Received: 15 October 2017 | First decision: 6 November 2017 | Accepted: 8 January 2018

DOI: 10.1111/apt.14540

WILEY AP&T Alimentary Pharmacology & Therapeutics

Review article: the evidence that vancomycin is a therapeutic option for primary sclerosing cholangitis

J. L. Damman[1] | E. A. Rodriguez[2] | A. H. Ali[3] | C. W. Buness[4] | K. L. Cox[5] | E. J. Carey[2] | K. D. Lindor[6]

[1]Pediatrics/Gastroenterology and Hepatology, Stanford University, Stanford, CA, USA

[2]Gastroenterology and Hepatology, Mayo Clinic, Arizona, USA

[3]Hepatology, Mayo Clinic, Arizona, USA

[4]National Patient Advocate Foundation, Paradise Valley, AZ, USA

[5]Pediatric Gastroenterology and Hepatology, Stanford University, Stanford, CA, USA

[6]Gastroenterology and Hepatology, Arizona State University and Mayo Clinic, Arizona, USA

Correspondence
K. Lindor, Gastroenterologist and Hepatologist, Arizona State University and Mayo Clinic, Arizona, USA.
Email: keith.lindor@asu.edu

Summary

Background and Aims: PSC is an autoimmune biliary inflammatory disorder that is often associated with inflammatory bowel disease (IBD), with 50%-75% of patients with PSC having coexisting IBD, most commonly ulcerative colitis. Currently, no medical therapies have been shown to improve the disease course or slow its progression. However, ongoing research has resulted in a growing interest in the use of antibiotics for treatment of PSC, of which vancomycin is the most studied. In this review, we summarise the current evidence on the use of vancomycin in PSC and comment on future research areas of interest.

Methods: A comprehensive PUBMED and EMBASE literature search for articles on vancomycin, PSC, therapeutic options and microbiome was performed.

Results: Two randomised clinical trials, three case series and two case reports were included in the study. These include uncontrolled data from at least 98 patients that include promising improvements in biochemistry and imaging. Optimal dosing regimens are unclear.

Conclusion: Vancomycin is one of the most studied antibiotics used in the treatment of PSC with promising results. There is not currently sufficient evidence to support treatment recommendations. Further research is needed to establish if vancomycin is a PSC treatment.

Jennifer L. Damman and Eduardo A. Rodriguez are the first authors for this article.
The Handling Editor for this article was Professor Peter Hayes, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is a rare cholestatic disease that is characterised by inflammation and fibrosis of the large and small bile ducts, which can lead to liver cirrhosis and end-stage liver disease. PSC is an autoimmune biliary inflammatory disorder that is often associated with inflammatory bowel disease (IBD), with 50%–75% of patients with PSC having coexisting IBD, most commonly ulcerative colitis.[1]

PSC is an important cause of morbidity and mortality in Western society. In many cases, PSC progresses to cirrhosis and end-stage liver disease, with a life expectancy of 17-21 years (in adults) and 12 years (in children) without liver transplantation.[2-5] Currently, PSC is the leading indication for liver transplantation in the Scandinavian countries, and the fifth leading indication for liver transplantation in the US.[6,7] Recurrence of PSC in the liver allograft occurs in up to 17% of adults and 9.8% of children.[8,9] Cholangiocarcinoma, the most dreaded complication of PSC, occurs in 5%-10% of patients with PSC.[10] PSC is associated with a 10-fold increased risk for colorectal cancer in patients with PSC/IBD compared with patients with IBD alone.[5] Taken together, these data highlight the significant burden of PSC on patients' quality of life and clinical outcomes.

Reports from large cohorts of patients with PSC have shown that serum alkaline phosphatase (ALK) in adults and gamma-glutamyl transferase (GGT) in children is important predictors of clinical outcomes. Specifically, normalisation of ALK in adults appears to be associated with long-term outcomes free of cholangiocarcinoma, need for liver transplantation, liver-related death and colorectal cancer, whereas persistently elevated levels of serum ALK have been associated with worse outcomes.[11-15] A recently published multicenter report demonstrated that children with PSC who had elevated levels of GGT, serum bilirubin and aspartate aminotransferase-platelet ratio index at the time of diagnosis of PSC had worse clinical outcomes compared to those who had lower levels.[16] Collectively, these data suggest that ALK (in adults) and GGT (in children) could serve as potential surrogate markers of treatment success/failure when designing clinical trials of drugs in patients with PSC. A consensus statement by the International PSC Study Group recommended ALK, in addition to liver histology, transient elastography and serum bilirubin, as surrogate endpoints when assessing progression of PSC.[17] A recent Food and Drug Administration/American Association for the Study of Liver Diseases workshop recommended that clinical trials in PSC should include both a biliary-specific test (ALK in adults and GGT in children) and imaging as surrogate endpoints (manuscript not published yet).

There are currently no medical therapies shown to improve the disease course or slow the progression of PSC. The association between PSC and IBD has led into a number of publications looking at immunological and microbiota therapies. Variations in the gut microbiota have been found to be associated with a number of diseases, including PSC, IBD, obesity, cardiovascular disease, endocrine disorders and autism.[18] PSC is associated with a particular gut microbiota profile; therefore manipulation of the gut microbiota may be an effective treatment for this complex disease.

2 | INTERPLAY BETWEEN THE GUT MICROBIOTA AND PRIMARY SCLEROSING CHOLANGITIS

PSC is a complex disease involving both genetic and environmental factors. Because the aetiology is not well understood, the development and implementation of therapies is challenging. The gut microbiota has been implicated in the pathogenesis of many diseases, including PSC, IBD, irritable bowel syndrome, obesity, metabolic syndrome, cardiovascular disease, as well as autoimmune, neuropsychiatric and endocrine disorders.[18] The human gut microbiota consists of thousands of different bacterial species with defined functions, and these microbial ecosystems maintain homeostasis through a tight balance of cell-to-cell signalling and the release of antimicrobial peptides to control neighbouring bacteria.[19] The interaction between the gut microbiota and immune system is not fully understood and is a topic of current research. One example is the role of short-chain fatty acids, which are end products of microbial fermentation of plant polysaccharides that cannot be broken down by human enzymes.[20] Short-chain fatty acids play a critical role in the human immune system, including cytokine production by T cells, modulating immune responses, protecting against enteropathic infections and promoting integrity of the intestinal epithelial barrier.[21-25] New technologies in rRNA sequencing, metagenomic sequency, metabolomics and other advanced techniques have led to the identification of the gut microbiome and an advanced understanding of their function.[19]

In recent years, researchers have begun to explore the potential relationship between the gut microbiota and PSC in humans. Patients with PSC have a marked decrease in gut microbiota diversity and dysbiosis, and a substantial overrepresentation of *Enterococcus*, *Escherichia*, *Fusobacterium*, *Lactobacillus*, *Veillonella*, *Blautia*, Lachnospiraceae, Barnesiellacea, *and Megasphaera* genera compared with healthy controls and patients with IBD alone.[26-30] In contrast, patients with PSC have marked reductions in Clostridiales II, *Prevotella* and *Roseburia*, and *Bacteroides*, compared to patients with IBD alone and healthy controls.[28,31] *Actinobacteria*, *Proteobacteria*, *Streptococcus and Rothia* have been reported to be overrepresented in patients with PSC compared with healthy controls and patients with inflammatory bowel disease.[32-34] Mucosa-associated bacteria as opposed to stool was also found with a lower bacterial diversity in patients with PSC, with an underrepresentation of an uncultured Clostriadiales II.[35] The results of these preliminary studies represent compelling evidence that PSC is associated with an altered gut microbiota. The overlap in the results of these studies could be due to the differences in the samples being used for the studies (mucosal bowel tissue, bile and stool), techniques used for sample storage, microbial analysis and/or different patient populations. Taken all

these together, these data that support the notion that PSC is associated with an altered gut microbiota profile, may help guide future studies examining new treatments that target the gut microbiome in patients with PSC. Further studies, using larger samples of diverse PSC patients' population studying faecal, bile and blood samples, are needed to better elucidate the role of the gut microbiota in the pathogenesis of PSC.

3 | TREATMENT OPTIONS INVOLVING THE MODIFICATION OF THE MICROBIOME

Treatment options in PSC are limited, partly due to an incomplete understanding of the disease aetiology and pathogenesis, as well as the wide variability in disease presentation, such as involvement of large ducts vs small ducts, the presence or absence of IBD and overlap with other autoimmune diseases such as autoimmune hepatitis.[36] Current therapies target the biliary contents, the gut-liver axis or hepatobiliary fibrosis; however, despite the availability of potential multiple therapies, there is no recommended medical therapy for PSC.[37-39] Although publications have shown short-term improvement of liver enzymes with medical therapies, liver biopsies and imaging, the long-term benefit of these therapies have not been reported.

4 | DISCUSSION OF TRIALS AND CASE REPORTS

Currently, there are no medical therapies approved for the treatment of PSC; however, many pharmacotherapies have been tried in the past. Studies attempting to modify the gut microbiota using faecal microbiota transplant (FMT) and probiotics are discussed below. One group of medications studied includes antibiotics, and among this group, vancomycin is a promising medication with possible benefits in patients with PSC. To date, there have been few published studies reporting the use of vancomycin in patients with PSC, and the number of patients in these publications has been small. Nonetheless, the results of these studies, also reviewed below, are of great interest.

4.1 | Faecal microbiota transplant

Faecal microbiota transplant has emerged as a promising treatment for a number of diseases with gut dysbiosis or immune dysregulation. FMT increases gut microbial diversity and introduces microbes that are essential for maintaining epithelial integrity, limiting gut permeability, and reducing inflammation.[18] There have been many publications on the use of FMT as a possible treatment for IBD, and the success of FMT for the treatment of *Clostridium difficile* infection has been well established. Studies have shown FMT to be more effective than standard treatment for recurrent *C. difficile* infection.[18,40,41] There have been a number of publications describing FMT as a potential therapy for many other diseases, including inflammatory bowel syndrome, obesity, metabolic syndrome, hepatic encephalopathy, neuropsychiatric disorders and haematological diseases, among others.[18] Based on the assumption that the gut microbiota in patients with PSC contributes to the disease, FMT has been postulated to be a possible treatment option.

Borody et al published a case report of an adult male with PSC and UC who underwent FMT.[42] After 4 weeks of daily FMT enemas, the patient's IBD symptoms dramatically improved and his liver enzymes normalised. Current studies are looking at the long-term benefit of FMT to treat PSC and IBD, and there is currently a clinical trial examining FMT in patients with PSC at Brigham and Women's Hospital Boston (ClinicalTrials.gov Identifier: NCT02424175).

4.2 | Probiotics

Probiotics are nonpathogenic viable microorganisms that can benefit host health, disease prevention and/or treatment.[43] The mechanism is thought to be due to blocking bacterial pathogenic effects by bactericidal products, as well as competing with other pathogenic bacterial and toxins for adherence to the intestinal epithelium.[43] Probiotics also maintain gut homeostasis. Clinical trials have shown some benefit of probiotics in IBD.[44] In a randomised controlled trial by Mittal et al, authors showed that adults with cirrhosis and minimal hepatic encephalopathy improved significantly when given probiotics.[45] Shimizu et al published a case report describing a 13-year-old boy with IBD and PSC who failed to respond to ursodeoxycholic acid and mesalazine.[43] Mesalazine was then replaced with steroids, salazosulfapydridine and probiotic, and the patient improved clinically and on laboratory results. Steroids were tapered off and he remained in remission 3 years later on ursodeoxycholic acid, salazosulfapyridine and probiotics. Vleggaar et al published a randomised placebo-controlled crossover study that showed no difference between patients with IBD and PSC treated with probiotics alone or placebo.[46]

4.3 | Antibiotics

Given the growing evidence that immune mechanisms within the gut play a role in the pathogenesis of PSC, as well as other non-immune mechanisms through toxins released by gut bacteria, there has been a growing interest in the use of antibiotics for treatment of PSC. Antibiotics have been used as a potential therapy for PSC, including vancomycin, metronidazole, minocycline, tetracycline and rifaximin.[39] Possible mechanisms include alteration of gut microbiota, which may reduce translocation of colonic bacteria and endotoxins, especially in patients with IBD. This may then reduce exposure of pathogens to the biliary epithelium via the portal vein.[39]

4.3.1 | Tetracyclines

Tetracyclines were the first group of medications described in the treatment of PSC.[47] In 1959, they were used for the first time in the treatment of the so called chronic pericholangitis associated with ulcerative

colitis, with an improvement of biochemical markers; however, a long-term study reported no clinical benefit, histological changes or changes in liver function tests.[48] Minocycline has been studied as well, but requires further investigation to support clinical use.[49]

4.3.2 | Rifaximin

Rifaximin has also been studied in patients with PSC.[50] Sixteen patients were enrolled in a 12-week, open-label pilot study to investigate the efficacy and safety of 550 mg of oral rifaximin twice daily. No significant changes in ALK (primary endpoint) nor in any of the other secondary biochemical end points (serum bilirubin and GGT) were noted at the end of the 12 weeks. Similarly, no significant changes were appreciated for the fatigue impact scale, chronic liver disease questionnaire or the short form health survey (SF-36).

4.3.3 | Metronidazole

Metronidazole has been studied in several randomised controlled trials and compared against other medications such as ursodeoxycholic acid or against other antibiotics such as vancomycin, with improved liver test profile and histology findings.[51,52] Farkkila et al[51] compared the use of metronidazole and ursodeoxycholic acid in 80 patients with PSC. He compared both metronidazole alone vs ursodeoxycholic acid with metronidazole and found out that the addition of the antibiotic lead to improved liver injury test results, histology scores and Mayo risk scores. Neither progression nor improvement was noted for liver histology/endoscopic retrograde cholangiogpancreatography (ERCP) changes. Long-term studies using a higher dose of ursodeoxycholic acid combined with metronidazole in larger populations are needed.

4.3.4 | Vancomycin

For decades, oral vancomycin has been a mainstay treatment for *C. difficile*-associated diarrhoea given its minimal oral absorption and high faecal concentration relative to the minimum inhibitory concentration (MIC) of *C. difficile*. Given the demonstrated efficacy and tolerability of oral vancomycin in clinical studies,[53] it has been widely used in solid organ transplant recipients for the treatment of *C. difficile* infection.[54] Although oral vancomycin is associated with minimal toxicity, it has been shown to modify the gastrointestinal flora. In particular, oral vancomycin treatment has been associated with reduced intestinal bacterial counts of *Bacteroides* and *Prevotella* species.[55,56] It has also been associated with increased rates of stool colonisation with vancomycin-resistant *Enterococcus* and *Candida* species.[57] The clinical significance of these observations in immunocompromised hosts is unclear and needs investigation.

Oral vancomycin has been shown to treat both PSC and associated IBD.[1,52,58-62] Vancomycin is a glycopeptide antibiotic active against Gram-positive bacteria. It inhibits bacterial cell wall synthesis by binding to the D-alanyl-D-alanine terminus of cell wall precursor units, thereby preventing cell wall cross-linking.[63-65] Oral vancomycin demonstrates minimal systemic absorption and concentrates in the intestine acting both as an immunomodulator by reducing cytokine release from T cells, and as an antimicrobial agent[58] (Figure 1).

Vancomycin has also demonstrated immunomodulating effects in the gut.[58] This suggests that PSC may be caused by an autoimmune disorder of lymphocytes in the intestine or abnormal intestinal microbiota. Patients with PSC often have a return of liver enzymes back to baseline when vancomycin is stopped.

Furthermore, patients have recurrence of PSC in their transplanted liver, which is responsive to oral vancomycin therapy.[60] This may suggest that PSC is caused by abnormal T cells in the intestine.

4.3.5 | Resistance to antibiotics

Bacterial infections are an important cause of morbidity and mortality after liver transplantation, particularly during the first 2 months post-transplant.[66] In the 1980s and 1990s, the reported prevalence of bacterial infections in the first 2 months post-transplant was 52%-59%.[67,68] In a Swiss cohort in the 2000s, the reported prevalence of bacterial infections in the first month following liver transplant was 47%.[69] Nosocomial infections in the first 2 months post-liver transplant are the most feared ones. The important sites of infection are the abdomen, surgical wounds, biliary tract, urinary tract, respiratory tract and the blood stream.[66] Patients with cirrhosis

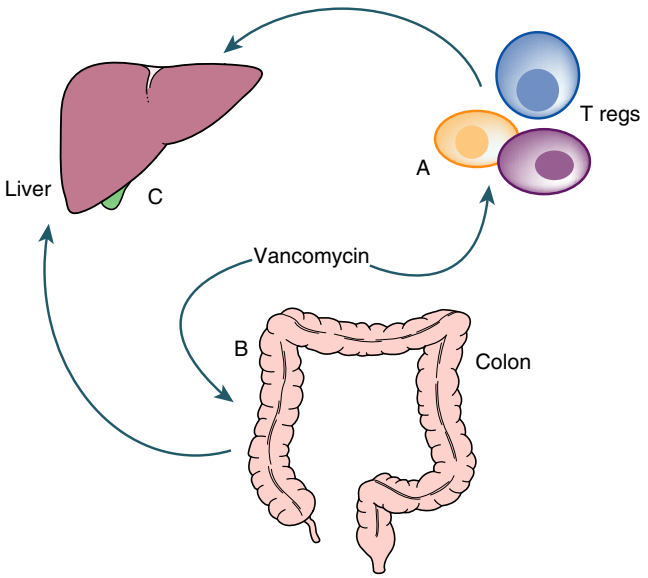

FIGURE 1 Based on the published reports, we suggest that vancomycin changes the host microbiome and this changes mucosal immune and inflammatory signals, which changes systemic immune function as well as the microbial products delivered to the liver. We propose the following potential mechanism(s) of action of OV in PSC: A) OV modulates the immune system by increasing the number of peripheral $CD4^{+}FoxP3^{+}$ regulatory T (Tregs), and/or B) eliminates the pathogenic bacteria in the colon, thereby decreasing the amount of toxic metabolites reaching the liver via the portal circulation. The end result is a down-regulation of immune/inflammatory response in the liver of PSC patients, resulting in reduction in liver enzymes, improved histological and imaging abnormalities, which may translate to improved overall clinical outcomes' in PSC

are immunocompromised and are susceptible to infection, with a reported prevalence of bacterial infections of up to 34% of cirrhotic patients who are hospitalised.[70] Enterococci, important causes of nosocomial infections, can develop resistance to a number of glycopeptide antibiotics, such as vancomycin. A recent study by Remschmidt et al reported a very low incidence of infections with vancomycin-resistant enterococci. This ranged between 0.03% and 0.68%, according to the type of hospital ward (0.68 in the intensive care unit).[71] Cirrhotic patients treated with vancomycin may have resistance, so other antibiotics should be used to treat infections in the post-transplant setting.

The published trials and case reports of vancomycin as a treatment for PSC are discussed in the next section of this paper (Table 1).

4.4 | Vancomycin and metronidazole mayo clinic study

Tabibian et al[52] published in their 2013 study the use of either vancomycin or metronidazole in adult patients with PSC. Patients were randomised into four groups to receive either vancomycin (125 mg 4 times a day, n = 8 or 250 mg 4 times a day, n = 9) or metronidazole (250 mg 3 times a day, n = 9 or 500 mg 3 times a day, n = 9). The primary endpoint was a decrease in ALK at 12 weeks as compared to baseline result. Secondary end points included a decrease in aspartate aminotransferase (AST), total bilirubin, Mayo PSC risk score, fatigue severity, pruritus and C-reactive protein at 12 weeks as compared to baseline value, as well as adverse effects at any time during the 12 weeks.

The median patient age in the sample was 40 years (range: 20-70), 60% of patients were men, 71% had IBD and median baseline ALK value was 383 U/mL. All patients had an elevated ALK (at least two separate measurements) for >6 months (median 19 months).

A significant decrease in ALK, the primary endpoint, was observed in the high-dose vancomycin group (250 mg 4 times a day) (−40%, $P = 0.02$). The low-dose vancomycin group had a larger decrease in ALK, and after excluding an outlier (1 patient who did not take the study medication for 1 month), the change in ALK became statistically significant (−43%, $P = 0.03$). Mayo PSC risk score also decreased significantly in the low-dose vancomycin group (−0.55, $P = 0.02$). There was a trend towards a significant decrease in total bilirubin (−33%, $P = 0.06$) and CRP (−0.69, $P = 0.06$) with the low-dose vancomycin group. No statistical changes were appreciated for the AST, C-reactive protein, the Fisk fatigue impact scale and the visual analogue scale score (scale that graded pruritus using a 10-cm visual analogue scale), after using vancomycin for 12 weeks. Reported adverse effects included one patient with migraine headaches and diarrhoea in the low-dose vancomycin and diarrhoea and increased fatigue in the high-dose vancomycin group.

Although both vancomycin doses reached the primary endpoint and had an overall favourable adverse effect profile, only low-dose vancomycin demonstrated a statistically significant reduction in the Mayo PSC risk score and a trend towards significant decrease in C-reactive protein and total bilirubin. Also, low-dose vancomycin was the only group with patients who had normalisation of ALK. At this point there is not enough information to be able to speculate why perhaps low-dose vancomycin was more effective than higher dose

TABLE 1 Summary of clinical trials and case reports

Clinical trial or Case report	Number of patients (n = x)	Summary of findings
Tabibian et al[52]	35	*Adults.* Decrease in alkaline phosphatase (both high and low vancomycin dose groups) and decrease in Mayo PSC score (low-dose vancomycin group) at the end of the 12 wk of treatment. Adverse effects: diarrhoea. 500-1000 mg per day for 3 months.
Rahimpour et al[61]	29	*Adults.* Decrease in Mayo PSC score, alkaline phosphatase, ESR, GGT, fatigue, pruritus, diarrhoea and anorexia in the oral vancomycin group after 12 weeks of treatment. 500 mg per day for 3 months.
Davies et al[1]	14	*Paediatrics.* Clinical and laboratory (ALT, GGT and ESR) improvement after 1-2 mo of oral vancomycin. Worsening findings when it was stopped and overall improvement when resumed. Decreased clinical and laboratory improvement for patients with cirrhosis. 50 mg per kilogram per day for 54 months +/− 43 months.
Abarbanel et al[58]	14	*Paediatrics.* GGT, ALT, WBC, MRCP findings, liver biopsy and immunological improvements noted with 12 wk of oral vancomycin. 50 mg per kilogram per day for 12 months.
Cox & Cox[62]	3	*Paediatrics.* Clinical, laboratory and pathological improvement during treatment with oral vancomycin. Not all patients improved after stopping the treatment. 375-1000 mg per day for 18 months.
Buness et al[59]	1	*Paediatrics.* Single case, clinical, laboratory and endoscopic improvement after escalating dose of oral vancomycin until optimal dose was determined. 1500-2250 mg per day for 5.5 years.
Davies et al[60]	1	*Paediatrics.* Single case, normalisation of liver enzymes after orthotopic liver transplantation and PSC recurrence. 1500mg per day for 5 yrs.

vancomycin. More studies are needed to come up with more conclusions.

4.5 | Iran vancomycin pilot study

In 2016, Rahimpour et al[61] carried out a triple blinded, randomised, placebo-controlled trial on 29 patients with PSC. Patients were randomised into two groups: placebo 11 (37.9%) and vancomycin 18 (62.1%). Vancomycin (125 mg 4 times a day) was given for 12 weeks to the intervention group. Patients in both groups were also given ursodeoxycholic acid (300 mg 3 times a day) before and during the study. Patients were followed up at week 0, 4 and 12 of treatment. Primary endpoints included statistical decrease in the Mayo PSC risk score and ALK level at week 12. Secondary end points consisted of a significant decrease in erythrocyte sedimentation rate, alanine aminotransferase (ALT), AST, total and direct bilirubin, white blood cells, platelets, GGT and improvement in patients' symptoms (including fatigue, pruritus, abdominal pain, diarrhoea, blood in stool, nausea, vomiting and anorexia) at 12 weeks. Adverse effects were also monitored during the 12 weeks of treatment.

Overall, from the 29 studied patients, the median age was 34 years (range 19-65), 17 (58.6%) were male and 21 (75%) had concomitant IBD. Statistical analysis of both groups showed a significant decrease in the Mayo score in the vancomycin group ($P = 0.026$) at 12 weeks compared to the baseline score: mean difference (3rd month-Baseline) = −0.59, decrease rate = −322.03%, $P = 0.026$), whereas no significant changes were seen in the placebo group. The ALK level in the vancomycin group significantly decreased at the end of the 12 weeks month as compared to its level at the first month of treatment: mean difference (3rd month-1st first month) = −142.92, decrease rate = −18.24%, $P = 0.023$. No significant findings were seen for the ALK levels in the placebo group ($P = 0.67$).

For secondary endpoints, erythrocyte sedimentation rate level at baseline, first month and 3 months overall showed a statistically significant reduction = −41.25%, $P = 0.005$. Similarly, there was a significant decrease in the GGT by the third month of treatment as compared to its level the first month (mean difference, 3rd month–1st first month = −96.6, decrease rate = −35.29%, $P = 0.02$). Patients in the vancomycin group also showed significant improvements of fatigue ($P = 0.002$), pruritus ($P = 0.022$), diarrhoea ($P = 0.018$) and anorexia ($P = 0.04$). No statistical significant results were found for the placebo group, except for improvement of pruritus ($P = 0.011$). No AEs related to drug administration were reported.

Overall, primary and secondary endpoints were reached. The PSC Mayo risk score significantly decreased during follow-up, the ALK level diminished significantly at the end of third month in contrast to its level in first month, and erythrocyte sedimentation rate, GGT, fatigue, pruritus, diarrhoea and anorexia showed a significant decline/improvement in patients on the vancomycin group. During the time of the study, two patients discontinued the intervention; one patient in the vancomycin group due to cholangitis and emergency endoscopic retrograde cholangiopancreatography (ERCP), and another in the placebo group due to pulmonary embolism.

4.6 | Case series

Davies et al[1] published a series of 14 children diagnosed with PSC and IBD in 2008. They treated all 14 patients with oral vancomycin, except for 1 patient who was also treated with sulfasalazine for colitis, and another with amoxicillin for a cough. Short- and long-term clinical and laboratory responses were reported.

The mean age of the patients was 12 ± 4 years, ranging from 2 to 17 years. The male: female ratio in the study was 2.3:1. Four patients had cirrhosis seen on biopsy before initiation of vancomycin. Liver function tests and ESR were measured before, during and after completion of oral vancomycin. Twelve of the patients also had serological markers such as antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver kidney antibody (anti-LK), antimitochondrial antibody (AMA), antineutrophilic cytoplasmic antibody (p-ANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) measured before and while receiving oral vancomycin.

Vancomycin was instituted at an initial dose of 50 mg/kg/day with a maximum dose of 1500 mg/day for those weighing >30 kg. Patients were treated until there was normalisation or no further improvement of the liver enzymes and erythrocyte sedimentation rate. An initial improvement of ALT, GGT and erythrocyte sedimentation rate was observed after 1-2 months of oral vancomycin in all 14 patients, but to a lesser degree for cirrhotic patients. Treatment was discontinued resulting in a recurrence of clinical symptoms and an increase in liver enzymes in noncirrhotic patients. Resumption of treatment in noncirrhotic patients again resulted in normalisation of liver enzymes. Cirrhotic patients were not retreated because they had not been as responsive to the initial treatment.

Twelve patients had 1 or more positive serum autoantibody tests before treatment, with an overall decrease in positive antibodies after 3.5 months taking vancomycin. Of these 12 patients, 5 had a positive antinuclear antibody, 3 had a positive ASMA; all of the patients were negative for anti-liver kidney microsomal antibody. Eleven patients were positive for p-ANCA. In 4 patients, ANA, ASMA and p-ANCA was positive before treatment and became negative after an average of 3 months of treatment. For the other 8 patients, repeat serologies were not performed or were pending when the manuscript was submitted.

In 2013, Abarbanel et al[58] examined in vivo immunological, biopsy, imaging changes in 14 children with PSC and IBD after receiving oral vancomycin. The antibiotic dosing was 50 mg/kg/day divided 3 times per day with a maximal dose of 1500 mg/day for that weighing ≥30 kg. Patients undergoing parallel treatments with other medications that could possibly affect their immune cell populations and phenotype were excluded from this study (except 5-aminosalicylic acid and/or mercaptopurine). Nine subjects were included as healthy controls to identify the method-specific baseline levels of peripheral regulatory T cells as determined by surface and intracellular staining.

Testing GGT, ALT, white blood cell counts, biliary imaging studies, liver biopsies and IBD symptoms were compared before and after 3 months of treatment with oral vancomycin. Additionally, plasma transforming growth factor beta (TGF-β) levels, cytokines such as Th1, Th2, CD25hiCD127lo and CD4+FoxP3+ regulatory T (Treg) were also compared with flow cytometry

Abnormally high GGT and ALT values were found before oral vancomycin with normalisation within 3 months of therapy and similar findings after 12 months of therapy. At the same time, an improvement in symptoms associated with PSC and IBD, biliary imaging (magnetic resonance cholangiopancreatography) and biopsies of liver and intestine were observed, which coincided with a reduction in white blood cell counts ($P < 0.05$, median $\Delta = -5.05$), a reduction in neutrophil population size ($P < 0.05$, median $\Delta = -3.22$) and in lymphocyte population sizes ($P < 0.05$, median $\Delta = -0.75$). Plasma TGF-β levels were increased without concurrent shifts in Th1- or Th2-associated cytokine production ($P = 0.031$). Peripheral levels of $CD4^+CD25hiCD127lo$ and $CD4^+FoxP3^+$ regulatory T (Treg) cells also increased comparing the pre- and post-treatment levels ($P = 0.023$). Subject 01 showed that the therapeutic effects of oral vancomycin in the treatment of PSC+IBD does not always persist after discontinuation of the medication, as a decrease in blood $CD4^+FoxP3^+$ regulatory T (Treg) levels was noted; however, a rise of it and normalisation of liver tests were noted when oral vancomycin was resumed.

Cox & Cox[62] described a case series of 3 children with PSC and IBD responded to treatment with oral vancomycin. This article was published in 1998, which shows that the use vancomycin in patients with PSC has been present for almost 20 years. Case one described a 15-year-old boy who was treated with oral vancomycin initially for concomitant *Clostridium difficile* infection. His symptoms and blood test results normalised during vancomycin therapy and worsened within 2–4 weeks after vancomycin was discontinued. Additionally, liver biopsy results revealed less portal inflammation and portal fibrosis while the patient was taking vancomycin. An ERCP study performed during vancomycin therapy also demonstrated a normal biliary tract. Similarly, case two described a 14-year-old girl who showed clinical, laboratory and imaging improvement after initiating treatment with oral vancomycin. However, after poor pharmacological compliance, she demonstrated recurrence of symptoms and worsening laboratory results, which did not respond to further oral vancomycin. Finally, case three described the case of a 14-year-old boy who showed remarkable clinical and laboratory improvement while on oral vancomycin, which worsened when the medication was stopped. In his case, after vancomycin was re-introduced, symptoms and laboratory results again successfully improved.

4.7 | Case reports

Buness et al[59] published a case report of a 15-year-old girl with PSC and UC who achieved normalisation of her liver enzymes and bile ducts, and resolution of her UC symptoms with colonic mucosal healing after treatment with oral vancomycin. Monotherapy was at a dose of 500 mg 3 times per day (35 mg/kg), with rapid improvement in diarrhoea, weight gain, and fatigue. After 9 months, transaminases had not normalised, therefore dose was increased to 750 mg 3 times per day, leading to normalisation of her liver enzymes and bile ducts, as well as resolution of her UC symptoms with colonic mucosal healing.

Davies et al[60] published a case report of a 12-year-old girl with recurrent PSC after orthotopic liver transplantation. She was treated with oral vancomycin at a dose of 500 mg 3 times per day, after which her liver enzymes returned to normal, and liver biopsy after 3 years from recurrence of PSC showed a return to normal liver structure and anatomy.

5 | COST EFFICACY OF TREATMENT WITH VANCOMYCIN

Assuming a patient with PSC, who will also likely have concurrent IBD, is responsive to vancomycin, the cost/benefit of this treatment must be considered from several different perspectives. First, the cost of no treatment or treatment with ursodeoxycholic acid, second, the cost of treatment with vancomycin, and third, the effect of either option on the patient's quality of life.

5.1 | No treatment or treatment with ursodiol

Because there is no accepted treatment and ursodeoxycholic acid has not shown to stop disease progression, the patient may need transplantation and possibly a colectomy within 12-15 years of diagnosis.

5.2 | Treatment with vancomycin

Vancomycin is now available in a kit form (CutisPharma FIRST-Vancomycin; Manufacturer: CutisPharma, Inc., Wilmington, Massachusetts, United States) as a compounded drug at a price comparable to IV formulation. In 2016, the average *price per gram* of liquid vancomycin (kit or IV formulation) was $7 vs $54 for generic oral capsules (Source: IMS National Sales Data [2012-2016]). While many insurers do not currently cover the cost of compounded drugs, given the cost savings, they may reconsider this decision if vancomycin is found to be an effective treatment for some patients. The cost of treatment per year of vancomycin for a patient taking 1 gram per day of liquid kit or IV vancomycin would be $2520 ($7 × 30x12) vs $19 440 ($54 × 30x12) per year for 1 gram per day of capsules. This cost will vary by patient because some patients are successfully treated on a lower daily dose,[52,61] and others have required a higher dose to achieve normalisation.[58,59] Further studies will be necessary to confirm if vancomycin is an effective treatment, and if so, initial dosing strategies and subsequent dose reduction after a patient has achieved normalisation.

5.3 | Quality of life issues

Quality of life issues for the patient who has disease progression is significant (ie pruritus, fatigue, loss of function, hospitalisation,

medical procedures, colitis, etc.). Patients who have been responsive to vancomycin treatment have experienced complete resolution of liver and colon related symptoms.[58,59,62] The degree of symptom resolution may depend on the stage of disease when vancomycin treatment is initiated. Further studies are needed to confirm ideal treatment time.

6 | FUTURE STEPS

Multiple reports on the use of vancomycin in patients with PSC have been published; however, many questions remain unanswered. A standardised treatment protocol, including dosing strategies, length of treatment and monitoring for response to therapy is needed. Many questions regarding an ideal dose remain unanswered, as well as the differences between adult and paediatric patients. The length of treatment is also not well established. Questions to be answered include when vancomycin dosing can be reduced, or stopped, as well as what dose to use when therapy is re-initiated. Similarly, is there a difference in the form of vancomycin used? Is there a difference between tablet vs liquid form or between different vancomycin brands? How should treatment response be monitored? Some markers that have been reported include ALK, GGT, p-ANCA, transaminases, as well as liver biopsy and bile duct imaging; however, the question of which are superior remains unclear. Finally, there is the question of whether there are differences in therapeutic response between different PSC groups, and if certain types are more responsive than others (small vs large duct disease, ulcerative colitis vs. Crohn's disease, different age groups and different racial/ethnic backgrounds). By identifying characteristics of those patients responsive to therapy, it is our hope that we will be able to tailor more individualised therapy for all patients with PSC.

To assess vancomycin as a potential treatment for PSC ,we suggest a prospective, randomised, and placebo-controlled phase 2 clinical trial with a minimum of 1-year duration. Subjects should be stratified by baseline presence of IBD and PSC severity. Treatment endpoints should be a combination of decrease in ALK and no worsening of imaging, or other relevant clinical endpoints that are currently being defined. Separate clinical trials are necessary for adults and children because of potential differences in disease presentation, progression, and response to treatment. Additionally potential adverse effects should also be carefully monitored, with emphasis on those that are severe.

ACKNOWLEDGEMENTS

Declaration of personal interests: Jennifer L. Damman, Eduardo A. Rodriguez, Ahmad H. Ali, Cynthia W. Buness & Elizabeth J. Carey have no competing personal interests. Ken L. Cox has received funding from the PSC Foundation & Keith D. Lindor has consulted for Henry Ford, HighTide & Takeda.

Declaration of funding interests: None.

AUTHORSHIP

Guarantor of article: Keith Lindor.

Author contributions: All listed authors have drafted and critically revised the paper as well as approved the submitted final version of it.

ORCID

E. A. Rodriguez http://orcid.org/0000-0001-9684-8273
K. D. Lindor http://orcid.org/0000-0003-1046-5621

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How to cite this article: Damman JL, Rodriguez EA, Ali AH, et al. Review article: the evidence that vancomycin is a therapeutic option for primary sclerosing cholangitis. *Aliment Pharmacol Ther*. 2018;00:1–10. https://doi.org/10.1111/apt.14540