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ORIGINAL ARTICLE

Open-label prospective therapeutic clinical trials: oral vancomycin in children and adults with primary sclerosing cholangitis

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ABSTRACT

Background: Oral vancomycin (OV) in primary sclerosing cholangitis (PSC) has been evaluated as a potential therapeutic agent. We report the long-term biochemical course and outcomes of patients with PSC treated with OV.

Methods: Patients were enrolled in 2 open-label clinical trials (ClinicalTrials.gov Identifier: NCT01802073 and NCT01322386) and offered OV at 50 mg/kg/day in 3 divided doses if weight <30kg, and 500 mg 3 times/day if weight ≥30kg. Patients with biliary strictures requiring stenting or awaiting liver transplant were excluded. Liver biochemistry, MRCP and histology were documented at baseline and while on OV. The primary outcome was a decrease in elevated gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), and/or alanine aminotransferase (ALT) from baseline.

Results: 30 subjects were enrolled, and 29 additional subjects who learned of the clinical trial requested OV (total $n = 59$; median age was 13.5 years [range, 1.5–44 years]; 64.4% were male; and 94.9% had inflammatory bowel disease [IBD]). The median treatment duration was 2.7 years (range, 0.2–14 years). Ninety-six percent (57/59), 81.3% (48/59), and 94.9% (56/59) experienced reduction of GGT, ALP, and ALT, respectively. Furthermore, 39% (23/59), 22% (13/59), and 55.9% (33/59) experienced normalization of GGT, ALP, and ALT, respectively, within the first 6 months of OV treatment. One patient underwent liver transplantation 8 years after beginning OV treatment, and one developed biliary strictures requiring endoscopic intervention. OV was well-tolerated by patients, and no patient developed treatment-related adverse events.

Conclusion: In PSC, OV was well-tolerated and was associated with improvement in liver chemistry. A randomized placebo-controlled clinical trial is warranted.

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KEYWORDS
Primary sclerosing cholangitis; cirrhosis; liver biochemistry; cholangiography; inflammatory bowel disease; and ulcerative colitis

Introduction

Primary sclerosing cholangitis (PSC) is a chronic, fibroinflammatory, immune-mediated disease of the bile ducts, which often leads to cirrhosis, end-stage liver disease (ESLD), and an increased risk of hepatobiliary and colorectal malignancy [1]. Currently, there is no medical regimen approved by the regulatory agencies or by the leading scientific societies for the treatment of PSC.

PSC is strongly associated with inflammatory bowel disease (IBD), namely, ulcerative colitis (UC) [2]. The 'leaky gut' theory implies that the pathogenic gut microbiota crosses through the inflammed gut wall into the portal circulation, and then into the biliary tree, leading to PSC [3]. This theory is supported by several observations [4]. Stanford University was the first to report the use of oral vancomycin (OV) in pediatric patients with PSC [5,6]. The use of OV resulted in biochemical, cholangiographic, and histological improvement of the PSC and decreased intestinal inflammation of the IBD on colonic biopsies [7]. Several studies have reported similar results in children and adults with PSC [8–13].

In this paper, the results of two prospective open-label clinical trials of OV in patients with PSC, and data on patients with PSC treated with OV outside of the prospective open-label clinical trials, with follow-up for up to 14 years are reported.

Methods and materials

Data collection

The trials reported herein were approved by the Stanford University Institutional Review Board (IRB) and registered at

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Supplemental data for this article can be accessed here.

ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT01802073 and NCT01322386). The study protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from adults, and informed assent was obtained from children prior to their inclusion in the study. The two prospective open-label clinical trials aimed to evaluate the effects of daily dosing with OV on the clinical and biochemical course of PSC in both children and adults. The diagnosis of PSC was made if there was persistent cholestasis for ≥6 months *and* cholangiographic or histopathological findings consistent with PSC. Patients with PSC were enrolled in the two prospective open-label pilot clinical trials using OV. We note that 22 pediatric patients (ages 2–18 years) who were included in this paper, were also described in part in two previous papers [7,14]. After completion of enrollment in the two pilot clinical trials, 29 additional patients with PSC who learned of the clinical trial requested the OV treatment; these 29 additional patients were not enrolled in the clinical trials identified above but they followed the same protocol for OV treatment, described below. Patients with concomitant IBD who were already on 5-aminosalicylic acid (5-ASA) or mesalamine were included.

Patient exclusion criteria included PSC complicated by biliary strictures requiring biliary stenting; end-stage liver disease secondary to PSC listed for liver transplantation (LT); autoimmune hepatitis; PSC overlap with autoimmune hepatitis (PSC-AIH overlap); presence of other liver disease including Alagille's syndrome, cystic fibrosis liver disease, histiocytosis, immunoglobulin G4-sclersoing cholangitis, Caroli's disease in addition to immunodeficiency and sickle cell disease; Wilson's disease; alpha-1 antitrypsin deficiency; and/or if prednisone or a biological agent was required for management of their IBD.

For each patient in this study, the following data was collected: age at the time of diagnosis of PSC; gender; presence of IBD; type of IBD (ulcerative colitis [UC], Crohn's disease [CD]; or indeterminate colitis); stage of PSC at the time of diagnosis of PSC [15]; presence or absence of cirrhosis at the time of diagnosis of PSC; OV dose and frequency; duration of treatment with OV; serum GGT, alkaline phosphatase (ALP), and alanine aminotransferase (ALT) at baseline; follow-up serum GGT, ALP and ALT at month 1, 3, 5, 6, 8, 10, and 12 of OV treatment; last known serum GGT, ALP and ALT; side effects and/or adverse events related to the use of OV; and development of liver/bile duct cancer, development of cirrhosis, listing in the liver transplantation list, and/or need for liver transplantation.

Treatment with oral vancomycin

OV was offered to all PSC patients who met the criteria for the OV treatment, regardless of whether they were on any PSC treatment, including ursodeoxycholic acid (UDCA). The protocol for dosing and frequency of OV in pediatric PSC has been previously described in detail. Briefly, pediatric patients with an established diagnosis of PSC were treated with OV at a dose of 50 mg per kilogram per day divided into 3 times per day if weight was < 30 kg, and at a dose of 500 mg 3 times a day if weight ≥ 30 kg. Adult patients with PSC were treated with OV at a dose of 500 mg 3 times a day. The dose of OV used in the two prospective clinical trials and in those who requested OV treatment outside of the two prospective clinical trials is the same dose we used in the prior clinical pilot studies [5,7,14,16]. OV was provided by local pharmacies.

With respect to duration of treatment with OV, patients who agreed to the treatment were treated for a minimum of 3 months. After completion of 3 months of treatment, patients were offered to continue OV, particularly if they experienced clinical and/or laboratory evidence of flare of PSC while being off OV, depending on their compliance, willingness to continue OV, and the ability to obtain the drug. Patients with concomitant IBD continued 5-ASA or mesalamine for IBD during treatment with OV. If patients needed escalation of medical therapy for management of IBD (addition of prednisone or biological agents), OV would be discontinued.

Assessment of treatment with oral vancomycin

For each patient, blood samples for analysis of serum GGT, ALP, and ALT were drawn at baseline, and at month 1, 3, 5, 6, 8, 10, and 12 of OV treatment. The percentage change of each laboratory parameter (i.e. GGT, ALP, and ALT) at month 1, 3, 5, 6, 8, 10, and 12 form baseline values was recorded for each patient. In addition, the percentage of patients who experienced normalization of ≥1 of the laboratory parameters at months 1, 3, 5, 6, 8, 10, and 12 of OV treatment was also recorded. Because patients had blood samples drawn for laboratory assessment at different clinical laboratories, serum liver biochemistry were normalized by dividing the actual values by the upper limits of normal for the clinical laboratory in which the lab test was performed. Compliance with OV treatment was reviewed at each clinic visit.

Primary and secondary outcomes

The primary outcome was defined as a decrease in elevated serum GGT, ALP, and/or ALT from baseline values in the first 12 months of OV treatment. Secondary outcomes were reduction in elevated serum GGT and/or ALT by ≥50% from baseline; normalization of serum GGT, ALT and/or ALP; development of hepatobiliary adverse events (progression to cirrhosis, development of biliary stricturing requiring biliary stenting, or cholangiocarcinoma); improvement in biliary strictures/dilatation on repeat cholangiography; improvement in liver histopathology; and improvement in IBD-related diarrhea.

Safety and adverse events

Adverse events (AEs) related to OV, including clinical and biochemical findings, were assessed and recorded at each clinic visit. AEs were defined as any untoward medical occurrence associated with the use of OV, whether or not considered related to OV. Special attention has been paid to the

occurrence of vancomycin-resistant enterococci (VRE). Patients were to be screened for VRE by stool culture only if they reported symptoms and/or developed signs suspicious for VRE infection.

Statistical analysis

Continuous data were expressed as median with range. Categorical data were expressed as frequency and percentage. The biochemical response to OV treatment was expressed as the median percentage change in normalized serum GGT, ALP, and ALT at months 1, 3, 5, 6, 8, 10, and 12 of OV treatment from baseline values. The paired Student's *t* test was used to compare the means of each liver biochemical parameter (GGT, ALP, and ALT) at months 1, 3, 5, 6, 8, 10, and 12 to baseline values. Because we are comparing the means of liver biochemistry parameters at several time points to the mean at baseline, we sought multiple testing correction to adjust our threshold for the *p* value using the Bonferroni correction [17]. After applying a Bonferroni correction, our corrected threshold for statistical significance was a p value $< .007$. Statistical analyses were conducted using STATA v12.1 (StataCorp LP, College Station, TX, USA), and graphs for laboratory parameters were constructed using the Prism v7, GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics

From 2002 to 2016, a total of 61 subjects with PSC were screened for eligibility for OV treatment. Of the 61 subjects, 96.7% (59/61) were treated with OV; 30 subjects were enrolled in the 2 open-label prospective clinical trials, and 29 additional patients requested to be on the OV treatment protocol (Table 1). The remaining 2 patients met the exclusion criteria (biliary strictures requiring endoscopic stenting in [$n = 1$]; and ESLD due to PSC listed for LT [$n = 1$]). Liver enzymes were frequently abnormal; GGT, ALP, and ALT were elevated in 91.5% (54/59), 47.5% (28/59), and 86.4% (51/59), respectively. Those who had normal GGT ($n = 5$; Supplementary Table 1) prior to OV treatment also had normal ALP; however, these 5 patients all had elevated ALT (normalized median, 1.5; range [1.1–2.1]), histological ($n = 4$), and cholangiographic findings ($n = 1$) consistent with PSC.

Patients were treated with OV for a median time of 2.7 years (range, 0.2–14 years) at median dose of 1500 mg (range, 500 mg–2250mg). None of the patients were on any other PSC treatment prior to OV treatment except one, who was on UDCA. That patient stopped the UDCA two months after initiating OV. The cumulative follow-up period for the entire cohort from the time of OV treatment until last known follow-up was 235.3 person-years.

Primary outcome assessment in the entire cohort

Table 2 and Figure 1(A–C) illustrate the biochemical response to OV treatment. Of the entire group, 96.6% (57/59), 81.3% (48/59), and 94.9% (56/59) experienced reduction in GGT, ALP, and ALT, respectively. Furthermore, 71.2% (42/59), 25.4% (15/59), and 76.3% (45/59) experienced reduction by $\geq$50% from baseline in GGT, ALP, and ALT, respectively. More importantly, 39% (23/59), 22% (13/59), and 55.9% (33/59) experienced normalization of GGT, ALP, and ALT, respectively, within the first 6 months of OV treatment (Figure 1(D)).

Primary outcome assessment according to age group

Pediatric patients (age <18 years). Forty-five were pediatric patients, of whom 55.6% (25/45) were male. Their median age was 12.5 years (range, 1.5–17.5 years), and were treated with OV for a median of 4.5 years (range, 0.8–14 years).

Biochemical response in serum GGT, ALP, and ALT compared to baseline values is illustrated in Figure 2 (A–C). Ninety-eight percent (44/45), 88.9% (40/45), and 100% (45/45) experienced reduction in GGT, ALP, and ALT, respectively, of whom 82.2% (37/45), 26.7% (12/45), and 64.4% (29/45) experienced $\geq$50% reduction in GGT, ALP, and ALT from baseline, respectively. Forty-nine percent (22/45), 20% (9/40), and 62.2% (28/45) experienced normalization of GGT, ALP, and ALT, respectively, within the first 6 months of OV treatment.

Adult patients (age $\geq$18 years). With regard to the adult patients ($n = 14$), their median age was 23.5 years (range, 18–44 years), and 92.9% (13/14) were male. The median duration of OV treatment was 0.8 years (range, 0.2–5.8 years).

Biochemical response in serum GGT, ALP, and ALT compared to baseline values is illustrated in Figure 2(D–F). Of the 14 patients, 92.8% (13/14), 57.1% (8/14), and 78.6% (11/14) experienced reduction in GGT, ALP, and ALT, respectively, of whom 35.7% (5/14), 21.4% (3/14), and 42.8% (6/14) experienced $\geq$50% reduction in GGT, ALP, and ALT from baseline, respectively. With regard to biochemistry normalization, 7.1% (1/14), 28.6% (4/14), and 35.7% (5/14) experienced normalization of GGT, ALP, and ALT, respectively, within the first 6 months of OV treatment.

Primary outcome assessment according to small- vs. large-duct PSC

Small- and large-duct PSC. Forty-two percent (25/59) had small-duct PSC and 57.6% (34/59) had large-duct PSC. Their biochemical responses are illustrated in Table 3 and Figure 3(A–C). Overall, there was no statistically significantly difference in the liver chemistry responses between the two groups.

Long-term follow-up and clinical outcomes

Stopping and restarting oral vancomycin. As part of the protocol, patients were instructed to stop taking OV after a minimum of 3 months of OV treatment with the anticipation to be re-challenged with it to examine the effects on liver biochemistry. Thirty patients did not agree to stop OV and continued taking it for a median of 3.1 years (range,

Table 1. Clinical features of all PSC patients treated with oral vancomycin at Stanford University between 2002 and 2016 ($n = 59$).

Variable	Descriptive statistics ($n = 59$)
Age, years, median (range)	13.5 (1.5 − 44)
Male gender, *n* (%)	38 (64.4%)
Liver biopsy, *n* (%)	49 (83.1%)
Stage of fibrosis[a]	
No fibrosis	7 (12.7%)
Stage I	13 (23.6%)
Stage II	22 (40%)
Stage III	5 (9.1%)
Stage IV	8 (14.6%)
IBD, *n* (%)	56 (94.9%)
Ulcerative colitis, *n* (%)	51 (91.1%)
Crohn's disease, *n* (%)	5 (8.9%)
Active IBD at the time of OV treatment, *n* (%)[b]	43 (82.7%)
Duration of IBD (months) at the time of OV treatment, median (range)	6 (0.5–192)
Baseline laboratory findings[c]	
Gamma glutamyl transferase (U/L)	6.03 (0.27–54.65)
Alkaline phosphatase (U/L)	1.17 (0.08–8.96)
Alanine aminotransferase (U/L)	2.57 (0.37–45.46)
Positive p-antinuclear cytoplasmic antibodies[d], *n* (%)	40 (77%)
Positive antinuclear antibodies[e], *n* (%)	16 (39%)
Positive antismooth muscle antibodies[f], *n* (%)	13 (34.2%)
Positive antimitochondrial antibodies[g], *n* (%)	2 (7.4%)
Positive anti-liver kidney microsomal-1 antibodies[h], *n* (%)	0 (0%)
Oral Vancomycin dose in mg, median (range)	1500 (500–2250)
Oral vancomycin treatment duration in years, median (range)	2.7 (0.2–14)

[a]Ludwig staging for PSC was used. Fibrosis staging was available for 56 patients (49 by liver biopsy and 6 by magnetic resonance elastography).
[b]Data available for 52 patients.
[c]Laboratory values were normalized by dividing the actual laboratory parameter by the upper limit of normal for the clinical laboratory in which the test was performed.
[d]Data available for 52 patients.
[e]Data available for 41 patients.
[f]Data available for 38 patients.
[g]Data available for 27 patients.
[h]Data available for 27 patients.

Table 2. Responses of serum GGT, ALP and ALT in the entire cohort ($n = 59$).

Time point	Value[b] (median [range])	Median % change from baseline	*p* Value
Serum GGT			
Baseline	6.03 (0.27–54.66)		
Month 1 (48)[a]	1.61 (0.13–27.23)	−67.8%	.0002
Month 3 (42)	0.73 (0.2–24.78)	−71.9%	.0003
Month 5 (28)	0.66 (0.15–17.58)	−77.5%	.006
Month 6 (32)	0.92 (0.15–24.84)	−68.5%	.002
Month 8 (29)	0.58 (0.13–15.2)	−72.2%	.003
Month 10 (12)	1.05 (0.18–8.65)	−82.2%	.014
Month 12 (33)	0.71 (0.13–10.12)	−76.9%	.0001
Serum ALP			
Baseline	1.17 (0.08–8.96)		
Month 1 (47)	0.84 (0.14–4.45)	−32.8%	.0001
Month 3 (42)	0.87 (0.15–4.06)	−28.1%	.008
Month 5 (28)	0.78 (0.36–3.56)	−21.3%	.017
Month 6 (31)	0.81 (0.36–3.71)	−35.6%	.0006
Month 8 (28)	0.75 (0.43–3.06)	−35.4%	.006
Month 10 (14)	0.69 (0.42–1.39)	−31.6%	.041
Month 12 (33)	0.88 (0.29–2.67)	−33.8%	.006
Serum ALT			
Baseline	2.57 (0.37–45.46)		
Month 1 (51)	0.88 (0.24–5.19)	−61.9%	.006
Month 3 (44)	0.89 (0.26–3.83)	−54.8%	.006
Month 5 (29)	0.89 (0.24–3.26)	−64.3%	.017
Month 6 (34)	0.91 (0.25–2.87)	−62.1%	.019
Month 8 (29)	0.69 (0.21–3.47)	−64.3%	.0003
Month 10 (15)	0.82 (0.33–1.53)	−77.6%	.0017
Month 12 (37)	0.87 (0.21–3.24)	−65.9%	.009

[a]Numbers between parentheses in the Time point columns represent the number of patients analyzed at that particular time point.
[b]Laboratory values represent the normalized labs, which were calculated by dividing the actual value by the upper limits of normal for the clinical laboratory in which the test was performed.

0.6–14). Of the remaining 29 patients, 12 stopped and did not resume OV due to socioeconomic reasons and lack of follow-up; and 17 patients stopped and restarted OV. Of the 17 patients who stopped and restarted OV, 13 patients experienced worsening of GGT and ALT (median percentage increase in GGT and ALT from last levels while on OV were +457% and +271%, respectively), followed by improvement of GGT and ALT after restarting OV in 11 patients (median percentage decrease in GGT and ALT from the levels while off of OV were −67% and −71%, respectively).

Laboratory assessment at the end of follow-up. Forty-nine patients had liver chemistry available for review at their last known visit. After a median treatment period of 2.7 years (range, 0.2–14), serum GGT and ALT were found to be normal in 29 and 33 patients, respectively.

Cholangiography, histological, and liver stiffness assessment at the end of follow-up. Of the 25 patients with small-duct PSC, 12 underwent follow-up liver biopsy (median time from OV initiation until follow-up liver biopsy was 1.2 years, range [0.8–12]), of whom 11 patients were found to have less portal/periportal inflammation, and 1 patient was found to have no change in portal/periportal inflammation compared to the baseline liver biopsy.

With regard to the 34 patients with large-duct PSC, all had follow-up MRCP (median time from OV initiation until follow-up MRCP was 2.4 years, range [0.7–12.5]), of whom 26 were found to have improved strictures/less beading/less biliary dilatation, and 8 were found to have stable biliary strictures/dilatation. In addition to the MRCP, 5 of the large-duct

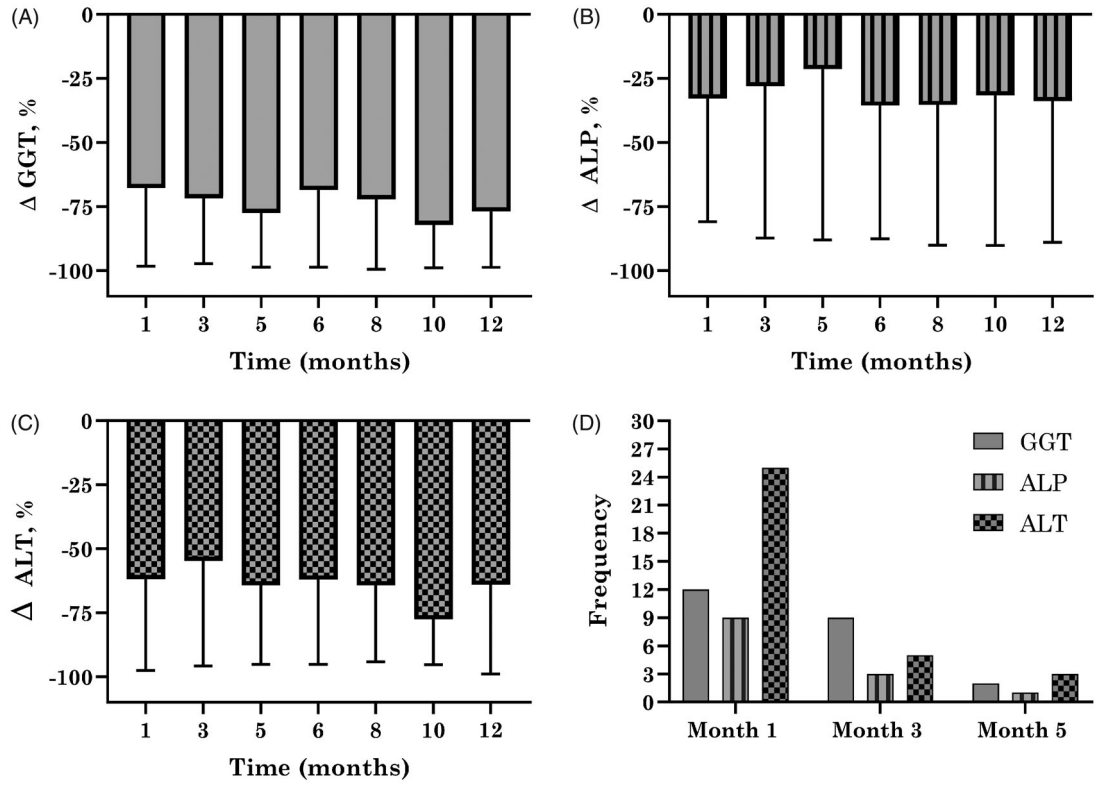

Figure 1. Biochemical response to oral vancomycin in the *entire* group of patients with PSC ($n = 59$), showing normalized median percentage change at months 1, 3, 5, 6, 8, 10, and 12 from baseline (panels A, B, and C). The proportion of patients with PSC who experienced normalization of GGT, ALP, and ALT at months 1, 3, and 5 after treatment with oral vancomycin is shown in panel D. The error bars represent the standard deviation.
Abbreviations: PSC: primary sclerosing cholangitis; GGT: gamma glutamyl transferase; ALP: alkaline phosphatase; ALT: alanine aminotransferase.

PSC patients also had follow-up liver biopsy (three patients at 1 year, one patient at 1.5 year, and one at 2 years of OV treatment), and all 5 were found to have less portal/periportal inflammation.

Two patients with large-duct PSC also had MR elastography at the time of OV treatment and at last follow-up; both patients had improved liver stiffness on the follow-up MR elastography (one patient from 3.7 kPa to 2.5 kPa at 2 years of OV treatment; and another patient from 2.3 kPa to 1.2 kPa at 3 years of OV treatment).

Clinical outcomes. During the follow-up, 2 patients developed PSC-related complications. One pediatric patient with large-duct PSC received LT 8 years after starting OV treatment. However, although this patient had cirrhotic-stage PSC at the time of beginning OV, this patient experienced significant improvement in GGT (from an actual lab value/upper limit normal ratio of 1.9 pre-OV to 1.1, 1.3, and 1 at month 1, 3, and 6 post-OV, respectively) and ALT normalization (from an actual lab value/upper limit normal ratio of 4.3 pre-OV to 0.8, 0.7, and 0.6 at month 1, 3, and 6 post-OV, respectively) with OV treatment. One adult patient with large-duct PSC had progression of biliary stricturing requiring endoscopic intervention and stenting after 11 months of treatment with OV; this patient experienced improvement in serum GGT and ALT at months 5 and 6 (reduction by −23% and −18%, and by −22% and −20%, respectively, from baseline GGT and ALT) with OV treatment. No patient developed hepatobiliary or colorectal cancer during the treatment and follow-up period.

Patient-reported effects of OV on IBD

Of the 59 patients, 56 of these had concomitant IBD. Of these 56, 76.8% (43/56) reported IBD-related diarrhea prior to initiation of OV. Of the 43 patients, 95.3% (41/43) reported improvement of diarrhea (median time from beginning OV until patient-reported IBD response to OV was 3 months [range, 0.3–24]).

Side effects/adverse events related to oral vancomycin

Patients received OV for a median of 2.7 years (range, 0.2–14 years). The use of OV was found to be well-tolerated. No patient developed renal function impairment, hearing deficits, rash, antibiotic-associated diarrhea, or bone marrow suppression, and more specifically, no patient developed clinical symptoms of VRE infection. No patient discontinued treatment due to adverse events or side effects.

Discussion

The primary objective of this paper is to report the results of the largest experience of OV treatment in patients with PSC. Our results show that the use of OV in patients with PSC was well-tolerated and was associated with improvement in serum liver biochemistry.

A main barrier for developing effective therapies for PSC is the incomplete understanding of the etiopathogenesis of PSC. It has been postulated that the gut microbiota plays a

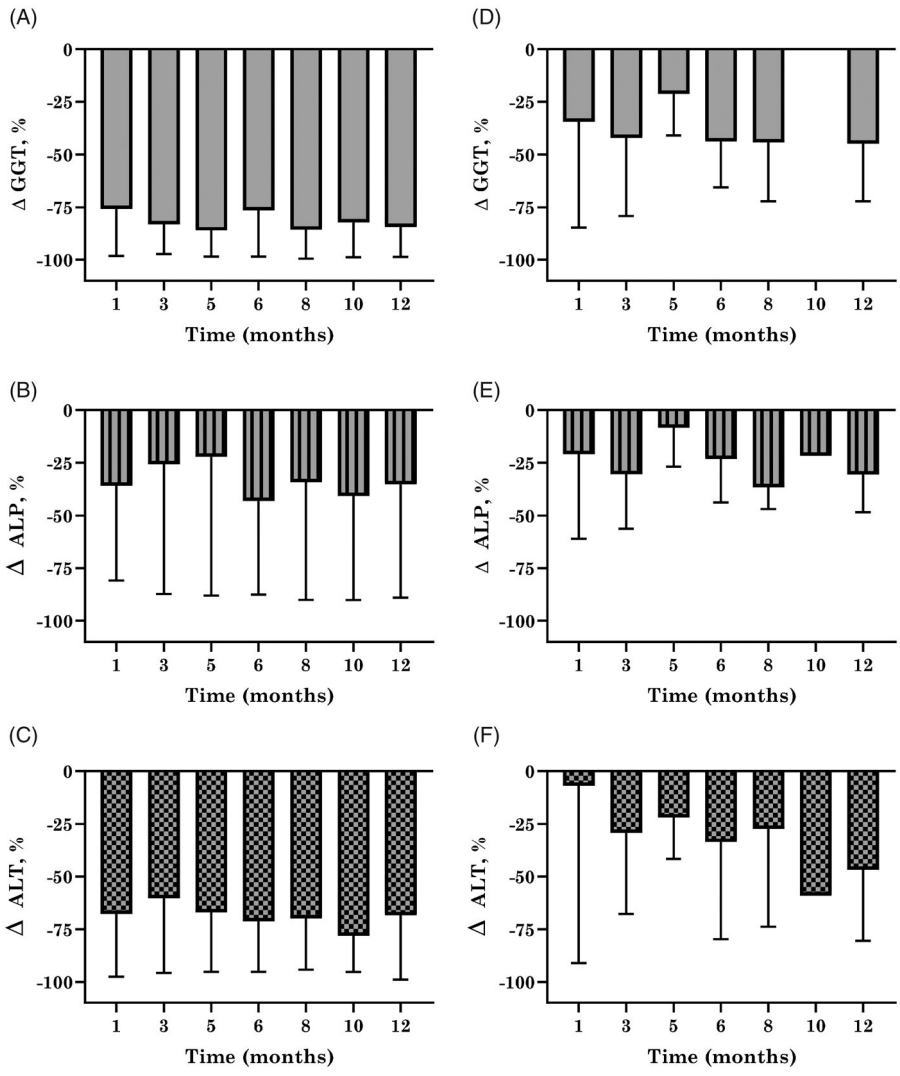

Figure 2. Biochemical response to oral vancomycin in the *children* ($n = 45$; panels A,B, and C) and *adults* ($n = 14$; panels D, E, and F) with PSC, showing normalized median percentage change at months 1, 3, 5, 6, 8, 10, and 12 from baseline. The error bars represent the standard deviation.
Abbreviations: PSC: primary sclerosing cholangitis; GGT: gamma glutamyl transferase; ALP: alkaline phosphatase; ALT: alanine aminotransferase.

Table 3. Biochemical responses to oral vancomycin in all patients with PSC according to the phenotype of PSC (small- versus large-duct).

	Large-duct PSC ($n = 34$)			Small-duct PSC ($n = 25$)		
	GGT	ALT	ALP	GGT	ALT	ALP
Any reduction[a], *n* (%)	34 (100%)	33 (97%)	27 (79%)	23 (92%) $p = .18$[b]	23 (92%) $p = .57$[c]	21 (84%) $p = .49$[d]
≥50% reduction[a], *n* (%)	23 (67.6%)	25 (73.5%)	9 (26.5%)	19 (76%) $p = .56$[e]	20 (80%) $p = .77$[f]	6 (24%) $p = .88$[g]
Normalization[a], *n* (%)	11 (32.4%)	17 (50%)	8 (23.5%)	12 (48%) $p = .28$[h]	16 (64%) $p = .31$[i]	5 (20%) $p = .91$[j]

Statistical comparison between the two groups was performed using the Fisher's exact test.
PSC: primary sclerosing cholangitis; GGT: gamma glutamyl transferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase.
[a]Any reduction, ≥50% reduction, and normalization of liver biochemistry reported here are within the first 6 months of treatment with oral vancomycin.
[b]*p* value representing difference in any GGT reduction between large- and small-duct PSC.
[c]*p* value representing difference in any ALT reduction between large- and small-duct PSC.
[d]*p* value representing difference in any ALP reduction between large- and small-duct PSC.
[e]*p* value representing difference in ≥50% reduction in GGT between large- and small-duct PSC.
[f]*p* value representing difference in ≥50% reduction in ALT between large- and small-duct PSC.
[g]*p* value representing difference in ≥50% reduction in ALP between large- and small-duct PSC.
[h]*p* value representing difference in frequency of GGT normalization between large- and small-duct PSC.
[i]*p* value representing difference in frequency of ALT normalization between large- and small-duct PSC.
[j]*p* value representing difference in frequency of ALP normalization between large- and small-duct PSC.

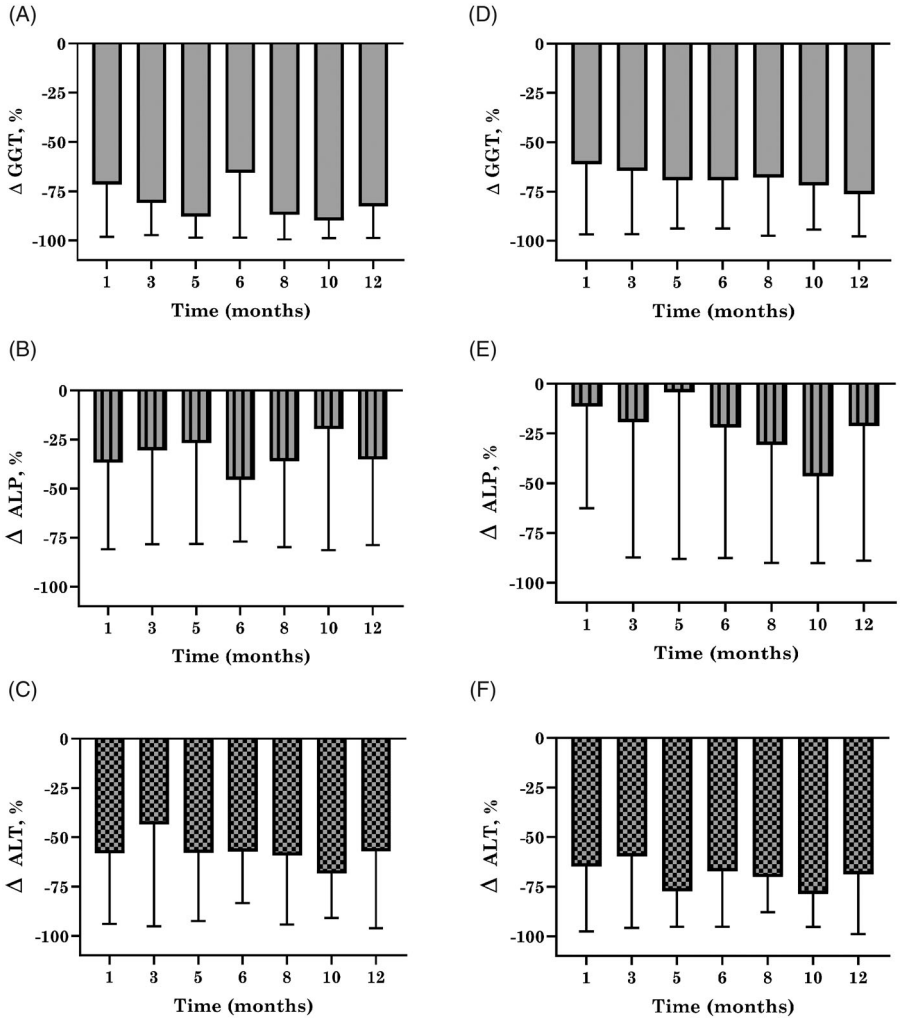

Figure 3. Biochemical response to oral vancomycin categorized based on *small-duct* PSC ($n = 25$; panels A, B, and C) and *large-duct* PSC ($n = 34$; panels D,E, and F) showing normalized median percentage change at months 1, 3, 5, 6, 8, 10, and 12 from baseline. The error bars represent the standard deviation.
Abbreviations: PSC: primary sclerosing cholangitis; GGT: gamma glutamyl transferase; ALP: alkaline phosphatase; ALT: alanine aminotransferase.

key role in the pathogenesis of PSC [18]. There has been growing interest in developing drugs targeting one or more gut microbiota targets. Several reports have consistently shown that the use of OV in PSC leads to biochemical improvement [6,10,12,19–21]. Indeed, this was our experience. Specifically, the use of OV in patients with PSC led to normalization of GGT and ALP in 39% and 22% of the patients, respectively. In a subgroup analysis, one-half of the pediatric patients experienced GGT normalization, and 28.6% of the adults experienced ALP normalization within the first 6 months of OV treatment. Upon further subgroup analysis, we found that the use of OV was equally effective in terms of improvement and/or normalization of liver chemistry in patients with small- and large-duct PSC. Importantly, these favorable biochemical effects were maintained after a median time of 2.7 years of OV treatment, with one-half of our cohort were found to have normal GGT. For assessment of treatment response in children, we chose GGT because serum ALP in children is a less reliable measure of bile duct injury due to the fact that total serum ALP is a sum of both liver- and bone-specific ALP. Throughout childhood, there is a high degree of variability of normal serum ALP levels during periods of rapid growth. Furthermore, in five large retrospective studies of pediatric PSC, only 53–81% of patients had elevated serum ALP at the time of diagnosis of PSC [22–26]. Observational studies have shown that normalization of GGT in children and ALP in adults is associated with better hepatobiliary-related survival in PSC [27–31]. While it is too early to make a recommendation, our results are encouraging because of the prognostic relevance of GGT and ALP normalization in PSC, suggesting that a randomized trial is warranted.

The mechanism by which OV leads to biochemical improvement is uncertain; however, several explanations have been proposed. Abarbanel et al. suggested an immunomodulatory mechanism evidenced by the changes in peripheral transforming growth factor-β and regulatory T cells [7]. The downregulation of tumor necrosis factor-alpha (TNF-α) production by monocytes may be a therapeutic effect of OV observed in the patients with PSC [32,33]. More recently, Nakamoto et al. have shown that *Klebsiella pneumoniae* is a key player in disrupting the epithelial intestinal barrier, promoting bacterial translocation and eventually initiating a T helper 17 inflammatory response in the liver [34].

Interestingly, treatment with vancomycin of a gnotobiotic mice using fecal samples from a PSC resulted in amelioration of the immune response. Vaughn et al. shown that treatment of PSC-IBD subjects with OV resulted in significant decrease in production of secondary bile acids, namely, deoxycholic acid, decrease in fecal microbiota alpha diversity, and decrease in the predominant genera *Bacteroides, Blautia, Roseburia, Faecalibacterium*, and *Clostridium XIVa* [35].

The biochemical response to OV was more favorable in the pediatric compared to the adult group. The small sample size of adults is a plausible explanation for why we observed less biochemical response in adults. In addition, the pediatric patients in our study were more likely to be diagnosed with early-stage PSC (fibrosis stages 0, I, and II) compared to adults (77% vs. 65%, respectively). Furthermore, pediatric patients were less likely to be diagnosed with late-stage PSC (fibrosis stages 3 and 4) compared to adults (23% vs. 35%, respectively). It is possible that the pediatric group had a better biochemical response to OV because children tended to have PSC with less severe fibrosis, compared to adults, at the time of OV treatment.

Strengths

The strengths of our study are that it is the largest experience on the use of OV in patients with PSC. In addition, this study included a heterogeneous group of patients with PSC; small- and large-duct PSC; early- and late-stage PSC, and with and without IBD. In addition to treating patients with large-duct PSC, we also elected to treat patients with small-duct PSC because it has been shown to be aggressive in some cases. In a pediatric cohort of PSC patients, nearly one-half of the small-duct PSC patients had advanced fibrosis on liver biopsy at the time of initial presentation [26]. Furthermore, 23% of small-duct PSC progress to large-duct PSC, and 10% progress to liver failure requiring liver transplantation [36,37]. Further supporting the notion that small-duct PSC progresses to large-duct PSC is a recent international multicenter study which showed that small-duct PSC is strongly associated with HLA-DRB1*13:01 allele, previously found to be associated with large-duct PSC [38], and a very recent paper reported that more than one-half of their small-duct PSC cohort developed cholangiographic features after a mean follow-up of ten years [39]. Our study included both children and adults with PSC; studies that demonstrated biochemical response to OV have been reported in the two groups [6].

Finally, our study included a small number of PSC patients who were found to have normal GGT at the time of OV treatment. Interestingly, the five patients who had normal GGT at the time of OV treatment also had normal ALP (Supplementary Table 1). The presence of IBD along with elevated ALT in all five cases at the time of initial encounter were the main indications for further workup to rule out PSC; indeed, all had cholangiographic and/or histological evidence of PSC. In fact, three of the five patients had fibrosis stage $\geq$2. An old report described a series of PSC patients who continued to progressed to liver failure despite having normal ALP [40]. Recent evidence suggest that many patients with PSC do not have biochemical evidence of cholestasis during the course of their disease. A landmark Norwegian study of 756 patients with IBD, 5.3% of patients with IBD and normal liver biochemistry were found to have cholangiographic features consistent with PSC [41]. A Japanese nationwide survey showed that abnormal ALP was found in only 54.2% [42], and a recent Mayo Clinic study evaluating the efficacy of Curcumin in PSC reported that 38% of those screened for eligibility were ultimately excluded based on the finding of low serum ALP [43]. Given that PSC patients may have progressive disease course and significant fibrosis despite the absence of biochemical evidence of cholestasis, as is the case in our current study, we felt compelled to treat these patients, all of whom experienced normalization of ALT within the first three months of OV treatment. We also note that after a median OV treatment of 1.2 years (range, 1–5.5 years), no patient of those who had normal GGT at the time of OV treatment had evidence of progression of fibrosis or development of portal hypertension.

Limitations

There are important limitations to this study. The overall and subgroups' sample size (pediatric and adults; small- and large-duct; and with and without IBD) was small. Forty-two percent had small-duct PSC; patients with small-duct PSC experience less rates of clinically-important endpoints compared with patients with large-duct PSC [36,37]. Lack of a placebo and a control group did not allow comparison of the effects of OV versus placebo. In addition, the follow-up time while on OV (median 3 years) on a disease with a median LT-free survival of 17 to 21 years was rather short, and the primary outcome of these open label trials was only biochemical improvement rather than impact on clinically-important PSC endpoints. We acknowledge that one-half of the patients in the current study were not part of the clinical trials' group, however, they followed the same OV treatment protocol, periodic liver biochemistry, and follow-up imaging and/or liver biopsy. We observed no differences in clinical and biochemical outcomes between those on protocol vs. off protocol. Ideally a trial should be designed in a randomized placebo-controlled blinded fashion. The effect of OV on the biochemical course of advanced-stage PSC cannot be precisely estimated because the proportion of patients with advanced stage PSC was underrepresented; 78% patients had stage 0, I, or II PSC. The effect of OV on the biochemical course of PSC may not be applicable to patients with PSC complicated by liver failure and biliary strictures requiring stenting, since they were excluded.

We recognize that we likely did not identify all patients with PSC-AIH overlap, and therefore our results may not be applicable to this subgroup. Liver biochemistry fluctuates in patients with PSC; therefore, whether the biochemical improvement observed in our studies is related to the natural history of PSC or treatment with OV is unknown. Liver

chemistry analyses in our study were performed at 1–2 months intervals; future studies evaluating OV in PSC studies should consider liver biochemistry measurement at narrower intervals to better understand the dynamic changes in liver biochemistry in relation to OV. PSC patients without biochemical evidence of cholestasis are often not included in therapeutic clinical trials, largely due the perception that such patients have better outcomes. Our finding that more than one-half of those with normal GGT (who also had normal ALP) at the time of OV treatment had evidence of fibrosis stage 2 or higher suggests that these patients are at high risk for serious events; therefore, more accurate biomarkers for prognostication are urgently needed. Although no patient reported symptoms or signs indicative of VRE infection, this finding should be interpreted with caution. A standardized VRE surveillance protocol was not in place, and thus the true rates of VRE in our study patients is unknown.

Assessment of fibrosis and cholangiography as tools for assessment of treatment response in PSC clinical trials have been advocated by experts [44,45]. Our findings with regard to the follow-up MRCP and liver biopsy should be interpreted with caution. We acknowledge that there were limitations associated with reporting the cholangiography and histological findings at follow-up in our study based only on interpretations by the radiologists and pathologists. While the radiologists and pathologists were blinded to the OV treatment, these interpretations are subjective assessments of these tests; there was a lack of standard validated protocols in place for staging and grading the findings; and the inherent liver biopsy limitations including procedural invasiveness, sampling errors and inter- and intraobserver variability related to histological interpretation. Furthermore, the length of time between OV treatment and follow-up MRCP and liver biopsy was rather short for a disease with a transplant-free survival of 17 to 21 years. Even though a conclusion with regard to the findings on follow-up MRCP and liver biopsy cannot be made, these data provide insights into designing future clinical trials of OV in PSC. Similar to our follow-up MRCP and liver biopsy findings, it is too early to make any conclusions regarding the effects of OV on MR elastography and whether these changes are clinically meaningful, but it is hoped that future clinical trials consider using MR elastography to further explore our preliminary findings.

Several recent case series reported clinical and endoscopic improvement of IBD with OV [12,21,46]. In our study, 95.3% of those who self-reported IBD-related diarrhea did report improvement in their diarrhea after OV initiation. A recently published paper reported improvement in IBD indices with the use of OV among pediatric patients with IBD [47]. Although our observation is in line with previous reports on the effects of OV on IBD, a strong conclusion cannot be made which requires data on noninvasive IBD assessment scores, endoscopic/histological remission of IBD, and other IBD laboratory assessment tools. Future clinical trials examining the effects of OV on PSC should also focus on examining the effects of OV on the clinical, biochemical, and endoscopic course of IBD.

Conclusions

In conclusion, this is the largest report on the long-term use of OV in patients with PSC to date, with follow-up available for up to 14 years. The use of OV in patients with PSC was safe, well-tolerated, and was associated with biochemical improvement. These results justify a large, randomized, placebo-controlled clinical trial in children and adults to examine the impact of OV on the clinical course and outcomes of PSC. A randomized clinical trial in adults with PSC has already launched (ClinicalTrials.gov Identifier: NCT03710122).

Author contributions

All authors approved the final version of the article and the authorship list.

Disclosure statement

All authors declare no conflict of interest.

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