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Case and Review

Vancomycin Therapy for Induction and Maintenance of Remission in a Patient with Refractory Ulcerative Colitis and Primary Sclerosing Cholangitis: A Case Report and Literature Review

Naama Lang[a] Yana Davidov[b] Tomer Hoffman[c] Sivan Harnik[a]
Abraham Rami Eliakim[a] Shomron Ben-Horin[a] Bella Ungar[a]

[a]Department of Gastroenterology, Sheba Medical Center and Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel; [b]Liver Disease Center, Sheba Medical Center and Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel; [c]Infectious Diseases Unit, Sheba Medical Center and Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel

Keywords
Primary sclerosing cholangitis · Cholangitis · Vancomycin · Inflammatory bowel disease · Case report

Abstract
Introduction: Ulcerative colitis is a chronic inflammatory bowel disease that affects the colon. About 5% of ulcerative colitis patients also present with primary sclerosing cholangitis, a chronic inflammatory disease marked by cholestasis and progressive fibrosis of the bile ducts, and results in the necessity of liver transplantation. Ulcerative colitis treatment in primary sclerosing cholangitis patients is challenging due to potential resistance to conventional therapies. ***Case Presentations:*** We describe a patient with ulcerative colitis and primary sclerosing cholangitis, whose ulcerative colitis relapsed following a liver transplant. After failure of conventional treatment and further deterioration in her colitis, with negative clostridium difficile, she was treated with vancomycin with beneficial long-term clinical and endoscopic responses. ***Conclusion:*** This case report, along with others we reviewed, suggests that vancomycin treatment should be considered as a treatment for ulcerative colitis and primary sclerosing cholangitis patients after conventional therapies for the colitis prove ineffective.

Correspondence to:
Bella Ungar, bella.geyshis.ungar@gmail.com

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) with unknown etiology that affects the colon. About 5% of UC patients also present with primary sclerosing cholangitis (PSC), which increases the risk of cholangiocarcinoma and colorectal cancer [1, 2]. PSC is a chronic inflammatory disease marked by cholestasis and progressive fibrosis of the bile ducts and results in a diminished quality of life, cirrhosis, and the necessity of liver transplantation, typically within 12 years. Patients with UC and PSC typically exhibit mild symptoms alongside a higher incidence of pancolitis, rectal sparing, backwash ileitis, and colorectal malignancy [2, 3].

The primary therapy used in mild UC to induce and maintain clinical remission is 5-aminosalicylic acid. Cases resistant to first-line therapy may be treated with azathioprine, antitumor necrosis factor antibodies, or inhibitors of α4β7 integrin, IL-23, or JAK inhibitors. Currently, there is no effective treatment for PSC and no specific treatment recommendations for the combination of UC-PSC. The efficacy of antibiotics in treating PSC in both adult and pediatric patients remains inconclusive. Liver transplantation is known to be the only effective treatment that prolongs survival. However, up to one-third of the patients with UC-PSC who undergo liver transplantation may experience an exacerbation of colitis even with full immunosuppression [4–6].

Changes in gut microbiota, particularly a decrease in intestinal microbial diversity, have been linked to chronic gut inflammation in IBD. However, consistent benefits have not been demonstrated for antibiotic therapy in cases of non-severe colitis. Indeed, there is evidence that certain antibiotics may enhance markers of cholestasis and may alter the disease trajectory in PSC patients. In conclusion, the effectiveness of antibiotics in managing PSC in both adult and pediatric populations remains uncertain [7, 8].

Vancomycin, which is classified as a glycopeptide antibiotic, demonstrates bactericidal activity against numerous gram-positive bacteria, including staphylococcus, streptococcus, enterococci, and certain clostridium species. The drug reaches a particularly high concentration in the intestine, where it functions as an immunomodulator by reducing cytokine release from T cells. Oral administration of vancomycin is associated with minimal absorption and is typically well tolerated, when employed as a treatment for clostridium difficile infection (CDI), with minor side effects like nausea, abdominal discomfort, or bloating. Additionally, oral vancomycin has shown efficacy in treating PSC. Clostridium species are primarily responsible for the dihydroxylation of primary bile acids into secondary bile acids in the distal small intestine and colon. Elevated levels of secondary bile acids in the liver are associated with inflammation, cholestasis, gallstone formation, and carcinogenesis. Therefore, it is plausible that vancomycin therapy influences bile acid metabolism. Some evidence suggests that vancomycin administration in patients with both UC and PSC may also mitigate colonic inflammation [9–11].

In this case report, we will describe a patient with clostridium difficile-negative UC who responded to vancomycin. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000544161).

Case Presentation

A 51-year-old female patient was diagnosed with PSC (2013) and UC (pancolitis, 2015). She had been stable on 3 g mesalamine/day since UC diagnosis. Due to worsening PSC, she underwent a liver transplantation in 2017 and was subsequently treated with tacrolimus monotherapy with normal graft function.

In 2018, 1 year after the transplantation, her UC flared (despite sufficient tacrolimus levels of 5–6 μg/L). Two stool samples tested negative by PCR for toxigenic CDI and were negative for CD toxin (CDT) and also for other pathogens. Colonoscopy revealed moderate inflammation of the sigmoid colon, with a Mayo endoscopic score of 1–2 (shown in Fig. 1a). She consequently received oral prednisolone therapy (40 mg/day) with tapering down. Two months later, due to an ongoing exacerbation of UC, she was hospitalized and treated with intravenous (IV) hydrocortisone. Due to clinical nonresponse, she then received salvage IV therapy with cyclosporine (tacrolimus was stopped) with clinical improvement.

While on oral cyclosporine with decreasing doses of prednisone, the patient experienced another flare of UC, with a calprotectin level of 700 μg/g. Two stool samples tested negative for CDT. Subsequent colonoscopy (2019) demonstrated mild to moderate colitis, with a Mayo score of 1. The patient was then started on IV vedolizumab treatment with partial clinical improvement until therapy was stopped due to increased liver enzymes and suspected graft rejection.

In May 2020, there was clinical deterioration and the patient presented with diarrhea, abdominal pain, and IBD-related arthritis, with a calprotectin level above 1,000 μg/g. A stool test was positive for CDT, and treatment with oral vancomycin (125 mg*4\day) was initiated.

In 2021, the patient experienced two recurrent episodes of CDI as evidenced by positive results for CD antigen and toxin. Initial fidaxomicin treatment did not provide any improvement in symptoms, so therapy was switched to vancomycin, which did elicit a clinical response. Overall, the two episodes of CDI were treated with a total duration of approximately 8 weeks of a tapered dose of vancomycin.

In 2022 and 2023, there were several episodes of clinical exacerbation of UC but with negative stool results for CDI. Recurrent courses of prednisolone (40 mg/day with tapering down) did not yield clinical improvement. Colonoscopies in 2022 and 2023 had a Mayo score of 2 (shown in Fig. 1b). Because of a previous failure with vedolizumab and reluctance to start an anti-TNFα agent in addition to tacrolimus (due to fear of adverse events), the patient was then started on a tapered dose vancomycin regimen as a treatment for UC exacerbation (despite having negative stool CD PCR results) along with tapering down of steroids. The tapering concluded with a dose of 125 mg vancomycin every 3 days. Currently, this treatment has now been administered for 9 months, and the patient is in clinical remission with endoscopic improvement (shown in Fig. 1c). There were no side effects related to the use of vancomycin, and the patient's liver function improved during the treatment (shown in online suppl. Fig. S1a–S1e).

Literature Review

In total, including our case, we were able to find reports (7 case reports and 5 case series) on 58 patients with UC and PSC, who received vancomycin as a deliberate treatment for a UC flare (shown in Table 1). Most were pediatric patients, 13 were liver transplant recipients, and only two had previously documented CDI. All patients were treated with oral vancomycin for a minimum of 3 months, with improvement in their clinical status, inflammatory markers (calprotectin levels), and endoscopic findings (Mayo scores).

Discussion

We present the clinical history of a 51-year-old liver transplant recipient with UC-PSC, whose UC remained active despite treatment with steroids, tacrolimus, cyclosporine, and vedolizumab, but improved after vancomycin induction and low-dose maintenance treatment

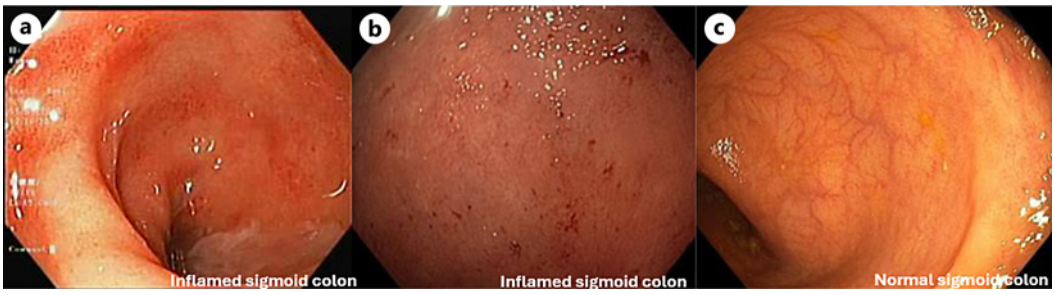

Fig. 1. Sigmoid colon endoscopic images throughout the disease course. **a** Endoscopy, September 2019 – one year after liver transplantation, UC flared; Mayo endoscopic subscore of 1–2 with hyperemic mucosa and spontaneous bleeding. **b** Endoscopy, April 2022 – deterioration of UC after 4 episodes of CD that were treated; Mayo endoscopic subscore of 1–2 with hyperemic mucosa and spontaneous bleeding. **c** Endoscopy, August 2023 – endoscopic remission (normal mucosa with a normal vessel pattern, no bleeding) after 7 months of vancomycin treatment.

despite negative test results for CDI. A literature review found reports of 23 adults and 35 children treated with vancomycin for a UC exacerbation [12–22]. Clinical and endoscopic improvements were reported in all patients. Although these reports may be prone to positive reporting bias, and some did not report stool CD test results, the results do suggest that oral vancomycin could be a feasible therapy for UC exacerbation in this challenging patient group of UC-PSC patients, regardless of CDI status. As for the use of vancomycin for UC without PSC, few studies reported vancomycin therapy for dioctyl sodium sulfosuccinate-induced colitis in mice [23, 24]. Additionally, one study describes vancomycin as part of a multidrug antibiotic regimen combined with IV corticosteroids in pediatric UC patients [25]. There are not enough data about the safety and side effects of long-term vancomycin treatment.

Vancomycin is a highly water-soluble glycopeptide with a heavy molecular weight (1,485.7 Da). As a result, it has low epithelial permeability and poor systemic absorption when orally consumed, making it an ideal drug for the gastrointestinal tract [26]. In addition to the acknowledged pathogenic bactericidal effect in the treatment of CDI, oral vancomycin has been shown to exert an immunological effect by decreasing the production of interleukin-17 (IL-17)-producing T cells (T helper 17) in the lamina propria of the small intestine [27]. This has been associated with the bactericidal effect on natural commensal microflora, since the T cells in mice with no commensal microflora do not produce IL-17 and the animals subsequently develop autoimmune arthritis. IL-17 expression in the gastrointestinal mucosa has long been connected to IBD, and the levels of IL-17 are known to increase during UC flare-up compared to the situation in remission [28]. Notably, further studies will be required to determine the mechanisms by which vancomycin therapy induces remission in UC-PSC patients, who are generally unresponsive to biological therapy. It is presently unclear whether the mechanism is related to altered microbial diversity or to shifts in IL-17 expression, which affect inflammation in this patient subgroup, with or without prior liver transplantation [29]. This case report, along with others we reviewed, suggests that vancomycin treatment may be a viable option for UC-PSC patients after conventional therapies prove ineffective.

Statement of Ethics

This study protocol was reviewed and approved by Sheba Helsinki committee, Approval No. 4530. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Table 1. Previous cases of UC-PSC patients treated with vancomycin for UC

Case No.	First author	Year	Patients, *n*	Diagnosis	Liver transplant	CD status	Vancomycin dose	Duration of therapy	Outcome
1	Buness et al. [12]	2016	1 child	UC-PSC	None	NA	Started at 500 mg 3/day and increased to 1,000 mg 2/day	3 years	The patient gained weight; fatigue improved. Subsequent colonoscopies nearly normal, only quiescent to mild chronic colitis on biopsy
2	de Chambrun et al. [13]	2018	3 adults	UC-PSC	None	Negative	500 mg 2/day	6 months	Sustained clinical and endoscopic remission
3	Dao et al. [14]	2019	8 adults	UC-PSC	6/8	NA	250 mg a day	6 months	All patients maintained clinical and endoscopic remission
4	Tan et al. [15]	2019	17 children	UC-PSC	None	NA	Not reported	3 months	Colonoscopies: Mayo 0. PUCAI scores improved
5	Turner et al. [16]	2020	16 children	UC	None	Negative	Children above 8 y/o 250 mg 4/day, under 8 y/o 125 mg 4/day	3 weeks	Decrease in day 5 PUCAI score
6	Rahman et al. [17]	2021	1 adult	UC-PSC	V	Negative	125 mg 2/day	10 months	Significant clinical improvement. Colonoscopy: resolution of inflammation
7	Buness et al. [18]	2021	1 adult	UC-PSC	None	NA	Started at 500 mg 3/day and was increased to 1,000 mg 2/day	8 years	Normalization of liver enzymes and resolution of UC symptoms with colonic mucosal healing for over 8 years
8	Britto et al. [19]	2021	1 child	UC-PSC (Crohn's colitis)	Not reported	NA	125 mg 4/day	90 days	Clinical symptoms resolved within 90 days, fecal calprotectin normalized within 70 days after vancomycin initiation and reached normal levels by 195 days
9	Shah et al. [20]	2022	7 adults	UC-PSC (six with pancolitis and one with J-pouch)	4/7	NA	Not reported	6 months	Complete clinical remission with reduction of fecal calprotectin by 634 μg/mg

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Table 1 (continued)

Case No.	First author	Year	Patients, *n*	Diagnosis	Liver transplant	CD status	Vancomycin dose	Duration of therapy	Outcome
10	Ahmed et al. [21]	2023	1 adult	UC-PSC (the UC was developed after the liver transplant)	V	Positive to negative	Started at 125 mg 4/day and was tapered down to 125 mg 3/day	3 months	Colonoscopy: Mayo score decreased from 3 to Mayo 0, calprotectin improved from 492 μg/g to 43 μg/g
11	Almomen et al. [22]	2023	1 adult	UC-PSC	V	Negative	500 mg 2/day	6 months	After 3 months – clinical remission After 6 months – fecal calprotectin decreased to 277 μg/g. Colonoscopy: complete endoscopic healing. Colonic biopsies: quiescent colitis without activity
12	Lang et al.	2023	1 adult	UC-PSC	V	Positive to negative	Started at 125 mg 4/day and was tapered down to 125 mg every 3 days	7 months	Colonoscopy: improvement from Mayo 2 to Mayo 1

UC, ulcerative colitis; PSC, primary sclerosing cholangitis; CD, clostridium difficile; PUCAI, pediatric ulcerative colitis activity index; CRP, C-reactive protein; NA, not available.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Naama Lang – medical student – acquisition of data, interpretation of data, and drafting the article. Dr. Yana Davidov and Prof. Rami Eliakim – interpretation of data and revising the article. Dr. Tomer Hoffman – acquisition of data, interpretation of data, and revising the article. Sivan Harnik – medical student – interpretation of data and drafting the article. Prof. Shomron Ben-Horin – interpretation of data, drafting the article, and revising the article. Prof. Bella Ungar – article guarantor – conception and design of the case, interpretation of data, drafting the article, and revising the article.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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