



# Alpha Fail: Ustekinumab to the Rescue After TNF $\alpha$ Failure in Patients with Moderate to Severe Crohn's Disease

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The overarching goals of the management of inflammatory bowel disease (IBD) include the induction of disease remission (with particular focus upon mucosal healing) followed by its maintenance over time [1]. Though standard therapies such as corticosteroids, mesalamine, and thiopurines have been effective, there is increasing emphasis upon advanced therapies, including biologics and small molecules [2–4].

A number of international guidelines have consistently advocated for the early use of biologics for luminal CD to both induce and maintain remission, particularly in cases that are not responsive to conventional therapy such as systemic steroids and/or thiopurines [5–8]. Though anti-tumor necrosis factor (TNF $\alpha$ ) agents are a popular first-line choice, owing to their high clinical efficacy and rapid onset of effect, primary or secondary failure of anti-TNF $\alpha$  treatment is common, affecting up to 50% of those treated [9]. Options to manage this situation include dose optimizing the current anti-TNF $\alpha$  agent either by increasing the dose and/or frequency of treatment, switching to a different biologic of the same or different class, changing to a new type of medication (e.g. small molecule drugs), or considering surgical intervention. To date, guidelines remain mixed as to how to best approach this challenging situation. One common strategy is to change the biologic to an agent that targets a cytokine other than TNF $\alpha$  such as the IL12/23 inhibitor ustekinumab. At present, only two trials [10, 11] have examined the use of ustekinumab following anti-TNF $\alpha$  failure in the setting of moderate-to-severe CD. Both the CERTIFI ( $n = 526$ ) [11]

and UNITI-1 trials ( $n = 748$ ) [10] found that ustekinumab at a dose of 6 mg/kg was significantly more likely than placebo to induce clinical response during induction at 6 weeks, with CERTIFI also reporting a positive effect on clinical response and remission during maintenance treatment at 22 weeks. In light of these findings, the recently updated European Crohn's and Colitis Organisation (ECCO) guidelines have suggested that ustekinumab or vedolizumab could be considered in individuals with moderate-to-severe luminal CD who have failed anti-TNF $\alpha$  therapy, although the strength of this recommendation was weak and the evidence base was graded as very low-quality [8].

In a recent issue of *Digestive Diseases and Sciences*, Latras-Cortés et al. [12] report their analysis of the use of ustekinumab in 68 adults with CD. All the study participants had failed first-line biologic therapy mostly with anti-TNF $\alpha$  agents;  $n = 66$ , 98%, and most had severe disease. The authors reported greater persistence with ustekinumab compared to anti-TNF $\alpha$  biologic treatment (86% vs 31% respectively at 3-year follow-up) with 87% of patients continuing on ustekinumab at the end of study follow-up although one-third ( $n = 25$ , 37%) of the participants required dose optimisation (either 90 mg or 130 mg every 4 weeks). Ustekinumab was also very well tolerated, with only three (4%) of the subjects discontinuing treatment due to adverse effects. Clinical remission rates were high at 41% at 4 weeks and 54% at 8 weeks, independent of dose optimisation. Latras-Cortés et al. [12] also reported high rates of perianal fistula healing, with seven (70%) achieving clinical remission and four (40%) achieving fistula resolution.

Although there are a paucity of trial data, multiple retrospective observational studies have examined the use of ustekinumab for CD following anti-TNF $\alpha$  failure [13], although most of the available literature is limited by short duration of follow-up and/or high rates of concomitant glucocorticoid use, which can complicate the analysis of the long-term effects of ustekinumab alone. Thus, a major strength of the current study is the prolonged duration of

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follow-up, where data were collected from the beginning of treatment until 60 months or the discontinuation of ustekinumab, with no patients being lost to follow-up [12]. Further, very few patients concurrently received corticosteroids ( $n=5$ , 7%) although there was no indication about whether other medications such as 5-aminosalicylates or immunomodulators were used. The authors' findings that ustekinumab was generally effective, persistent, and tolerable therefore strengthen its position as an attractive alternative treatment in this difficult-to-treat population. Nevertheless, the generalizability of their findings is limited by their single-center setting and modest sample size; further, their retrospective observational design precludes the identification of any causal relationships.

Overall, this analysis provides insight into the isolated impact of ustekinumab as a second-line biologic therapy following anti-TNF $\alpha$  failure in individuals with severe CD across an extended duration of follow-up [12]. Given the prevalence of anti-TNF $\alpha$  failure and the therapeutic quandary that it poses, future studies should seek to validate the role of ustekinumab as a second-line biologic in multicentre randomized trials, and investigate the efficacy of other advanced therapies such as Janus kinase inhibitors in this challenging-to-treat population.

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## Declarations

**Conflict of interest** None of the authors have any conflicts of interest to declare.

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