CLINICAL VIGNETTE

Infliximab plus Tofacitinib Combination Therapy in a Patient with Severe Ulcerative Colitis

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Introduction

Crohn's disease and ulcerative colitis, the principal forms of inflammatory bowel disease (IBD), are characterized by symptoms of chronic inflammation, rectal bleeding, and abdominal pain.[1] The landscape of treatment for IBD has expanded to include new monoclonal antibodies and small molecules. These new therapies have revolutionized the treatment and management of IBD. However, despite the availability of several new advanced therapies, clinical remission rates in patients with IBD remain low.[2,3] This underscores the need for a paradigm shift in the way we treat patients with IBD including the use of combination biologics or small molecules.

We present a patient with active severe Ulcerative Colitis (UC) who achieved clinical and endoscopic remission with combination therapy of Infliximab and Tofacitinib.

Case

Patient is a 20-year-old male with severe ulcerative pancolitis (UC) diagnosed in 2022. At the time of diagnosis, he had mild left-sided ulcerative colitis. He was induced with oral steroids with adequate response and transitioned to oral 5-aminosalcylates (5-ASA). Later, rectal 5-ASA was also added to the regimen to achieve clinical remission. He was in clinical remission until April 2023 when he had a severe flare with frequent bloody diarrhea, fatigue, and severe urgency. He was hospitalized and colonoscopy revealed mayo endoscopic subscore (MES) 1 in the right colon, MES 2 in the transverse colon and MES 3 in the left colon. Biopsies also revealed focal positive staining for Cytomegalovirus (CMV) in the transverse colon. His severe, active pancolitis was induced with intravenous corticosteroids and Infliximab (IFX) 10 mg/kg every 8 weeks. He was concurrently initiated on Valganciclovir, for CMV treatment. He finished Infliximab induction in July 2023. After his oral steroid therapy was tapered, he had recurrence of his flare and was hospitalized again. Flexible sigmoidoscopy revealed severe left sided UC (Mayo 3). There was no evidence of CMV infection on pathology. The patient did not want to consider surgical interventions. Therefore, he initiated combination therapy with Infliximab 10 mg/kg every 8 weeks and Tofacitinib 10 mg three times daily (TID). After hospital discharge, Infliximab was optimized to 10 mg/kg every 6 weeks. He was able to achieve clinical and endoscopic remission within 6 months. Repeated fecal calprotectin remained normal for the next year, after starting dual therapy treatment. After achieving clinical and endoscopic remission in the summer of 2024, the plan was to slowly taper Tofacitinib and maintain the patient on combination of IFX and Methotrexate. Tofacitinib was reduced to 5 mg twice daily in September 2024 and he continued Infliximab 10 mg/kg every 6 weeks. He continues to be in remission with a slow taper of Tofacitinib.

Conclusion

IBD includes Crohn's disease (CD) and Ulcerative colitis that are characterized by chronic intestinal inflammation.[4] These diseases are progressive and can lead to complications including hospitalization and surgery.[4]

The current landscape of treatment for CD and UC includes biologic therapies and small molecules as advanced therapies for moderately to severely active disease.[4] Biologic therapies include tumor necrosis factor (TNF) alpha antagonists, $\alpha 4\beta 7$ integrin antagonists, interleukin IL-12 and IL-23 antagonists, Sphingosine-1-phosphate receptor (S1PR) modulators and Jak inhibitors.[5] Despite these therapies, only about 40% of patients achieve clinical remission at one year.[6] There are limited treatment options in patients who have failed several advanced therapies.

Combination therapies with biologic agents and immunomodulators have been shown to have increased efficacy.[7] This was demonstrated in the SONIC study where patients on IFX plus Azathioprine or IFX monotherapy were more likely to have long-term clinical remission.[7] However, there is an increased risk of malignancy associated with thiopurines.[8] Therefore, a new strategy of combining biologic therapies or biologic and small molecules has emerged. This combination is thought to be more effective by targeting different inflammatory pathways. Dual advanced therapies also have potential to improve outcomes in refractory patients.[4] A recent meta-analysis reported the safety of dual advanced therapies is similar to biologic monotherapy.[4] The meta-analysis reported pooled clinical remission rates of 58.8%.[4] The pooled endoscopic remission rate was 34.3% and endoscopic response rate was 42.9%.[4] In addition, the need for surgical intervention was

reduced in the refractory patient population.[4] One limitation of dual biologic or small molecule therapy is concern for increased adverse events.[9] However, the favorable safety profile of newer agents such as Vedolizumab or Ustekinumab may reduce the concern. Further trials are needed to evaluate safety of dual biologic or small molecule treatment.

In conclusion, in a refractory patient population, treatment with dual biologic or small molecule may be a reasonable option to prevent severe adverse events including surgical resection, perforation, toxic megacolon and colorectal cancer. However, more randomized controlled trials are needed to document efficacy of dual biologic or small molecule treatment strategy.

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