2]. This is novel and has the potential to inform practice. Rather than focusing on the continued debate between top-down vs step-up therapy, these data inform paediatric gastroenterologists on the utility of induction therapy with infliximab, with the protocol dictating patients who are able should stop the drug after the final infusion at 22 weeks. The results of the study, conducted on 100 patients, highlight the efficacy of infliximab (59%) to induce clinical remission at 10 weeks compared to ‘conventional’ therapy (34%), comprising 6 weeks of EEN, or oral corticosteroids. Azathioprine was started early in both treatment arms and appears to have been well tolerated. At 52 weeks the results were less clear; the first-line infliximab group achieved clinical remission in 70% of patients, compared to 56% of the conventional group, p=0.42. Whilst remission without treatment escalation was observed in more first-line infliximab patients than in the conventional arm (41% vs 15% respectively), this was somewhat confounded by the effect of the induction regimen of infliximab (with azathioprine) lasting beyond 30 weeks, compared to the conventional arm who were on azathioprine monotherapy from as early as 6 weeks.

The difficulty is, if infliximab is safe and effective at diagnosis, should all cases be started on it? This is particularly important as in this study only 35/97 patients remained on monoclonal antibody treatment at 52 weeks, and as the authors discuss, in general recent guidance suggests once treatment is started it is continued.

It has long been established that many patients will achieve medium-term remission without immunosuppression, with Markowitz *et al* , in a paediatric cohort, demonstrating that at 1 year post-induction therapy 43% of patients remained in remission without the need for corticosteroids or thiopurines [3]. Therefore there is potential for large numbers of patients being on long-term monoclonal antibody therapy who don’t necessarily need it and so whilst Jongsma *et al* elegantly demonstrate the potential of infliximab to induce remission, further questions arise from this data set; which patients should have aggressive therapy? Who should continue on anti-TNF treatment beyond induction? Who will develop fistulating or stricturing disease? Who will have long-term quiescent disease? Answering these questions necessitates consideration of the heterogeneity of inflammatory bowel disease, and the need to better inform this by developing predictors based on characteristics or biomarkers at diagnosis, and during early therapy. This strategy moves away from a one size fits all approach, recognising there are multiple different phenotypes within the wide spectrum of inflammatory bowel disease [4]. Although this ambition is clearly at the forefront of translational inflammatory bowel disease research, this is confounded by realisation that genomic, transcriptional, microbial and clinical stratification tools, alongside genomic, transcriptomic and microbial biomarkers are difficult to identify, and even more problematic to implement. In paediatric Crohn’s disease, the landmark publication from Kugathasan *et al* in 2017, detailed risk-models including clinical features, gene expression, microbial profiles that predicted the occurrence of disease complications, with a maximal area under the receiver operator curve of 0.72 [5]. Biasci *et al* have published data detailing a CD8 T-cell transcriptional signature that is reported to separate all inflammatory bowel disease (IBD) patients into high *versus* low long-term disease activity, although this has not been replicated in paediatric cohorts [6,7]. Similarly, our own group has identified a Th17 cell signature in ileal biopsies of newly diagnosed paediatric Crohn’s disease patients associated with prolonged time to relapse [8]. However, despite increasing data clinical application of these findings has lagged behind scientific reporting. Moving forward it appears likely that precisely phenotyped prospective cohorts treated according to standardised criteria, rather than randomised controlled trials, should be employed to develop stratification models which can then be updated by continued study and refinement.

Moving from treating patients as homogenous cohorts, to assessing them as individuals with their own specific cause of IBD, their own disease course and their own responses to treatment has the potential to improve outcomes. The evidence that top-down therapy promotes remission in cohorts of patients is not in question, however the appropriateness of this approach is questioned by the potential to over treat [9]. For example, although the impact of anti-TNF therapy on fistulating complications is demonstrable, the progression of fibrostenotic disease does not appear to be prevented by anti-TNF therapy [10]. Jongsma and colleagues must be congratulated on their study, but we remain cautious that the findings should not be over-interpreted. The future implementation of these data must be centred on accurate identification of the patients who will benefit from anti-TNF induction therapy, sparing those not requiring it and using a better alternative in others. This study does not provide reason to advocate for the ubiquitous use of infliximab induction, rather it presents the opportunity to stratify patients and treat those who will benefit from the most effective therapy. Whilst this is not yet a reality, the possibility of precision therapy for paediatric inflammatory bowel disease now moves closer to clinical implementation.

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Competing interests

RMB is editor in chief of Frontline Gastroenterology and BMJ Open Gastroenterology. JJA is the social media editor of BMJ Open Gastroenterology.

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