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UPADACITINIB FOR CROHN'S DISEASE: AN ALTERNATIVE TO ANTI-TNF THERAPY?

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Introduction

Since its approval for Crohn's disease, following the successful U-EXCEL, U-EXCEED, and U-ENDURE Phase 3 trials, upadacitinib has been increasingly prescribed to Crohn's disease patients, including both biologic-naïve and biologic-experienced individuals. Although there are numerous clinical scenarios where this option is worth considering, it can be viewed as a highly reasonable alternative to anti-TNF therapy for Crohn's disease.

Background

Anti-TNF drugs, specifically infliximab, are considered the most appropriate treatment for perianal Crohn's disease. This confidence stems from the ACCENT-II trial, the only prospective randomized control trial to date with a primary endpoint focused on fistulizing response. The trial showed that infliximab had a greater long-term effect compared to placebo.[1] Beneficial effects were also shown when evaluating adalimumab for fistulizing disease in both a meta-analysis and a post-hoc analysis study.[2] While other biologics such as vedolizumab and ustekinumab are used to treat perianal disease, their data is limited by mixed results, a small number of studies, varying study quality, and small participant numbers. For example, a post-hoc analysis of the GEMINI-2 trial failed to show a statistically significant difference in fistula closure rates with vedolizumab.[3] For ustekinumab, while it did not demonstrate a statistically significant superiority over placebo,[4] a recent meta-analysis revealed a significantly higher fistula response rate compared with placebo.[5] Hence, owing to a superior quality of evidence, as well as a better clinical experience, infliximab is considered first-line therapy for fistulizing disease.[6] Upadacitinib is the most recent advanced molecule to be evaluated for perianal fistulizing disease. In a post-hoc analysis of the 3 clinical trials mentioned above, external closure of fistula openings was achieved in 20.8% of patients at week 12 and 21.1% at week 52 in the upadacitinib arm, compared to 6.4% and 0% in the placebo group, respectively. Complete resolution of drainage was observed in 47.7% of patients in the intervention group at week 12 compared to 9.1% in the placebo group. At week 52, a numerically higher proportion of patients in the upadacitinib group had complete resolution of drainage compared to zero in the placebo group, although owing to the small number of patients, this difference did not reach statistical significance **(Figure 1)**.[7] Unlike anti-TNF therapy, which is most efficacious when used as a dual therapy with an immunomodulator in this scenario,[8] upadacitinib, a chemical compound that does not elicit immunogenicity, is used as a monotherapy. This approach might be a more durable and easier one for patients to manage this challenging complication of Crohn's disease. However, the advantages of upadacitinib over other biologics, and as a result its potential as an alternative to cases traditionally treated with anti-TNF therapy, are not limited to the spectrum of perianal Crohn's disease. Regarding endoscopic remission, now considered one of the pillars of treatment goals in inflammatory bowel disease (IBD), upadacitinib achieved a success rate as high as 40.1% in Crohn's patients at week 52 with the 30 mg maintenance dose. Although these results have not been examined in a head-to-head trial, they are strikingly higher than the 31% endoscopic remission rate reported for ustekinumab at week 52 in the SEAVUE trial,[9] and the 17.9% rate for vedolizumab in a phase 3b trial.[10] As endoscopic healing predicts favourable outcomes, higher success rates translate, in turn, to lower relapse rates and a better quality of life.[11]

Efficacy

The effectiveness of upadacitinib was also demonstrated in patients who had previously failed biologic treatments, including those exposed to anti-TNF treatments. In a post-hoc analysis of the U-EXCEL, U-EXCEED and U-ENDURE Phase 3 trials, patients treated with upadacitinib showed higher rates of clinical remission compared to placebo both after a 12-week induction and at week 52 of maintenance, irrespective of previous biologic treatment failures. Surprisingly, the difference in success rates between the upadacitinib arm and the placebo arm was numerically higher in the biologic-failure subgroup.[12] Likewise, upadacitinib improved endoscopic outcomes (both response and remission) after the induction phase and the week 52 maintenance period. Again, the differences in outcomes between the upadacitinib and placebo groups were more pronounced in the biologic-failure subgroup.[13] In contrast, the EXTEND study, which evaluated mucosal healing at week 12 in Crohn's patients treated with adalimumab vs placebo after 2 injection doses, showed a marked difference in remission rates between anti-TNF-naïve patients and those previously treated with anti-TNF therapies.[14] Rates of endoscopic remission were even lower among anti-TNF-exposed Crohn's patients treated with vedolizumab. As shown in the VERSIFY study, only 5.5% of those previously exposed to anti-TNF therapies achieved endoscopic remission at week 26, and only 8.3% of them reached endoscopic remission by week 52. This was in marked contrast to the 19.6% and 25% endoscopic remission rates observed in anti-TNF-naïve patients, respectively.[10]

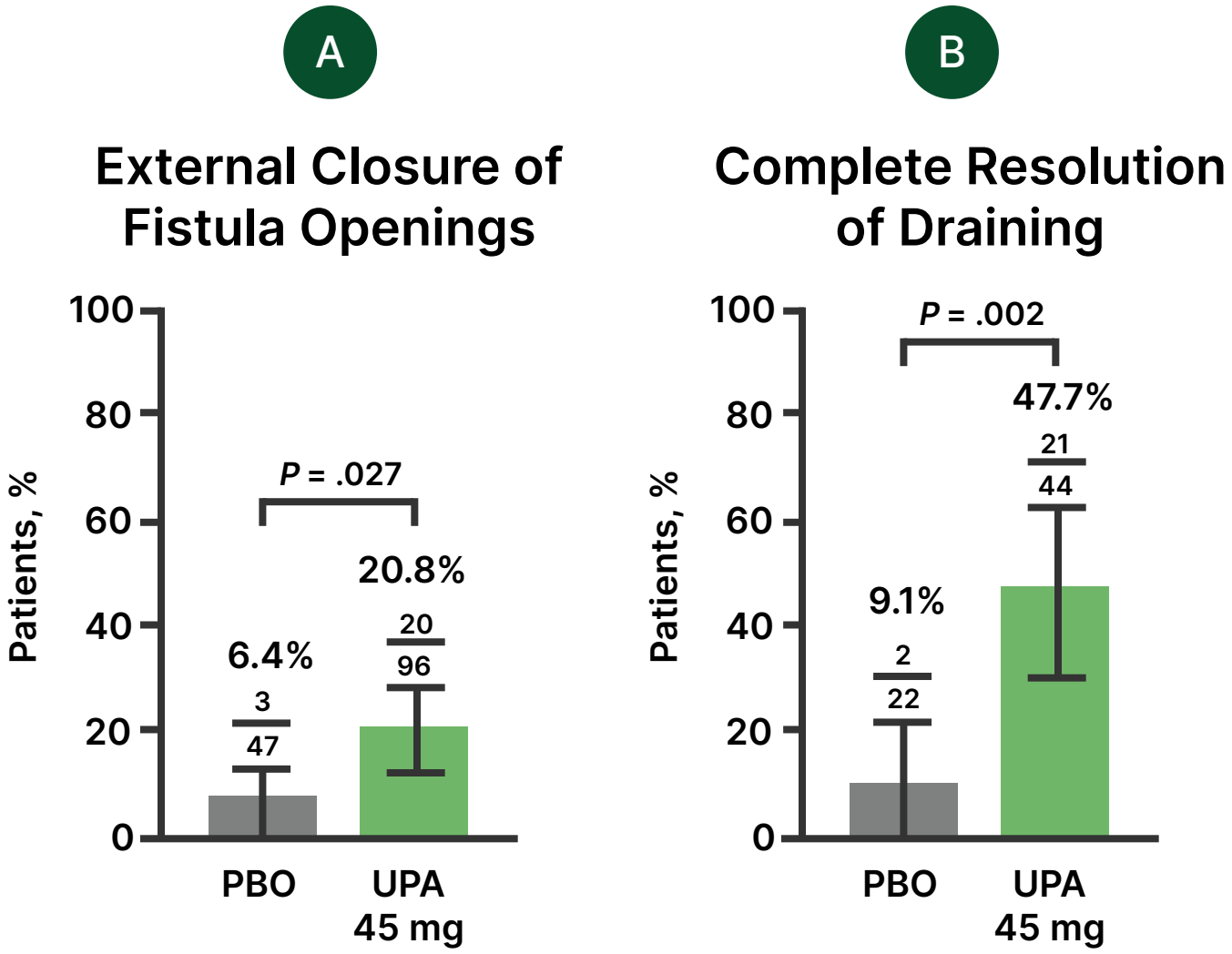

Figure 1. Proportion of patients who achieved closure of fistula openings and complete resolution of draining at week 12; adapted from Colombel, J.K. et al, 2024
Abbreviations: PBO, placebo; UPA, upadacitinib

A denominators are the number of patients with fistulas at baseline
B denominators are the number of patients with draining fistulas at baseline
External Closure of Fistula Openings: patients with absence of fistulas upon routine physical examination of patients with fistulas at baseline
Complete Resolution of Draining: patients with draining fistulas upon gentle compression, in patients with draining fistulas at baseline
Data are percent of patients (95% CI)

Co-morbidities

IBD often co-exists with other immune-mediated diseases such as ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, and more. Approximately one quarter of IBD patients have a concomitant immune-mediated disease, compared to a prevalence of 5–7% in the general population.[15] While other biologics such as vedolizumab are not used to manage such conditions, and ustekinumab is limited to treating psoriatic arthritis or plaque psoriasis,[16] anti-TNF drugs are used to manage a wider range of immune-mediated diseases.[17] Hence, for almost 2 decades, anti-TNF therapies have been the drugs of choice for treating IBD patients with other immune-mediated conditions. This was reflected in the most recent European Crohn's and Colitis Organization (ECCO) Guidelines.[18] Since upadacitinib offers the option of treating a wide spectrum of immune-mediated conditions, many of which overlap with those treated with anti-TNF drugs,[19] it serves as a good alternative to the latter.

Pharmacokinetics

Upadacitinib possesses unique pharmacokinetics and metabolic characteristics due to its rapid diffusion across cell membranes and quick absorption into the systemic circulation. Upadacitinib reaches its time to maximum concentration (Tmax) as early as 2–4 hours after administration, and steady-state concentrations are achieved within 4 days.[20] These characteristics have fundamental clinical implications. For example, a post-hoc analysis of the U-EXCEL, U-EXCEED, and U-ENDURE trials has shown that upadacitinib has a very rapid onset of action, with statistically significant

clinical response and clinical remission rates observed as early as day 5, regardless of prior biologic treatment. Moreover, these outcomes were sustainable throughout the induction period.[21] This relatively rapid onset of action is a characteristic that has traditionally been associated with infliximab[22] and adalimumab.[23] In contrast, vedolizumab and ustekinumab have slower responses to induction dosages, especially in biologic-experienced patients.[24,25] This evidence was recently incorporated into the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) clinical practice recommendations.[26] The time required for achieving a clinical response, clinical remission, normalization of inflammatory markers, and endoscopic healing was markedly longer with vedolizumab and ustekinumab compared to anti-TNF drugs. Another inherent property of upadacitinib, as a small chemical compound, is that circulating proteins, such as albumin, do not influence its pharmacokinetics. However, with biologics, albumin is essential for protection as well as transportation.[27] Consequently, low albumin levels result in low anti-TNF levels,[28] higher rates of primary non-response,[29] and secondary loss of response.[30] These characteristics could be critically important for patients with rapidly progressive disease, who are at a greater risk for complications and surgery.

Route of Administration & Storage

Another inherent advantage of upadacitinib is that, as an oral drug, it does not require special storage conditions and can be readily dispensed by pharmacies. In contrast, biologics require special cooling storage and a support system that includes infusion facilities and supporting health care providers such as nurses. This advantage of upadacitinib is underscored in remote areas where the availability of biologics is limited. This is especially true in Canada, where rural areas are not only geographically remote from health care services and pharmacies, but also face extreme weather conditions during the winter season, making health services and supply chains even more challenging. One study among IBD patients in rural areas in Canada highlighted the emotional challenges IBD patients experience as a result of these obstacles.[31] Other studies have shown that rural IBD patients have higher rates of emergency department visits, fewer gastroenterologist visits, lower endoscopy rates, and a greater risk of hospitalization compared to urban IBD patients.[32,33] A 2022 study found that individuals diagnosed with IBD in rural Saskatchewan had fewer prescription claims for biologics and more claims for 5-aminosalicylic acid (5-ASA) medications compared to urban residents. However, this does not mean that they had a less severe disease; in fact, they had a higher risk of IBD-specific and IBD-related hospitalizations than their urban counterparts.[33] This underscores the disparities among rural IBD patients, leading to poorer outcomes. Upadacitinib can potentially address these issues. Although the safety profile of Janus kinase inhibitors as a drug class is still of concern among many healthcare personnel, long-term follow-up has not revealed any new safety signals compared to previous clinical trials. These observations held true for both ulcerative colitis patients at week 288 of follow-up,[34] as well as for Crohn's disease patients at week 204 of treatment.[35] These results further confirm the tolerable safety profile of upadacitinib as observed in Phase 3 clinical trials.

Conclusion

In conclusion, upadacitinib, owing to its high potency in achieving endoscopic remission in both biologic-naïve and biologic-experienced patients, its proven high efficacy in fistulizing disease, its ability to treat other co-existing immune-mediated diseases, along with a rapid onset of action and lack of immunogenicity, could serve as an appropriate alternative for patients traditionally managed with anti-TNF drugs. This is of particular importance in countries such as Canada, where it is much easier managing a complex disease, such as Crohn's disease, with an oral pill that is more convenient for both the patient and health care authorities compared with using biologics.

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