# Oral vancomycin induces sustained deep remission in adult patients with ulcerative colitis and primary sclerosing cholangitis

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Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology. The treatment of UC is challenging, especially when it is associated with primary sclerosing cholangitis (PSC), a chronic inflammatory disease of the bile ducts that affects around 5% of patients with UC, and leads to an increased risk of cholangiocarcinoma and colorectal cancer. Microbiota is considered to play an important role in the pathogenesis of UC, although the efficacy of antibiotics in this context is only limited and transient. Several studies have investigated the use of antibiotics for the treatment of PSC in adult and pediatric populations, with conflicting results. In this brief report, we describe the effect of oral vancomycin treatment in three patients with UC and PSC refractory to conventional and biologic therapies. All three patients achieved clinical remission and mucosal healing with vancomycin 500 mg twice a day administered orally. Maintenance treatment with oral vancomycin was well tolerated and led to sustained clinical and endoscopic remission in all three patients. Oral vancomycin also improved liver function tests in two patients who did not have pre-existing cirrhosis. Eur J Gastroenterol Hepatol 30:1247–1252


## Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) of unknown etiology [1]. The treatment of UC is challenging, especially when it is associated with primary sclerosing cholangitis (PSC), a chronic inflammatory disease of the bile ducts affecting around 5% of UC patients and leading to an increased risk of cholangiocarcinoma and colorectal cancer [2]. When patients with UC and PSC have mild colonic disease, the European Crohn and Colitis Organization consensus recommends the use of 5-aminosalicylic acids as the first-line treatment for the induction and maintenance of clinical remission [3]. In UC patients refractory to conventional therapies (5-aminosalicylic acids, corticosteroids), azathioprine, antitumor necrosis factor (TNF)α monoclonal antibodies, or vedolizumab should be used to induce and maintain clinical remission [3].

Microbiota is considered to play an important role in the pathogenesis of UC, although antibiotics show only a mild and transient efficacy for the treatment of this disorder [4–6]. Several studies have also investigated the use of antibiotics for the treatment of PSC in adult and pediatric patients, with conflicting results [7]. Here, we retrospectively report three cases of adult patients with active UC associated with PSC who presented a dramatic response to antibiotics, in particular oral vancomycin, with sustained clinical remission and mucosal healing (MH).

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**Keywords: antibiotics, inflammatory bowel disease, mucosal healing, primary sclerosing cholangitis, remission, ulcerative colitis, vancomycin**

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## Case report

We carried out a retrospective observational study in two tertiary referral centers in France (Lille and Montpellier University Hospital). We included all consecutive patients who had UC associated with PSC and who were treated with oral vancomycin for active colonic disease (Table 1). The diagnosis of UC was made by clinical, endoscopic, and histological findings according to local and international guidelines [8]. The diagnosis of PSC was suspected from abnormal biologic liver function tests and confirmed in all patients by MRI. Clinical activity of the UC was assessed retrospectively using electronic charts and was based on the referring physician's global assessment. This study was approved by the institutional review board of Montpellier University Hospital.

### *First case*

The patient was a 20-year-old woman diagnosed with steroid-refractory UC in 2012. She was transferred to our

**Table 1.** Baseline characteristics and evolution with oral vancomycin

| | Patient no. 1 | Patient no. 2 | Patient no. 3 |
|---|---|---|---|
| Sex | Female | Male | Male |
| Age (years) | 20 | 69 | 24 |
| Montreal classification | E3 | E3 | E3 |
| Smoking status | Nonsmoker | Nonsmoker | Nonsmoker |
| Delay between UC diagnosis and start of OV (months) | 13.7 | 135.7 | 162.2 |
| Delay between UC and PSC diagnosis (months) | 6.8 | 134.8 | 0 |
| Previous UC treatment | Refractory to 5-ASA and steroids<br>Immunoallergic pancreatitis to thiopurine<br>Infusion reaction after first IFX infusion<br>Primary nonresponse to ADA | Refractory to 5-ASA<br>Steroid dependency<br>Intolerant to thiopurine<br>IFX withdrawal after severe pertussis infection<br>Recurrent fever when treated with ADA | Refractory to 5-ASA, steroids, and azathioprine<br>Secondary loss of response to IFX<br>Primary nonresponse to ADA |
| PSC ongoing treatment | Ursodeoxycolic acid 800 mg/day | Ursodeoxycolic acid 1250 mg/day | Ursodeoxycolic acid 1200 mg/day |
| Clinical activity before OV | PGA 3 | PGA 2 | PGA 3 |
| Endoscopic activity before OV | Pancolitis<br>Mayo endoscopic subscore of 2 | Pancolitis<br>Mayo endoscopic subscore of 2 | Pancolitis<br>Mayo endoscopic subscore of 3 |
| Liver function tests before OV (IU/l) | | | |
| AST | 142 | 99 | 126 |
| ALT | 202 | 177 | 139 |
| ALP | 191 | 98 | 909 |
| Vancomycin treatment | Oral<br>Maintenance treatment<br>500 mg, b.i.d. | Oral<br>Maintenance treatment<br>500 mg, b.i.d. | Oral<br>Maintenance treatment<br>500 mg, b.i.d. |
| Follow-up duration (months) | 20.9 | 49.2 | 15.3 |
| Short-term clinical efficacy | PGA 0 | PGA 0 | PGA 0 |
| Rectal bleeding | No | No | No |
| Follow-up colonoscopy | 5 months after starting OV<br>Mayo endoscopic subscore of 0 | 3 years after starting OV Mayo endoscopic subscore of 0 | 6 months after starting OV Mayo endoscopic subscore of 0 |
| Histological healing | Yes | Yes | Yes |
| Liver function tests after OV (IU/l) | | | |
| AST | 22 | < 35 | 146 |
| ALT | 21 | < 35 | 199 |
| ALP | 113 | < 120 | 932 |

ADA, adalimumab; ALP, alkaline phosphatase; ALT, alanine aminotransferase; 5-ASA, 5-aminosalicylic acid; AST, aspartate aminotransferase; b.i.d., twice a day; IFX, infliximab; OV, oral vancomycin; PGA, physician global assessment; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

facility because of severe active UC that had failed to respond to a course of intravenous steroids. Before her admission, a colonoscopy had reported marked inflammation of the entire colonic mucosa, with a Mayo endoscopic subscore of 2. She rapidly received ciprofloxacin, metronidazole, and a first infusion of infliximab at a dose of 5 mg/kg, with a good clinical response. Before hospitalization, she had also presented with abnormal liver enzyme tests, with elevated aminotransferase (202 UI/l) and alkaline phosphatase (ALP) (191 UI/l). MRI reported typical signs of PSC, with multiple strictures scattered along the biliary tree and diffuse enlargement of the bile ducts. Ursodeoxycolic acid was started at a dose of 15 mg/kg. During the second infusion of infliximab, she had a severe allergic reaction. After infliximab withdrawal, the patient had a clinical relapse of UC and azathioprine was started. She presented with immunoallergic pancreatitis a few days after commencing azathioprine, which was therefore ceased. She started an adalimumab induction regimen (160 mg at week 0, 80 mg at week 2), followed by a maintenance regimen (40 mg every other week), with primary nonresponse. Because of clinically active UC, ciprofloxacin and metronidazole were restarted, and rapidly induced clinical remission. These two antibiotics were withdrawn after several months because of poor tolerance with tendonitis and peripheral sensory neuropathy. Oral vancomycin at a dose of 500 mg twice a day was then started because of rapid recurrence of UC symptoms. This new treatment rapidly induced clinical remission. Oral vancomycin was well tolerated and the patient presented complete and sustained clinical remission during a follow-up period of 1 year. Oral vancomycin was then continued as maintenance therapy at a dose of 500 mg twice a day. Importantly, 5 months after starting oral vancomycin, the patient underwent a colonoscopy, showing MH of the entire colonic mucosa. Moreover, there were no signs of histologic inflammation on colonic biopsies (Fig. 1). It is noteworthy that liver enzymes were elevated during each UC flare-up and became strictly normal on oral vancomycin treatment.

### *Second case*

The patient was a 69-year-old man diagnosed with UC in 2002. He initially presented with pancolitis resistant to 5-aminosalicylates, and oral corticosteroid therapy was started rapidly, with a good initial response. Because of recurrence of the disease following corticosteroid tapering, azathioprine was started in May 2008, but was rapidly stopped because of elevated liver enzymes. Infliximab was started in December 2008, which induced clinical remission. In 2010, while on infliximab maintenance therapy, the patient presented severe pertussis infection, leading to infliximab withdrawal. Adalimumab was started and also led to clinical remission. However, during adalimumab treatment, the patient presented recurrent episodes of fever requiring adalimumab withdrawal. At this point, the patient was referred to our department. An echocardiogram

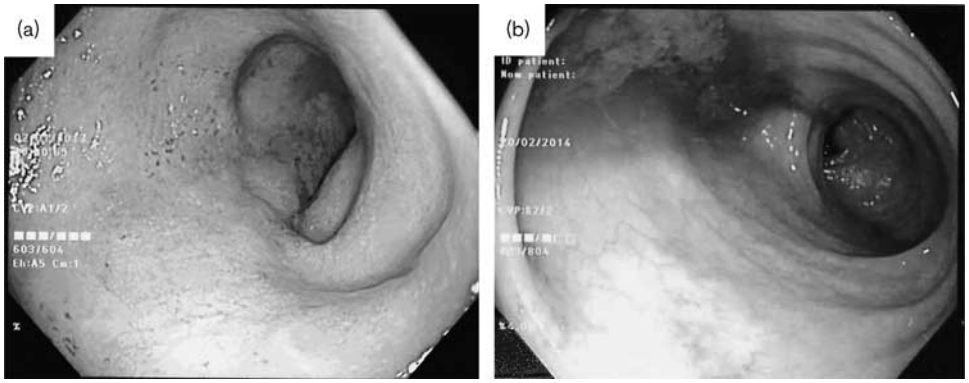


**Fig. 1.** Mucosal healing with oral vancomycin in a patient with ulcerative colitis and primary sclerosing cholangitis. (a) First colonoscopy performed before oral vancomycin treatment. (b) Follow-up colonoscopy performed 5 months after starting oral vancomycin.

did not find any sign of endocarditis, and a computed tomography scan showed no intra-abdominal disease explaining the recurrent fever. Laboratory testing found elevated liver enzymes (aspartate aminotransferase at 99 UI/l and alanine aminotransferase at 177 UI/l) and MRI confirmed the diagnosis of PSC. Ursodeoxycolic acid was started for the treatment of PSC. The patient did not present any new episodes of transient fever after adalimumab withdrawal, but had a clinical relapse of UC. Colonoscopy indicated pancolitis, with a Mayo endoscopic subscore of 2. Because of corticosteroid dependency, ciprofloxacin and metronidazole were started and corticosteroids were withdrawn successfully, without clinical relapse of UC. Six months after starting antibiotic treatment, a colonoscopy showed MH with a Mayo endoscopic subscore of 1 in the sigmoid colon. Liver enzyme levels were normal. Because of several clinical relapses of UC following the withdrawal of antibiotics, the patient was treated with maintenance oral vancomycin 500 mg twice a day, with good efficacy. The patient then remained on oral vancomycin maintenance therapy with sustained clinical remission. Notably, the patient remained in clinical remission over 3 years after the introduction of oral vancomycin, with a normal colonoscopy and colonic biopsies reporting no histological signs of inflammation.

### *Third case*

The patient was a 24-year-old man diagnosed with UC associated with PSC in 2001. The initial colonoscopy showed pancolitis. The patient was first treated with oral mesalamine at 2 g/day and ursodeoxycolic acid at 1200 mg/day. In 2011, the patient presented a flare of UC and needed oral corticosteroid therapy to achieve clinical remission. Azathioprine 100 mg/day was then introduced because of corticosteroid dependency. In 2013, infliximab maintenance therapy at 5 mg/kg every 8 weeks was started because of active disease despite treatment with azathioprine. The patient was also diagnosed with cirrhosis, which was confirmed by a liver biopsy. Because of a secondary loss of response to infliximab, adalimumab was started at 40 mg every other week following an induction regimen. In 2014, the patient was hospitalized in our department for a severe flare of UC while on adalimumab treatment. Colonoscopy showed ulcerated pancolitis, with a Mayo endoscopic subscore of 3. *Clostridium difficile* infection was ruled out by stool examination. Ciprofloxacin and metronidazole were started. After a few days, the patient achieved clinical remission with normal bowel movements and no rectal bleeding. With respect to PSC, the patient had clinical signs of cirrhosis with jaundice and splenomegaly. Liver enzymes were elevated, with aspartate aminotransferase at 126 UI/l, alanine aminotransferase at 139 UI/l, ALP at 909 UI/l, and γ-glutamyl transferase at 371 UI/l. The patient was discharged from hospital with only oral vancomycin 500 mg twice a day. One month after starting oral vancomycin, the patient was still in clinical remission, with only two normal stools per day. Six months after starting vancomycin, a colonoscopy showed MH with a Mayo endoscopic subscore of 0. Histological healing was also observed in this patient. Whereas his colonic disease was in remission, the patient's liver disease worsened. At the end of follow-up, the patient had inactive UC on maintenance oral vancomycin therapy at a dose of 500 mg twice a day and was on a waiting list for liver transplantation.

## Discussion

The etiology of IBD is unknown, but may be related to an unidentified bacterial pathogen or an immunological reaction to gut microbiota in genetically susceptible individuals [1]. Antibiotics have therefore been proposed as a therapy for Crohn's disease and UC both for inducing remission in active disease and for preventing relapse [5]. Numerous randomized-controlled trials have been conducted evaluating the efficacy of different antibiotic combinations in UC, and a recent meta-analysis of the most relevant randomized-controlled trials showed a statistically significant beneficial effect of antibiotics over placebo for treating UC patients [4]. To date, these results have been poorly translated into clinical practice because of the heterogeneity of trials in terms of inclusion criteria, concomitant therapies, types of antibiotics, and endpoints.

In this brief report, we have described the use of antibiotics, especially vancomycin, in patients with UC associated with PSC. In these three patients refractory to immunosuppressant and anti-TNFα therapy, we observed a surprising and dramatic effect of oral vancomycin on the clinical and endoscopic activity of UC. Importantly, in these patients, we also observed deep remission with

complete MH and no histological inflammation after the start of oral vancomycin.

Vancomycin is a broad-spectrum antibiotic that is bactericidal for staphylococci, streptococci including enterococci, diphtheroids, *Listeria monocytogenes*, and species of clostridium, lactobacillus, actinomyces, and bacillus [9]. Vancomycin is poorly absorbed after oral administration and oral vancomycin is indicated for the treatment of colonic luminal *C. difficile* infection [10]. Previous reports on *C. difficile* infection indicate that this treatment is well tolerated, with minor side effects such as nausea, abdominal pain, or bloating [11]. In our three patients, oral vancomycin was well tolerated, with no side effects observed even after several months of treatment.

Several randomized-controlled trials using antibiotics for the treatment of active UC have been published [4] (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A326*). A 2011 meta-analysis [4] included nine of these randomized-controlled trials with matching quality criteria that reported remission as an outcome measure. These trials involved 662 patients, mostly with moderately active UC, and tested numerous antibiotics (metronidazole, ciprofloxacin, tobramycin, vancomycin, amoxicillin, tetracycline, and rifaximin) either alone or in combination. The pooling of the results of these randomized-controlled trials found a statistically significant beneficial effect of antibiotics for the treatment of active UC (relative risk of active UC not in remission 0.64; 95% confidence interval: 0.43–0.96; $P = 0.03$) [4]. It is noteworthy that three randomized-controlled trials have evaluated the use of broad-spectrum antibiotics (vancomycin, tobramycin, and rifaximin) for the treatment of active UC. Each antibiotic was used alone orally for a short period of 1–2 weeks as an adjunct to standard medical therapy. The results from these three studies were pooled in the 2011 meta-analysis, showing that antibiotics have a significant effect compared with placebo (relative risk 0.46; 95% confidence interval: 0.29–0.71) [4]. However, the effect of antibiotics, especially ciprofloxacin, remains modest compared with placebo. Moreover, although the authors reported that antibiotic therapy may induce remission in active CD and UC, they did not evaluate long-term antibiotic efficacy. Here, we report deep and sustained remission in three highly refractory UC patients, including one patient with a follow-up of more than 3 years. Deep remission, defined as clinical remission and MH, has been established as a new therapeutic goal in UC and is associated with higher clinical remission rates, and fewer flares, hospitalizations, and surgeries [12].

The use of vancomycin as maintenance therapy in our three patients was motivated by the remarkable effect of ciprofloxacin and metronidazole on the activity of colonic disease during hospitalization. Indeed, all three patients achieved clinical remission following antibiotic treatment. Antibiotics are currently not recommended for the treatment of moderate to severe UC refractory to conventional therapies [3], except in patients with proven *C. difficile* infection responsible for the flare of UC. Our patients all underwent stool testing for *C. difficile*, with negative results. Two of our patients were refractory to azathioprine and anti-TNFα therapy, and one patient had severe side effects with adalimumab treatment. At that time, vedolizumab was not available and the physicians who were managing the patients believed that antibiotic maintenance therapy was a reasonable option to avoid colectomy. The side effects observed with ciprofloxacin and metronidazole in our patients limited their use as maintenance therapy, and oral vancomycin was chosen, with good efficacy and tolerance. The recommended dosing regimen of oral vancomycin for the treatment of *C. difficile* infection ranges from 125 to 500 mg four times a day [10]. The same vancomycin dosing regimen was used in adult patients for the treatment of PSC. For children, oral vancomycin was used at 500 mg three times a day. The physicians who managed the patients in our study chose to use a daily dose within the range of what was recommended previously for adult patients (1000 mg/day), but with only two administrations per day to improve treatment compliance. However, in this retrospective study, we could not obtain data on treatment compliance for the three patients.

PSC is a biliary disease characterized by progressive fibrosis and sclerosis of biliary ducts. According to published studies, 2.5–7.5% of patients with UC or Crohn's disease develop PSC [13]. Previous studies have suggested that patients with PSC and IBD differ from IBD patients without PSC in several aspects. Patients with PSC and IBD have been reported to show an increased incidence of pancolitis, rectal sparing, backwash ileitis, mild symptoms, and colorectal malignancy [2,14]. Moayyeri *et al.* [15] reported that the number of hospitalizations and courses of corticosteroid therapy decreased significantly in UC patients with PSC compared with UC controls. Our patients were all diagnosed with PSC with elevated ALP and aminotransferases, with the diagnosis confirmed by MRI. One of our patients presented severe liver disease with cirrhosis confirmed by liver biopsy. Although patients with UC and PSC typically have a milder intestinal disease, our three patients had refractory colonic disease with failure of conventional and biologic therapies. In these UC patients refractory to conventional therapy, surgery should be considered an option. However, avoiding surgery with an alternative treatment such as vancomycin could be of clinical benefit.

Several studies have previously investigated the use of antibiotics for the treatment of patients with PSC with or without associated IBD, some of which have yielded favorable results primarily on the basis of reduction in serum aminotransferases or ALP [16] (Supplementary Table 2, Supplemental digital content 2, *http://links.lww.com/EJGH/A327*). A recent randomized placebo-controlled clinical trial evaluated the efficacy of oral vancomycin in PSC patients ($n = 29$) [17]. They received either placebo or oral vancomycin, 125 mg four times a day, for 12 weeks. In this particular study, the authors investigated the evolution of digestive symptoms in 75% of patients with concomitant IBD as a secondary endpoint. Interestingly, in the vancomycin group, only 22% of the patients had diarrhea and 6% had rectal bleeding at the start of the study, indicating that these patients had a milder course of UC. Nonetheless, all patients with diarrhea experienced significant symptom improvement on vancomycin. Preliminary reports in children with UC and PSC have shown a similar clear positive effect of vancomycin on liver and intestinal disease activity [9,18–20]. It is noteworthy that a relapse of liver disease was

observed when vancomycin was withdrawn, showing the need for antibiotic maintenance therapy. Our case series confirmed that vancomycin is extremely effective for the treatment of UC in adult PSC patients, with achievement of deep remission. Moreover, in two of our patients, we observed normalization of liver function tests on oral vancomycin. Liver function tests remained abnormal in the third patient despite endoscopic remission because of advanced cirrhosis.

Evidence from animal models and the success of antibiotic treatment in PSC patients suggest that disruption of the gut microbiota may play a significant role in the pathogenesis of PSC [7,21,22]. Recently, several studies have described specific changes in the gut microbiota of PSC patients that were independent of concomitant IBD [21]. In a recent study, PSC-associated and UC-associated dysbiosis was characterized by reduced bacterial diversity, significant changes in the global bacterial composition, and the relative abundance of distinct taxa, primarily at the genus and species levels. Several microbes including *Akkermansia muciniphila*, *Butyricicoccus pullicaecorum*, and *Clostridium colinum* clearly distinguished the UC and PSC-IBD phenotypes [21]. We suspect that our PSC patients presenting with a refractory course of IBD have distinct abnormalities in their gut microbiota that could explain the course of the disease and the efficacy of vancomycin. Unfortunately, we could not carry out microbiota analysis in these patients to compare their gut flora with controls and other UC patients. Moreover, there have recently been major concerns about the colonization of gut microbiota by vancomycin-resistant enterococci (VRE) in patients treated with vancomycin [23]. As described in our study, long-term treatment with oral vancomycin may increase the risk of selecting such resistant bacteria. None of the three patients were tested for the appearance of VRE in stools over time and we would recommend a systematic analysis of microbiota composition and screening for the presence of VRE in future studies involving patients treated with oral vancomycin as maintenance therapy for UC.

In this brief report, we have described the dramatic effect of oral vancomycin in three patients with UC associated with PSC. All patients achieved clinical remission and MH. Vancomycin was well tolerated and also improved liver function tests in two patients without preexisting cirrhosis. These findings highlight the particular pathophysiology of UC and PSC, which likely involves specific dysbiosis, and the analysis of the microbiota of these specific patients before and after oral vancomycin treatment would be of particular interest. In addition, these results indicate that further larger controlled studies are needed to investigate the use of broad-spectrum antibiotics such as vancomycin or rifaximin in the treatment of patients with UC associated with PSC.

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### *Conflicts of interest*

There are no conflicts of interest.

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