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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Vancomycin and Ustekinumab Combination Therapy in Acute Ulcerative Colitis

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ABSTRACT

The role of antibiotics in the treatment of ulcerative colitis is limited. We present a case of a 25-year-old woman who presented with a flare of ulcerative colitis after an episode of infectious gastroenteritis on a background of known primary sclerosing cholangitis. After the flare, she experienced persistent abdominal pain and diarrhea associated with elevated fecal calprotectin and deep rectosigmoid ulcerations on endoscopy. After unsuccessful trials of vedolizumab, infliximab, and tofacitinib, the patient was commenced on ustekinumab, tacrolimus, and oral vancomycin. Tacrolimus was ceased successfully, but while on maintenance ustekinumab therapy, 2 attempts to cease vancomycin resulted in symptom recurrence and rising fecal calprotectin that improved with vancomycin recommencement. To date, the patient has been on vancomycin continuously for 18 months and remains clinically well with colonoscopy demonstrating inactive colitis. This case highlights how vancomycin may be beneficial in the management of treatment-refractory ulcerative colitis as an adjunct to biologic therapy.

KEYWORDS: ulcerative colitis; vancomycin; ustekinumab

INTRODUCTION

Ulcerative colitis is a chronic inflammatory bowel disease characterized by diffuse inflammation of the colonic mucosa with a relapsing, remitting course. Although the advent of biologic therapies has transformed the treatment landscape for ulcerative colitis, the role of antibiotics remains limited, and little is known about the use of vancomycin, a glycopeptide antibiotic, in combination with biologic therapy to treat patients with ulcerative colitis that is refractory to standard treatment.[1] To date, several studies have explored the use of vancomycin to treat patients with ulcerative colitis and concurrent primary sclerosing cholangitis, particularly in the post–liver transplantation setting.[2–4] We describe the case of a young adult patient with ulcerative colitis and primary sclerosing cholangitis whose treatment-refractory ulcerative colitis achieved and maintained remission after the use of vancomycin as an adjunct to biologic therapy with ustekinumab.

CASE REPORT

A 25-year-old woman was admitted to hospital with worsening diarrhea, abdominal pain, and weight loss on a background of active panulcerative colitis diagnosed at age 15 years. Her medical history was significant for primary sclerosing cholangitis with mild-to-moderate cholestasis on liver function tests.

In terms of previous treatments for ulcerative colitis, the patient had active disease on 5-aminosalicylic acid therapy, azathioprine, and intermittent corticosteroids and had been commenced on vedolizumab as monotherapy in 2018 and achieved clinical, biochemical, and endoscopic remission with mucosal healing. In December 2020, an episode of presumed infectious gastroenteritis 14 months earlier precipitated a flare of her colitis, which was difficult to control. No causative bacterial pathogen was identified. During the flare, the patient experienced persistent diarrhea and abdominal pain, which failed to improve with

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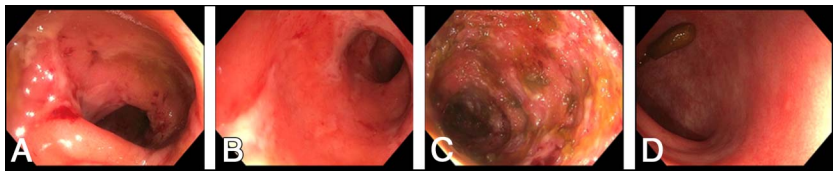

Figure 1. Flexible sigmoidoscopy performed on the patient's hospital admission showed deep ulceration of the anal canal (A) and extensive deep serpentiginous ulceration of the rectosigmoid colon (B and C) to the point of insertion. Colonoscopy performed at 16 months later when the patient was on maintenance ustekinumab and oral vancomycin therapy demonstrated inactive colitis and mucosal healing (D).

corticosteroids and escalated vedolizumab therapy. She was switched to infliximab and azathioprine. Despite escalated infliximab therapy, her illness was unimproved, and infliximab and azathioprine were switched to tofacitinib 10 mg twice daily. Over the course of the 14-month period since her initial flare of colitis, the patient required 3 courses of oral corticosteroids for symptom control.

Two months after the switch to tofacitinib therapy, the patient was admitted to hospital with ongoing symptoms of active colitis. At this time, C-reactive protein had risen to 70 mg/L and fecal calprotectin was 3,500 μg/g. Fecal culture and *Clostridioides difficile* polymerase chain reaction testing were negative. Hemoglobin count was 132 g/L. Surgical options were sought, and emergency subtotal colectomy was considered. Flexible sigmoidoscopy revealed deep ulceration of the anal canal and serpentiginous ulceration of the rectosigmoid colon to the point of insertion (Figure 1). Biopsy of the rectosigmoid colon was negative for herpes simplex virus and cytomegalovirus. She was commenced on intravenous hydrocortisone, oral tacrolimus (titrated to drug level 10–15 mcg/mL), intravenous ustekinumab induction (single 6-mg/kg dose), and oral vancomycin 500 mg twice daily. By 6 weeks after the hospital admission, her symptoms had completely resolved. Tacrolimus was ceased 9 months later. Flexible sigmoidoscopy at 3 months after discharge from hospital confirmed inactive disease.

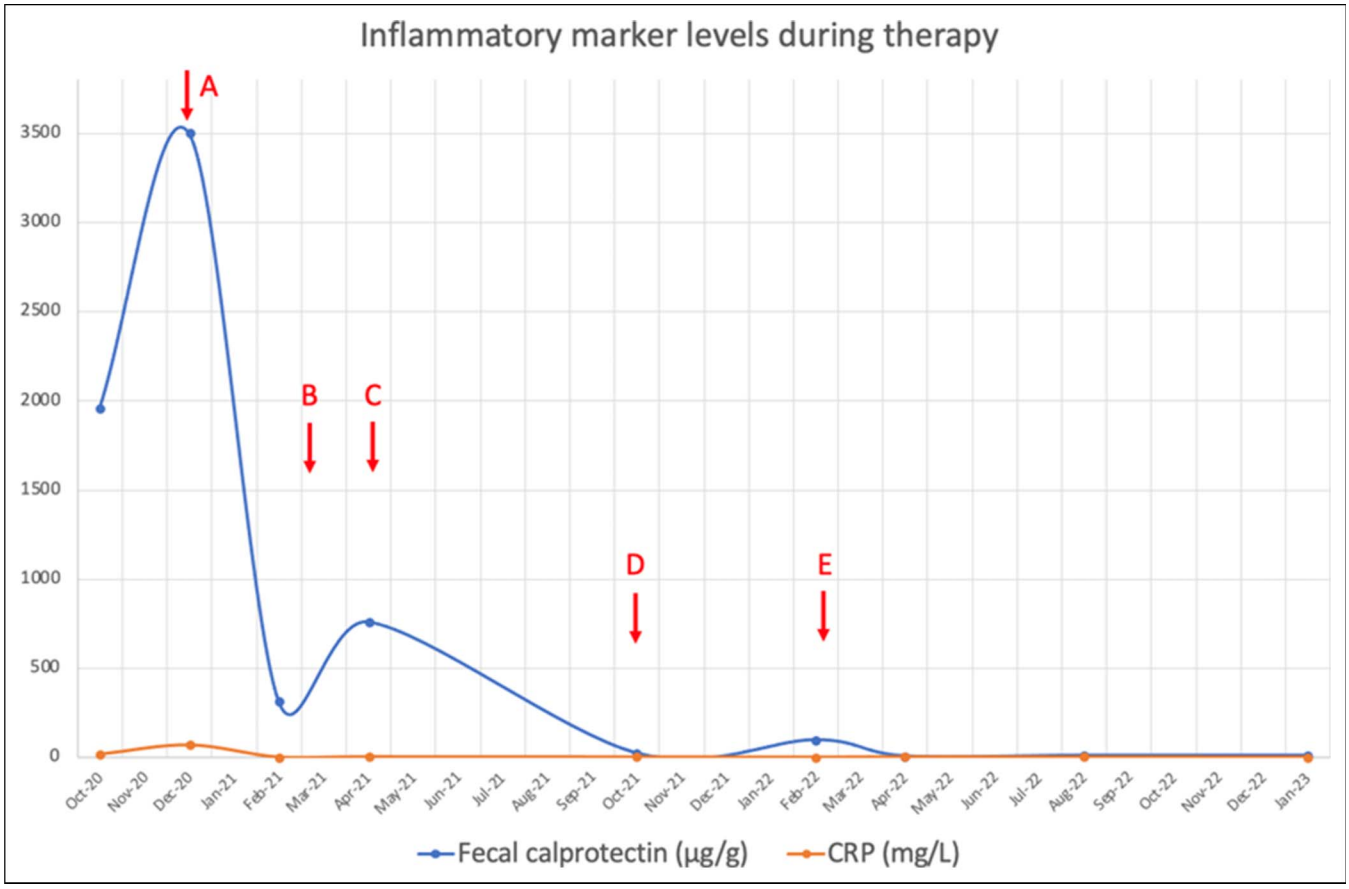

Figure 2. During her hospital admission (A), the patient was commenced on vancomycin 500 mg twice daily. Three months after hospitalization, vancomycin was ceased (B), and this was associated with a recurrence of gastrointestinal symptoms and an increase in fecal calprotectin from 312 to 759 μg/g. Vancomycin was recommenced (C), and fecal calprotectin decreased to 23 μg/g. After the second trial of vancomycin cessation (D), the patient developed symptom recurrence and fecal calprotectin elevation to 98 μg/g. After recommencement of vancomycin (E), symptoms resolved and fecal calprotectin declined to <50 μg/g where it has remained. CRP, c-reactive protein.

Although on maintenance 8-weekly subcutaneous ustekinumab 90 mg, 2 attempts to wean and cease vancomycin resulted in recurrence of symptoms, including fecal urgency and diarrhea with associated rectal blood and mucus, as well as elevations in fecal calprotectin (Figure 2). In the first attempt at vancomycin cessation, which occurred at 3 months after hospitalization (after flexible sigmoidoscopy demonstrated inactive disease), fecal calprotectin increased from 312–759 μg/g and decreased to 23 μg/g after vancomycin was recommenced. In the second attempt at vancomycin cessation, which occurred at 10 months after hospitalization and after another repeat flexible sigmoidoscopy showed quiescent colitis, fecal calprotectin rose to 98 μg/g. After recommencement of vancomycin, fecal calprotectin declined to $<$50 μg/g where it has remained. Fecal culture and *C. difficile* testing performed on each of these 2 occasions were unremarkable, and C-reactive protein remained normal (1–3 mg/L). Hemoglobin count was also normal (117–126 g/L). On each occasion, symptoms resolved with recommencement of vancomycin 125 mg daily. The most recent colonoscopy in May 2022 demonstrated inactive colitis and mucosal healing. To date, the patient has been on vancomycin continuously for 18 months and remains clinically well without any adverse effects to treatment. We anticipate that long-term treatment with vancomycin will be required, and there are no current plans to cease vancomycin.

DISCUSSION

Although antibiotics are generally not used to treat ulcerative colitis, several centers have successfully used vancomycin to induce and maintain remission in treatment-refractory ulcerative colitis in patients with concurrent primary sclerosing cholangitis.[2–4] A case series by Chambrun et al featured 3 patients with primary sclerosing cholangitis and ulcerative colitis that were previously refractory to immunomodulatory and biologic therapies.[2] After commencement of oral vancomycin at a dose of 500 mg twice daily, they achieved sustained clinical and endoscopic remission. In another case series, Dao et al reported on 8 patients with treatment-refractory ulcerative colitis and primary sclerosing cholangitis, including 6 who had undergone liver transplantation.[3] Patients were started on vancomycin at 125 mg 4 times daily for 6–8 weeks, then tapered down to the lowest effective dose of 125 mg 2 or 3 times daily. Over the follow-up period ranging from 9 to 36 months, all patients had clinical and endoscopic response or remission without significant adverse effects to vancomycin. Dysbiosis in the gastrointestinal microbiota, marked by a decrease in microbial diversity and increase in proinflammatory species, is believed to be a key driver in the pathogenesis of ulcerative colitis.[5] Vancomycin, a glycopeptide antibiotic often used in the treatment of *C. difficile* colitis, has been shown to induce short- and long-term effects on the human intestinal microbiota.[6]

The role of the gastrointestinal microbiota, as a mediator of gut inflammation, is likely to be important in ulcerative colitis.[7] In ulcerative colitis, vancomycin-induced microbial changes may help improve dysbiosis and reduce colonic inflammation. Vancomycin, when combined with other therapies targeted to reduce inflammation, may be synergistic and offer improved outcomes for patients. We propose that the use of vancomycin in combination with biologic therapy may be considered in patients with active ulcerative colitis who are refractory to standard therapy. This benefit may be greater in patients who also have primary sclerosing cholangitis, although the mechanisms by which this is achieved are not fully understood.

DISCLOSURES

Author contributions: KM Nguyen: initial manuscript preparation; KM Nguyen and EK Wright: concept and design, data collection, and critical revision of the manuscript. EK Wright is the article guarantor.

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Informed consent was obtained for this case report.

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