

Triple biologic therapy for refractory Crohn's disease

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Abstract

Background: Despite significant advances in the therapeutic management of Crohn's disease (CD), a subset of patients remains refractory to available treatments. Dual-targeted therapy (DTT), combining biologics or biologics with small molecules, has emerged as a promising approach. While evidence supporting DTT continues to grow, reports of patients treated with a combination of 3 biologic or targeted agents remain exceptionally rare.

Case Presentation: We report the case of a 30-year-old male with a complex clinical course, initially diagnosed with ulcerative colitis and later reclassified as CD following ileal pouch-anal anastomosis, due to subsequent small bowel and perianal involvement. The patient also had concomitant ankylosing spondylitis. Despite multiple lines of therapy, including, anti-tumor necrosis factor agents, vedolizumab, ustekinumab, and upadacitinib, both CD and ankylosing spondylitis remained clinically active. In the absence of alternative therapeutic options and continued refusal of surgery, a triple combination of certolizumab pegol, ustekinumab, and vedolizumab was initiated and maintained over 10 months. While the treatment was well tolerated and ankylosing spondylitis remained in remission, no impact was observed on CD.

Discussion: This case highlights the challenges of managing refractory inflammatory bowel disease with overlapping immune-mediated conditions. Although the combination of biologics targeting distinct inflammatory pathways is conceptually appealing and supported by emerging data on DTT, the effectiveness of triple therapy remains uncertain in some patients.

Conclusions: Triple biologic therapy remains experimental and should be approached with caution, pending more robust evidence. Larger and translational studies are needed to better identify patients who may benefit, define optimal combinations, and clarify long-term safety of these combinations.

Keywords: triple biologic therapy; refractory Crohn's disease; case report.

1. Introduction

In recent years, the therapeutic arsenal for Crohn's disease (CD) and ulcerative colitis (UC) has expanded significantly.¹ However, despite the growing number of available treatment options, a substantial proportion of patients continue to experience intolerance, primary non-response, or secondary loss of response over time.^{2,3} These medically refractory patients remain at increased risk of requiring surgical intervention. Although surgery can be effective, it is associated with the risk of postoperative recurrence, and repeated intestinal resections may result in short bowel syndrome and long-term complications. Furthermore, patients with refractory disease are often excluded from clinical trials due to extensive prior treatment exposure and other disease-related factors, which further limits their therapeutic options.⁴ In this challenging context, dual-targeted therapy (DTT), the combination of 2 biologic agents, or a biologic with a small molecule, each targeting distinct inflammatory pathways, has emerged as a potential therapeutic strategy.⁵ While an increasing number of cases involving DTT have been reported, the use of triple biologic or targeted therapy remains exceedingly rare.⁶ Here, we describe a case of CD refractory to both monotherapy and DTT, managed with a triple biologic regimen in the context of coexisting ankylosing spondylitis.

2. Case report

We report the case of a 30-year-old male who was initially diagnosed with UC and underwent ileal pouch-anal anastomosis at the age of 17. He later experienced disease recurrence, characterized by small bowel involvement and the development of perianal abscesses, which led to a reclassification of his diagnosis as CD. The patient also had a history of ankylosing spondylitis. Despite multiple lines of therapy, including various biologics and small molecules (even after treatment optimization) such as anti-tumor necrosis factor (TNF) agents, vedolizumab, ustekinumab, and upadacitinib, along with repeated courses of antibiotics for suspected pouchitis, he continued to experience both symptoms related to ankylosing spondylitis and persistent gastrointestinal complaints secondary to CD. In April 2023, the patient reported up to 15–20 liquid bowel movements per day, despite the use of antidiarrheal agents, including 1–3 nocturnal episodes that significantly disrupted his sleep. Each bowel movement was associated with blood and mucus, severe anal pain, and a persistent rectal prolapse. Endoscopy confirmed the presence of inflamed mucosa, with extensive ulcerated areas extending along the entire length of the J-pouch reservoir (Figure 1). At that time, anti-interleukin-23 therapies and sphingosine-1-phosphate modulators were not yet

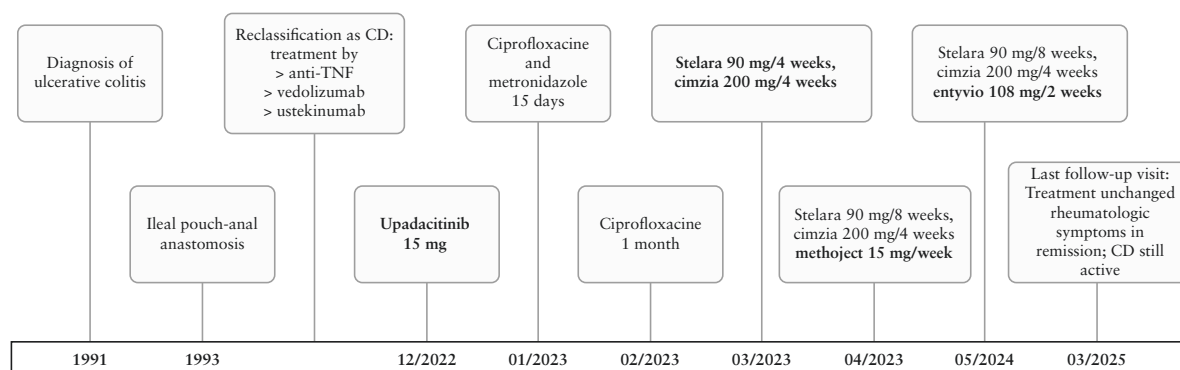


Figure 1. Patient medical history timeline. Figure created with BioRender.com.

available in France. A proximal diverting stoma was proposed to reduce fecal flow through the affected areas but was repeatedly declined by the patient. Enrollment in a clinical trial was also not feasible, primarily due to his surgical history and prior exposure to multiple lines of therapy. A combination of certolizumab pegol and ustekinumab was therefore initiated, along with methotrexate (15 mg/week). While his rheumatologic symptoms were well controlled on this regimen, gastrointestinal symptoms persisted. The patient was followed regularly throughout the year; however, in the absence of alternative therapeutic options, the existing combination was maintained. In May 2024, methotrexate was discontinued, and a triple biologic therapy was initiated. This included continued treatment with certolizumab pegol (200 mg every 4 weeks) and ustekinumab (90 mg every 8 weeks), along with the addition of vedolizumab (108 mg every 2 weeks). Despite this combination therapy, maintained for 10 months and still ongoing as of mid-March 2025 (due to the lack of alternative therapeutic options and the patient's persistent refusal of surgery), there was no clinical improvement in gastrointestinal symptoms, although rheumatologic disease remained in remission. Notably, the triple therapy was well tolerated, with no significant adverse events reported.

3. Discussion

The combination of 2 biologic agents or a biologic with a small molecule, referred to as DTT, has emerged as a promising treatment strategy for patients with severe, refractory inflammatory bowel disease (IBD),^{7–9} particularly those with extraintestinal manifestations or coexisting immune-mediated conditions.^{10,11} To date, only Braden et al. have reported 2 cases in which patients with IBD achieved both clinical and endoscopic improvement over a relatively short period following treatment with a combination of 3 advanced therapies.⁶ One case involved a patient with UC treated with vedolizumab, ustekinumab, tofacitinib, and mesalamine. The second described a patient with CD and concomitant ankylosing spondylitis, who was successfully treated with ustekinumab, vedolizumab, upadacitinib, and methotrexate.⁶ While clinical improvement was observed in both cases, our patient did not experience gastrointestinal benefit despite receiving a triple combination targeting 3 distinct inflammatory pathways, although notably, a Janus kinase inhibitor was not included in this regimen due to previous treatment failure. Interestingly, despite persistent digestive symptoms,

the patient's ankylosing spondylitis remained successfully controlled.

Given the complex network of inflammatory pathways and cytokines involved in the pathogenesis of IBD, strategically combining agents with distinct mechanisms of action may provide more effective inflammatory control and lead to improved clinical, endoscopic, and biochemical outcomes.⁷ In this patient, we employed the most commonly reported DTT regimens—typically involving the combination of an anti-TNF agent with vedolizumab or ustekinumab, or the pairing of vedolizumab with ustekinumab—as these strategies currently have the strongest supporting clinical data.⁷ According to recent systematic reviews and meta-analyses, DTT achieves clinical remission rates of approximately 50%–60% and endoscopic remission rates of around 33% in patients with refractory IBD.^{11–13} Adverse events (AEs) have been reported in 30%–40% of cases, with serious adverse events (SAEs) occurring in approximately 1%–10% of patients, infections being the most frequently reported complication.^{5,11,14} The variability in outcomes across DTT studies is likely influenced by differences in patient populations (particularly disease severity), as well as the specific combinations of biologic agents or small molecules used. Additional factors, such as prior treatment history and study design, may also contribute to the heterogeneity of findings.⁵ Despite the limited number of studies and patients included in these studies, combining advanced therapies with distinct mechanisms of action appears to be both safe and effective in patients with refractory IBD and those with extraintestinal manifestations. These results support the potential role of DTT as a viable therapeutic option in difficult-to-treat IBD.⁵

The use of triple advanced therapy in IBD remains experimental and should be approached with caution due to the potential risk of AEs. A thorough, individualized assessment is essential, weighing the risk–benefit ratio and considering the availability of alternative therapeutic options. In addition to the case reports mentioned above, the EXPLORER study is a prospective, phase 4, single-arm, open-label trial designed to evaluate the efficacy and safety of a combination of vedolizumab, adalimumab, and methotrexate in biologic-naïve patients with newly diagnosed moderate-to-severe CD.¹⁵ At week 26, 55% and 35% of patients achieved clinical and endoscopic remission, respectively.¹⁵ The study reported no new safety signals, with AEs and SAEs rates comparable to those observed with the individual monotherapies. The overall AE rates were approximately 87%, and SAE rates were around 10% at week 26.¹⁵ These findings suggest a potential

synergistic benefit of combining advanced targeted agents with complementary mechanisms of action; however, larger, controlled studies are needed to validate these observations.

The reasons why some patients continue to exhibit treatment failure and maintain active disease despite combination therapy remain poorly understood and warrant further investigation. Potential explanations include suboptimal control of known inflammatory pathways by the selected agents, activation of alternative pathways in response to treatment, or the involvement of highly specific, possibly patient-specific, inflammatory mechanisms. Further research is needed to better elucidate the underlying immunologic pathways in patients with refractory IBD and to evaluate the impact of strategic treatment combinations on mucosal inflammation. Key unanswered questions also include identifying the most effective drug combinations, potentially personalized on a per-patient basis, determining optimal dosing strategies, and defining the appropriate duration of therapy (eg, induction only vs maintenance, and if maintenance, for how long and at what dose).⁷ These challenges may be addressed through pre-clinical models and translational studies.⁷ Moreover, larger multicenter studies are essential to more comprehensively assess the efficacy and safety of these therapeutic combinations, particularly as new pharmaceutical agents become available, expanding the potential for novel combination strategies. Finally, the effects of combination therapy on specific disease phenotypes, such as pouchitis and perianal disease, remain poorly characterized and require further dedicated investigation. Altogether, these knowledge gaps underscore the need for continued exploration in this evolving therapeutic landscape.

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Author contributions

Laurent Peyrin-Biroulet was the treating physician, responsible for patient management, data collection, and manuscript review. Sophie Vieujean drafted the initial version of the manuscript and created the figure.

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Conflicts of interest

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Data availability

The data underlying this article are available in the article.

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