**Letter to the Editors- Anti-TNF therapy and intestinal resections in Crohn’s disease - are we just delaying the inevitable?**

*Reply to- Increased prevalence of anti‐TNF therapy in paediatric inflammatory bowel disease is associated with a decline in surgical resections during childhood*

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We read with interest the recent publication in *Gut* from Murthy *et al*, reporting no impact on rates of intestinal surgery in patients with Crohn’s disease (CD) since the introduction of widespread anti-TNF therapy in Ontario, Canada [2]. In contrast, recent data published in *Alimentary Pharmacology and Therapeutics,* from our centre, identifying a significant reduction in intestinal resections during childhood, parallel to the increased use of monoclonal antibody therapy in paediatric onset disease [1].

Many factors influence surgical decision making in CD, however the major driver behind intestinal resection is the development of fibrostenotic disease [3]. Anti-TNF therapy has proven extremely effective in controlling inflammation and perianal disease, but it’s effect on intestinal fibrosis is less certain [4]. Blockade of TNF-alpha reduces the inflammatory response through decreased activation of downstream pro-inflammatory pathways [4]. The premise that anti-TNF therapy should reduce surgical resections in CD is based upon the assumption that stricturing disease is secondary to a TNF-alpha mediated process, which is the case in a subset of patients only [5]. Mutations in the *NOD2* geneare the most replicated basis for a stricturing phenotype, with studies also implicating variation in *ATG16L1, IL23R, MAGI1, IL12B* and *JAK2* [5]*.* A genetic predisposition appears to be the main driver of a distinct stricturing behaviour in some patients with CD, which may coexist with an inflammatory phenotype. However, only an estimated 10% of patients with purely inflammatory phenotype will progress to fibrostenotic complications, suggesting a separate process driving differing disease behaviours [6].

Some data suggests early initiation of anti-TNF may reduce the need for surgery in the longer term [7]. Conversely, our data indicates early anti-TNF therapy is more likely to delay resection until adulthood, through shrinking the inflammatory component of stricturing disease and buying time prior to resection of the fibrotic bowel [1]. It seems increasingly likely that anti-TNF therapy delays, but does not avoid, stricturing complications. This hypothesis makes the reports from Murthy *et al* even more intriguing, with similar data from Eberhardson *et al* in 2017 also demonstrating anti-TNF therapy lacking impact on bowel resections in the long-term management of CD [8]. At a molecular level it is possible these results are explained by anti-TNF agents merely delaying resection, through shrinking the inflammatory component of disease. In patients with the stricturing phenotype, the introduction of anti-TNF would not reduce the number of intestinal resections as the molecular cause for stricturing disease is, at least in part, distinct from the inflammatory aetiology. Testing this hypothesis will require prospective cohorts to determine the impact of anti-TNF therapy on stricturing disease incidence and intestinal resection rates. Novel medications targeting alternative pathways, such as *RIPK2* inhibitors in the *NOD2* signalling cascade, may prove more useful in the management of patients with a genetic predisposition to fibrostenotic disease [9]. Despite the lack of long-term evidence indicating a reduction in intestinal resections with anti-TNF therapy, controlling the inflammatory component, reducing the resection size and delaying surgery until after childhood are significant outcomes, which improve patient’s lives.

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