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Oral vancomycin is associated with less therapy intensification in adults with symptomatic inflammatory bowel disease and underlying primary sclerosing cholangitis

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Abstract

Background Case reports describe the use of oral vancomycin therapy (OVT) in adult patients with concomitant symptomatic inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC). OVT is associated with a higher likelihood of IBD remission in pediatric IBD-PSC patients. However, there are limited data on the association between OVT and IBD disease course in adult IBD-PSC patients.

Methods We retrospectively evaluated IBD therapy intensification in adults with IBD-PSC prescribed OVT at 2 centers. Subjects were stratified by time "on" and "off" OVT. Only those who spent a minimum of 12 months in each period were included. The primary outcome was the frequency of IBD therapy intensification events.

Results Of 31 patients initially considered, 22 met the inclusion criteria. Most patients (68.2%) had fewer or no intensification events while "on OVT" compared to those "off OVT". OVT was associated with fewer therapy intensification events (1.7 vs. 6.7, P=0.021) and steroid prescriptions (0.6 vs. 3.2, P=0.013) per 10 person-years.

Conclusions OVT use is associated with less need for IBD therapy intensification in symptomatic IBD-PSC adult patients. Prospective trials of OVT in such patients are warranted.

Keywords Inflammatory bowel disease, primary sclerosing cholangitis, oral vancomycin therapy, disease activity

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Conflict of Interest: None

*Both authors contributed equally to this work, and serve as co-first authors

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Introduction

Seventy percent of patients with primary sclerosing cholangitis (PSC), a cholestatic liver disease, have comorbid inflammatory bowel disease (IBD). Typically, comorbid symptomatic IBD in PSC is a milder phenotype of ulcerative colitis (UC), characterized by pancolitis, rectal sparing and ileitis [1,2]. Since PSC is associated with alterations in the gut microbiome, antibiotics are postulated to be beneficial in treatment [3]. While no proven therapy for PSC exists, oral vancomycin therapy (OVT) has received considerable interest, without demonstrating a clear benefit in PSC outcomes [4,5]. Therefore, recent guidelines concluded that there was insufficient evidence to recommend OVT for the treatment of PSC [6]. Notably, the guidelines did not address the role of OVT in the treatment of symptomatic comorbid IBD in patients with PSC (IBD-PSC).

Recent data in pediatric IBD-PSC patients show that OVT is associated with a higher likelihood of IBD clinical and endoscopic remission—although associations with IBD therapy changes, including therapy de-escalation, were not directly studied [7]. It is not yet clear whether this association also holds in adult IBD-PSC patients, who can have different response rates to IBD therapy than pediatric patients [8,9]; to date, the majority of data on OVT in adult IBD-PSC patients are from case reports [10,11]. We hypothesized that OVT would similarly be associated with a better IBD disease course in adults with IBD-PSC. We studied whether OVT was associated with differences in IBD disease activity, as assessed by the need for IBD therapy intensification, in adult patients with IBD-PSC.

Patients and methods

This was a 2-center (Stanford Medicine and Baylor College of Medicine; 2010-2022), retrospective cohort study of adult patients with PSC and IBD (as defined by American College of Gastroenterology [ACG] criteria) who were prescribed OVT at any time after their IBD diagnosis. Subjects were initially identified by International Classification of Diseases (ICD-10) coding for PSC, and were manually reviewed to ensure they met the ACG criteria for PSC. This cohort was subsequently further evaluated for IBD using ICD-10 coding. The diagnosis of IBD was verified by manual review of colonoscopy reports. Fig. 1 illustrates this identification of the study cohort. Patients suffering from any other cause of sclerosing cholangitis, those who received OVT prescriptions for the treatment of *Clostridioides difficile* colitis, or recipients of liver transplantation, were excluded. Data on OVT dosage and duration and timing (in relation to IBD disease activity) were collected and analyzed. OVT duration was defined as the time from OVT prescription to cessation of the drug; if a patient had multiple such periods, data for each period were recorded individually. Intensification of therapy was defined as therapy class change (e.g., 5-aminosalicylic acid to infliximab), dose escalation (e.g., infliximab 5 mg/kg to 10 mg/kg) or new steroid prescription, if they occurred at least 1 month after initiation of OVT. Given the uncertainty regarding the optimal latency time window, we also performed a secondary analysis with an exposure lag of 3 months, counting the first 3 months after prescription of OVT as being off therapy and the 3 months after discontinuation as being on therapy. Responders were defined as those who had fewer time-weighted events "on OVT", compared to time-weighted events "off OVT". Data on PSC-related complications (i.e., development of dominant or high-grade stricture, cholangitis, and development of cirrhosis) was also analyzed. All patients in the cohort underwent annual magnetic resonance cholangiopancreatography; dominant or high-grade stricture was determined by the radiologist, or an advanced endoscopist (if the patient underwent a follow-up endoscopic retrograde cholangiopancreatography). Cholangitis was identified by manual chart review, and defined as an episode of hospitalization requiring intravenous antibiotics for a condition that the treating physician (at the time of hospitalization) considered to be cholangitis. Cirrhosis was identified first via screening by ICD-10 coding, then confirmed with manual chart review using conventional clinical criteria.

Hypothesis testing was performed only on patients who had data available for more than 12 months, both "on" and "off OVT"; this allowed for patients to be used as their own controls. The primary outcome of this study was the intensification of IBD therapy, normalized to person-years. These data were normalized to person years in order to minimize bias due to variations in the length of follow up. A secondary outcome was the frequency of steroid prescription. These outcomes were chosen because of their high clinical significance in the IBD disease course. The outcomes were compared with Wilcoxon matched-pairs signed rank test. This study was approved by the Institutional Review Boards of both Stanford and Baylor Universities.

Results

We studied 31 patients, of whom 22 met the criterion of sufficient time both "on" and "off OVT" to serve as self-controls. Clinical characteristics are shown in Table 1. Fifteen of the 22 patients (68.2%) had fewer or no therapy intensification events "on OVT" compared to those who were "off OVT". Those with fewer treatment intensification events were otherwise not different from those with more treatment intensification events (Table 1). There were no significant differences between the 2 study sites in OVT prescription rates, baseline disease activity or outcomes.

Fewer OVT periods met the primary outcome of therapy intensification events, compared to control periods. Specifically, the mean number of therapy intensification events per 10 person-years "on OVT" was 1.7, compared to 6.7 when "off OVT" (P=0.021, Fig. 2A). OVT was also associated with less need for steroid prescriptions (0.6 prescriptions per 10 person-years with OVT vs. 3.2 prescriptions per 10 person-years without OVT, P=0.013; Fig. 2B). Using a lag time of 3 months, OVT was associated with a lower number of therapy intensification events per 10-person years (1.6 vs. 7.2, P=0.018) and steroid prescriptions per 10 person-years (0.5 vs. 3.7, P=0.020) compared to periods "off OVT". De-escalation of therapy was more frequently associated with OVT (2.57 de-escalations per 10 person-years "on OVT" vs. 0.11 de-escalations per 10 person-years "off OVT", P=0.001). While OVT did not correlate with objective

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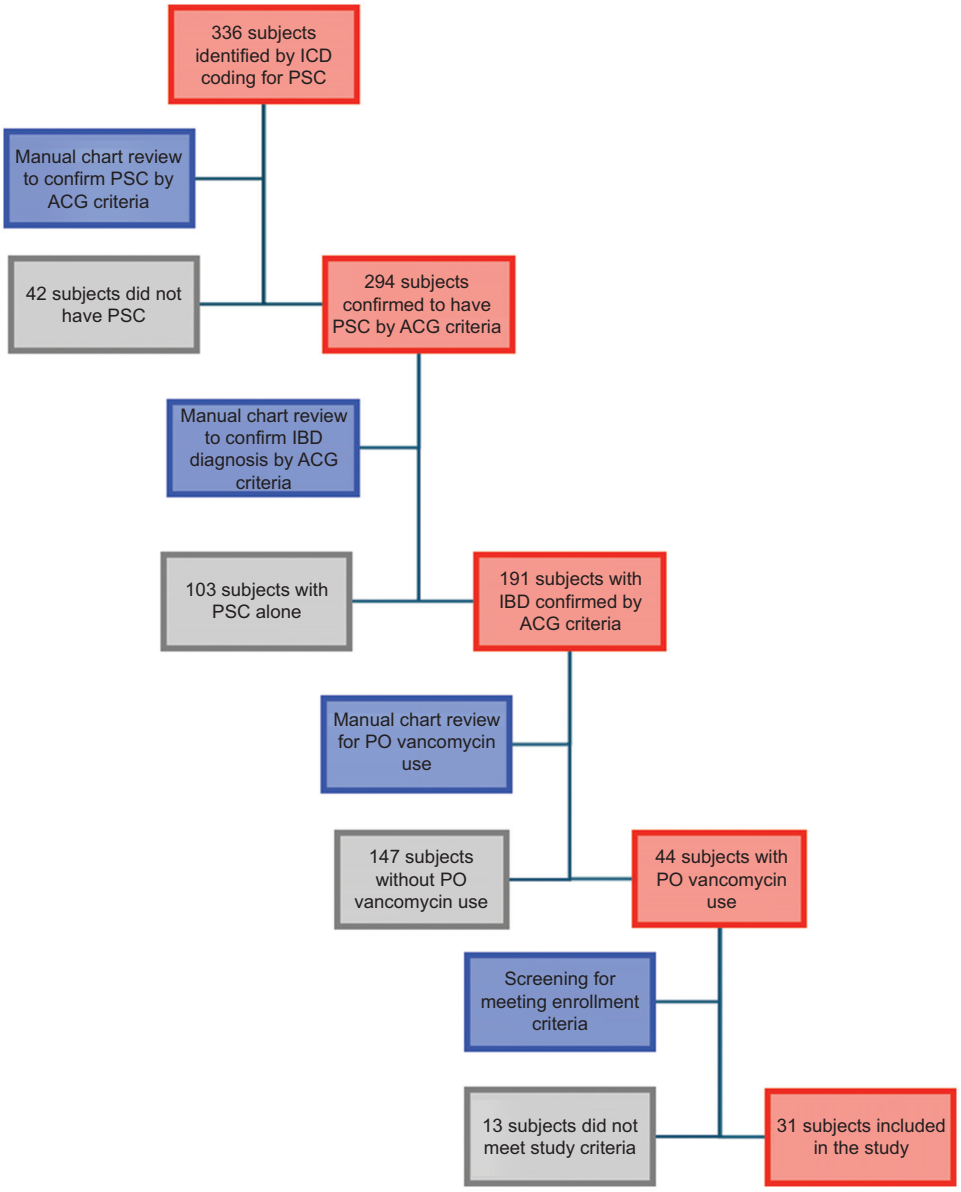

Figure 1 Study flow chart illustrating the process of identifying the study cohort. Exclusion criteria: Patients with any cause of secondary sclerosing cholangitis, OVT prescriptions for treatment of *Clostridioides difficile* colitis, or liver transplant recipient status
ACG, American College of Gastroenterology; ICD, International Classification of Diseases; OVT, oral vancomycin therapy; PO, per oral; PSC, primary sclerosing cholangitis

markers of inflammation (C-reactive protein, calprotectin or endoscopic disease by colonoscopy), objective data were only available for 10 patients (P=0.296); therefore, evaluation of the biochemical or endoscopic response was underpowered. OVT was equally likely to be prescribed during all periods of follow up.

Responders had a higher median total daily dose (TDD) of OVT compared to non-responders (1500 mg/day vs. 903 mg/day, P=0.032; Fig. 2C). Patients who received a TDD of OVT ≥1000 mg/day were less likely to have any therapy intensification event while on OVT (P=0.019), while those with a TDD <1000 mg/day did not differ in therapy intensification events "on" and "off OVT" (P=0.625), suggesting that the clinical response was dose-dependent and above a threshold of 1000 mg/day. OVT duration did not significantly impact the likelihood of response to OVT.

Twelve patients (54.5%) had extensive UC, and 8 of them responded to OVT. The proportion of patients who responded to OVT was similar (66.7% vs. 70.0%, P=0.999) in both those with and those without extensive UC. However, OVT responders without extensive UC had 19.5 fewer intensification events per 10 person-years than non-responders compared to 2.7 fewer intensification events per 10 person-years for those with extensive UC (P<0.001).

Table 1 Baseline demographics and clinical characteristics of patients, based on response to OVT

Characteristics	All patients (n=22)	LI (n=15)	MI (n=7)	P-value*
Median age, years (IQR)	23.5 [21-28.3]	25.5 [22.0-29.0]	21.5 [19.8-24.5]	0.174
Male sex, (%)	15 (68.2%)	11 (73.3%)	4 (57.1%)	0.642
Race and ethnicity, (%)				
Caucasian	11 (50.0%)	8 (53.3%)	3 (42.8%)	0.667
Black	2 (9.1%)	2 (13.3%)	0 (0.0%)	0.526
Asian	2 (9.1%)	2 (13.3%)	0 (0.0%)	0.526
Hispanic	5 (22.7%)	3 (20.0%)	2 (28.6%)	0.999
Other	2 (9.1%)	0 (0.0%)	2 (28.6%)	0.111
IBD, (%)				
Ulcerative colitis	21 (95.5%)	15 (100.0%)	6 (85.7%)	0.318
Proctitis	2 (9.1%)	2 (13.3%)	0 (0.0%)	0.999
Left-sided	4 (18.2%)	2 (13.3%)	2 (33.3%)	0.565
Extensive UC	15 (68.2%)	11 (73.3%)	4 (66.7%)	0.630
Crohn's disease	1 (4.5%)	0 (0.0%)	1 (14.3%)	0.318
Colon only	1 (4.5%)	0 (0.0%)	1 (100.0%)	0.318
Duration of IBD, months (IQR)	129.0 [108.5-184.8]	125.0 [99.3-167.0]	146.0 [110.8-206.0]	0.352
Median total daily dose (mg)	1385 [740-1500]	1500 [1067-1500]	903 [536-1427]	0.032
Time off vancomycin, months (IQR)	48.0 [27.0-80.3]	46.1 [17.0-82.8]	48.0 [31.3-80.3]	0.980
Time on vancomycin, months (IQR)	88.4 [47.5-102.0]	82.8 [41.8-101.3]	96.0 [63.8-136.3]	0.296
IBD medications				
5-ASA	14 (63.6%)	9 (60.0%)	5 (71.4%)	0.999
Immunomodulators	5 (22.7%)	3 (20.0%)	2 (28.6%)	0.999
Biologics	2 (9.1%)	2 (13.3%)	0 (0.0%)	0.999
Steroids	4 (18.2%)	3 (20.0%)	1 (14.3%)	0.999
Smoking status				
Current	0 (0.0%)	0 (0.0%)	0 (0.0%)	>0.99
Former	2	1 (6.7%)	1 (14.3%)	>0.99
Cirrhosis	7 (31.8%)	5 (33.0%)	2 (28.5%)	0.999
Compensated cirrhosis	4 (18.2%)	3 (20.0%)	1 (14.3%)	0.999
Decompensated cirrhosis	3 (13.6%)	2 (13.3%)	1 (14.3%)	0.999
Dominant stricture	9 (40.1%)	4 (26.7%)	2 (28.6%)	0.999
Episode of cholangitis	3 (13.6%)	3 (20.0%)	0 (0.0%)	0.523
Charlson Comorbidity Index	0.0 [0.0-1.0]	0.0 [0.0-1.0]	0.5 [0.0-1.0]	0.722

IBD medications recorded in this table are prior to the first prescription of OVT

Results are given as median [IQR] or N (%)

*P-value for comparison between LI and MI

5-ASA, aminosalicylic acid; IBD, inflammatory bowel disease; IQR, interquartile range; LI, less therapy intensification; MI, more therapy intensification; OVT, oral vancomycin therapy; PSC, primary sclerosing cholangitis

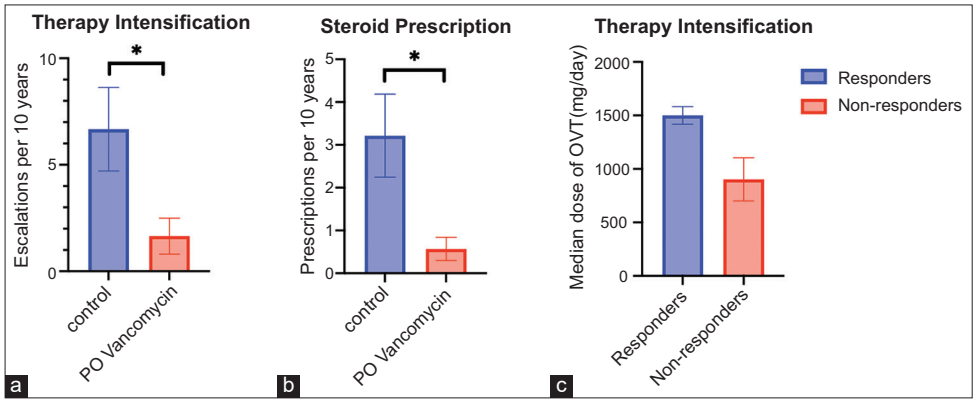

Figure 2 (a) Comparison of therapy intensification between periods "on" and "off OVT" per 10 person-years of follow up. (b) Comparison of steroid prescriptions between periods "on" and "off OVT" per 10 person-years of follow up. (c) Median daily dose of OVT (mg/day) in responders and non-responders *OVT, oral vancomycin therapy; PO, per oral*

The frequency of therapy intensification events (1.7 vs. 1.5 per 10 person-years, P=0.857) and steroid prescriptions (0.6 vs. 0.5 per 10 person-years, P=0.799) on OVT for the 22 patients who served as their own controls was not different from the frequency of intensification on OVT observed in the entire cohort.

Rates of key PSC-related liver complications, including the development of dominant strictures, cholangitis and cirrhosis, were not different between the 2 groups.

Discussion

This study found that OVT was associated with fewer IBD therapy intensification events and fewer steroid prescriptions in adults with IBD-PSC. These results suggest that OVT, at a minimum dose of 1000 mg/day, could be an effective pharmacologic therapy for IBD symptoms in adults with IBD-PSC. However, this finding requires validation in a larger, prospective study. Our data suggest that a TDD of >1000 mg/day may increase the likelihood of a clinical response to OVT, using our criteria.

Extensive UC was not associated with diminished odds of meeting the primary outcome, though the effect size was lower, suggesting that patients with limited UC may derive the largest benefit. OVT was equally likely to be prescribed at all points during the follow-up period, suggesting that results were not biased by OVT prescription being more common early in the IBD disease course, when disease severity is typically lower [12]. This study is congruent with prior case reports suggesting that OVT is associated with reduced disease activity in patients with IBD-PSC [10].

There are at least 2 possible mechanisms by which OVT may influence gut inflammation in IBD. Gut dysbiosis has been previously linked to altered bile acid metabolism and associated gut inflammation [13], and vancomycin may affect gut inflammation through one or more such alterations of the gut microbiota composition [14]. Another possible mechanism of action is through a direct immunomodulatory effect, as vancomycin may increase peripheral regulatory T cells [15].

Several limitations of our study need to be considered: 1) our small sample size limits its impact. Nevertheless, our findings are informative and intriguing, given the otherwise limited data on IBD outcomes of OVT use in adults with IBD-PSC; 2) the retrospective design of our study also limited our ability to stratify subjects by IBD disease activity, though this was mitigated using the self-control study design. Furthermore, the presence of similar baseline IBD therapies in both groups suggested that they had comparable IBD disease activity; 3) we encountered a relatively low event rate in both arms, which was probably the result of the mild IBD phenotype often observed in IBD patients with concomitant PSC [2]. This also probably explains why only 2 of the study subjects were on advanced IBD therapies, such as biologics; and 4) objective data, such as inflammatory markers or colonoscopy, were available only for a subset of patients, which limited our ability to study the relationship between OVT and objective measures of bowel inflammation. However, OVT has previously been associated with improved objective markers of inflammation in a study of pediatric IBD-PSC patients [6]. As our study only included IBD-PSC patients, the findings cannot be generalized to all patients with IBD. Further investigations are warranted to establish whether OVT is effective as an adjunctive IBD therapy in adults with IBD-PSC.

In summary, OVT use was associated with less need for IBD therapy intensification in IBD-PSC adult patients. Prospective trials of OVT in this population are warranted.

Summary Box

What is already known:

- The majority of patients with primary sclerosing cholangitis (PSC) develop comorbid inflammatory bowel disease (IBD)
- Oral vancomycin therapy (OVT) is associated with a higher likelihood of remission of IBD in pediatric patients with both IBD and PSC
- The only current data describing the use of OVT in adults with PSC-IBD come from case reports

What the new findings are:

- This is the first retrospective cohort study of OVT in adult patients with PSC-IBD
- OVT is associated with fewer IBD therapy intensification events and fewer steroid prescriptions in adults with PSC-IBD
- A total daily dose above 1000 mg/day of OVT may increase the likelihood of a clinical response to OVT in this population

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