Combining Cyclosporine With Ustekinumab in Acute Severe Ulcerative Colitis

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ABSTRACT

We have demonstrated the effectiveness and safety of combining cyclosporine and vedolizumab to treat ulcerative colitis (UC). We present 2 cases of hospitalized acute severe UC who had failed therapy with antitumor necrosis factor and vedolizumab and were treated successfully with induction cyclosporine and safely bridged to ustekinumab maintenance therapy. Both patients have avoided colectomy. There were no adverse events. We propose this novel treatment combination in medically resistant acute severe UC.

INTRODUCTION

Cyclosporine is a calcineurin inhibitor that has efficacy in treating ulcerative colitis (UC) and is an option for induction and short-term maintenance in medically resistant disease.1 Our group pioneered the effective and safe use of calcineurin inhibitors as a bridge treatment to successful management with vedolizumab, with a clinical remission rate of 45% at 12 months.2 The long-term follow-up from this study reported a 67% colectomy-free survival at 12 months and 55% at 2 years.3 Another study using cyclosporine induction with vedolizumab maintenance reported a 68% colectomy-free survival at 12 months.4 Furthermore, adverse events were infrequent. Ustekinumab is a p40 inhibitor of interleukin 12/23 approved by the Food and Drug Administration to treat moderately to severely active UC and has a very low incidence of adverse events.5 The combination of cyclosporine and ustekinumab for medically resistant UC has not previously been described. We present 2 cases of acute severe UC (ASUC) in which cyclosporine was effective as a bridge to maintenance therapy with ustekinumab.

CASE REPORT

Patient 1: A 21-year-old man diagnosed with extensive UC in 2016. He was initially treated with mesalamine but required escalation to vedolizumab in 2017. In 2019, he developed ASUC requiring hospitalization with an albumin of 2.8 g/dL on admission. An abdominal x-ray revealed a nonobstructive gas pattern with no megacolon present. Polymerase chain reaction assay for *Clostridioides difficile* infection (CDI) was negative, and a flexible sigmoidoscopy revealed severe colitis with biopsies negative for cytomegalovirus. No fecal calprotectin (FCP) was performed in the hospital, although the patient had an elevated C-reactive protein of 22 mg/L. He did not respond to 3 days of IV steroids and was therefore started on IV cyclosporine 3 mg/kg (target level 300–400 ng/mL) with rapid response into clinical remission by day 4 of therapy. He received the loading dose of ustekinumab 390 mg intravenous on day 4 and was immediately discharged home on oral prednisone and oral cyclosporine, as well as *Pneumocystis jiroveci* pneumonia prophylaxis with trimethoprim sulfamethoxazole double strength 160–800 mg 1 tablet 3 times weekly. Prednisone taper was started at week 2, and cyclosporine was discontinued at week 8. He remains in stable clinical remission with an undetectable C-reactive protein (<5 mg/L) and a FCP 242 μg/g 4 months after discharge on maintenance subcutaneous ustekinumab. There were no adverse events.

Patient 2: A 20-year-old woman diagnosed with pancolitis in 2018. She had been previously treated with adalimumab and tofacitinib before developing ASUC and CDI. She was treated with oral vancomycin for the CDI. Her albumin was 2.9 g/dL on admission, and flexible sigmoidoscopy revealed severe colitis with biopsies negative for cytomegalovirus. An abdominal x-ray did not
reveal any free air or an ileus. She did not respond to 3 days of IV steroids, but had a clinical response to IV cyclosporine, and started vedolizumab on the day of discharge. She received the initial vedolizumab loading doses; however, she did not maintain remission with vedolizumab, and after her 3 loading doses, her FCP was 1,150 µg/g. She did not receive any maintenance vedolizumab although remained on oral cyclosporine and Pneumocystis jiroveci pneumonia prophylaxis. Ustekinumab 260 mg IV was administered 5 weeks after the last vedolizumab dose and 11 weeks after cyclosporine initiation, with significant improvement within 2 weeks. The follow-up FCP 6 weeks after the IV ustekinumab was 380 µg/g. She is now off cyclosporine and clinically stable on maintenance subcutaneous ustekinumab for a total duration of 4 months. There were no adverse events.

DISCUSSION

We demonstrate the feasibility, effectiveness, and safety of cyclosporine as a bridge to maintenance ustekinumab to treat medically resistant severe UC. Cyclosporine is an effective therapy in patients with ASUC and provides a unique option for patients who have hypoalbuminemia and may have challenges to clearance of protein-based monoclonal antibody therapies. Although it is possible that these patients responded to ustekinumab alone, the severity and steroid resistance of these patients’ colitis make that mechanism of management alone unlikely to have been successful. It is important to note that the 2 patients in this report had low albumin, which we believe is one of the factors that explain their resistance to previous biological options. Therefore, as we have previously described in other reports, the small molecule cyclosporine was successful for induction of clinical remission and confirmed by both the clinical follow-up and the FCP values, aided in the healing of the bowel. This likely enhanced the likelihood of successful maintenance of remission with ustekinumab.

Patients with ASUC who require hospitalization have a 20% colectomy rate during their first admission and 40% colectomy rate at some point in their disease course. Importantly, both of these patients have avoided colectomy so far. Patients have limited options for treatment when admitted for ASUC, and cyclosporine is a therapeutic option for patients who do not respond to IV corticosteroids and who have previously failed infliximab, but its long-term toxicity limits its use as a maintenance option. Guidelines advocate that for those who achieve remission with cyclosporine, maintenance therapy with thiopurines, or vedolizumab can be considered. We propose that the use of cyclosporine combined with ustekinumab may be considered in select patients, especially those with previous failure/intolerance to antitumor necrosis factor, thiopurines, or vedolizumab. This treatment sequence is novel because this combination has not been previously reported. It should provide clinicians the confidence to use cyclosporine with ustekinumab in certain patients.

DISCLOSURES

Authors contributions: SR Shaffer, C. Traboulsi, N. Krugliak Cleveland wrote the article, revised the article for intellectual content, and approved the final article. DT Rubin revised the article for intellectual content, approved the final article, and is the article guarantor.

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Informed consent was obtained for this case report.

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