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CASE REPORT

Successful response of primary sclerosing cholangitis and associated ulcerative colitis to oral vancomycin may depend on brand and personalized dose: report in an adolescent

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Abstract

Primary sclerosing cholangitis (PSC) is a rare, progressive liver disease characterized by cholestasis and bile duct fibrosis that has no accepted therapy known to delay or arrest its progression. We report a 23-year-old female patient who at age 14 was diagnosed with moderate pancolonic ulcerative colitis (UC) and at age 15 with small-duct PSC unresponsive to conventional therapy. The patient began single drug therapy with the antibiotic oral vancomycin (OVT) and achieved normalization of liver enzymes and resolution of UC symptoms with colonic mucosal healing. These improvements have persisted over 8 years. There has been no colon dysplasia, liver fibrosis or failure, bile duct stricture, or cancer. Of note, the patient's response was dependent on the brand of oral vancomycin capsule, as well as dose. This raised the questions of possible differences in bioequivalence of different commercial versions of the drug and whether this factor might play into the variability of efficacy seen in published trials. Evidence suggests that oral vancomycin both alters the intestinal microbiome and has immunomodulatory effects. Its striking effectiveness in this and other patients supports further investigation in randomized trials, with careful attention to its bioavailability profile in the gut.

Keywords Primary sclerosing cholangitis · Ulcerative colitis · Vancomycin · Microbiome · Bioequivalence

Introduction

Primary sclerosing cholangitis (PSC) is a rare progressive disease of the bile ducts closely linked to inflammatory bowel disease (IBD), especially ulcerative colitis (UC). It is associated with an increased risk for cirrhosis and cholangiocarcinoma [1–3]. The etiology is poorly understood; one theory is that an abnormal gut microbiome activates innate immunity within the liver, resulting in bile duct-targeted inflammation and biliary fibrosis [4]. No therapy has yet been proven to be effective. UDCA is commonly prescribed for children with PSC [5], but two large randomized trials have shown no benefit for long-term outcomes [6, 7].

Recent work has shown the importance of gut microbiota in health and disease. In particular, patients with PSC have been shown to have microbiomes significantly different from normal controls. Interventions to alter the microbiome are attracting increasing interest for this and other diseases [8, 9]. Oral vancomycin, which is not absorbed from the gut lumen and is already known to have efficacy in *C. difficile* infections and pouchitis, is one of

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the drugs of interest. It has been employed in a number of published PSC case studies with some success [10, 11].

However, the manufacture of vancomycin is known to be a delicate process [12]. In vitro and preclinical studies have shown variable efficacy of different brands [13, 14]. In this paper, we describe a patient whose response to oral vancomycin showed a sensitivity to the brand of generic capsule used, as well as to dose. She had not responded to UDCA and other conventional treatments for UC and PSC. Single-drug therapy with oral vancomycin led to rapid resolution of all symptoms, normalization of liver chemistries, and eventually complete colonic mucosal healing.

The patient has given informed consent to this report. The first two and a half years of the 8 years course of OVT in this patient has been previously reported [15].

Case report

Diagnosis of ulcerative colitis

In April of 2010, the patient, a 13-year-old girl, started doxycycline daily for acne treatment. After 4 months, she presented with bloody diarrhea (a possible association between doxycycline and PSC has been previously raised [16]). First diagnosed with blastocystis hominis, she was treated with ciprofloxacin and metronidazole for 10 days, and subsequently for 4 days with nitazoxanide. Her symptoms improved but returned after the course of these medications was completed. She continued doxycycline during this time, until she was admitted to the hospital 5 months after initial symptoms with erythema nodosum. Her alanine aminotransferase (ALT 56, upper limit of normal 35 IU/L) and alkaline phosphatase (ALP 190, upper limit of normal 119 IU/L) were elevated, and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) were positive at 114 EU/ml (upper limit of normal 20 EU/ml). Total and direct bilirubin were normal. Colonoscopy biopsies showed moderate chronic active colitis with no granulomas throughout the colon and acute and chronic inflammation in the terminal ileum and cecum. The erythema nodosum resolved once the doxycycline was stopped.

She was started on mesalamine, which caused worsening bloody diarrhea and abdominal pain. Subsequent treatment with budesonide 9 mg/day and then balsalazide 6750 mg/day, also caused worsening diarrhea. The patient elected to stop all medications and started non-prescription remedies for 6 months: VSL#3 probiotic, curcumin, and Nopalea™ (cactus juice. She continued to experience diarrhea up to 4–5 times a day, Bristol stool scale type 7.

Diagnosis of primary sclerosing cholangitis

In July 2012, she had screening blood tests (for initiation of azathioprine therapy for UC) that revealed elevated liver chemistries: ALT 221 IU/L (range 7–35), ALP 434 IU/L (range 45–119), AST 88 IU/L (range 8–41), and GGT 397 IU/L (range 9–29). Screening for anti-nuclear antibodies, anti-smooth muscle antibodies, and anti-liver/kidney microsomal antibodies was negative. Total IgG was normal as was IgG4, 67.3 mg/dl (range 11–157). Magnetic resonance cholangiopancreatography (MRCP) showed common hepatic duct dilatation measuring 7 mm proximally at the porta hepatis, but no other changes suggestive of PSC. No stricture was seen distal to the dilated common duct. It was unclear whether the dilatation was physiologic (e.g. sphincter of Oddi spasm) or truly anatomic. There was no intrahepatic large duct involvement on MRCP (Fig. 1). A liver biopsy was performed and showed portal lymphocytic infiltrates with focal infiltration of bile duct epithelium with concentric fibrosis and bile ductular proliferation (Fig. 2). These findings were interpreted as small-duct primary sclerosing cholangitis (PSC). Small-duct PSC generally has a more benign course than large-duct PSC [17]. The patient was started on ursodeoxycholic acid (UDCA) 300 mg BID, in addition to azathioprine for the UC. The liver chemistries improved but did not normalize.

Within 10 days of initiation of azathioprine, she developed symptoms of nausea, vomiting, and epigastric pain. These symptoms resolved with discontinuation of azathioprine but she continued to have diarrhea.

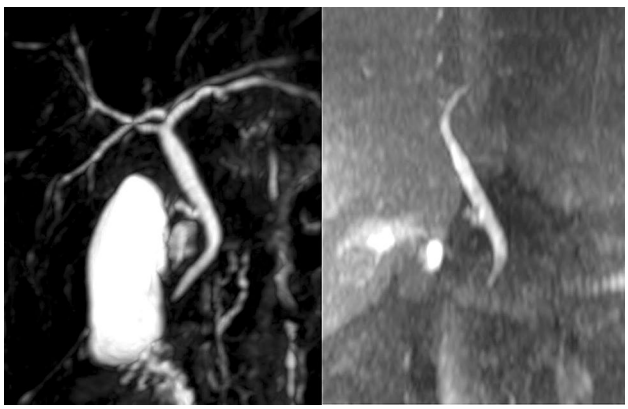

Fig. 1 Magnetic resonance cholangiography (MRCP). The initial gradient echo scan at age 15 (left) showed dilatation of the common bile duct to 7 mm; significant beading of the other ducts was not felt to be present. A post-Eovist scan at age 22 (right) showed resolution of common duct dilatation, now 4.7 mm

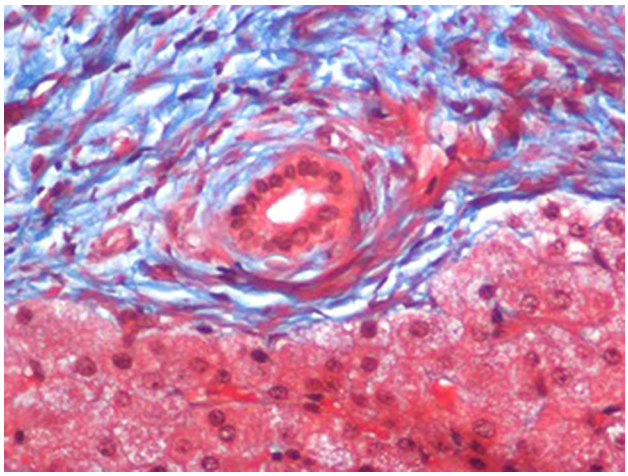

Fig. 2 Histopathology from liver biopsy at initial diagnosis. Trichrome stain shows concentric fibrosis around a bile duct. The diagnosis of small duct primary sclerosing cholangitis was made, since there was no segmental narrowing or strictures of the large ducts on MRCP

The switch to vancomycin

Since the multiple therapeutic measures outlined above failed, infliximab and 6-mercaptopurine were suggested as the next options. She and her family were reluctant to start either of these because of concerns over serious side effects. Based on published literature [18], in October 2012, she was started instead on a trial of oral vancomycin 500 mg TID (35 mg/kg/day) in capsule form. Because of only partial biochemical response to UDCA, it was discontinued. Bezafibrate was not used.

Within 2 weeks, diarrhea resolved and stools became solid (Bristol Stool Scale type 4). The patient began to gain weight and within 2 months she began menarche. At 5 months of oral vancomycin treatment, liver chemistries were: ALT 9 IU/L (range 7–35), ALP 180 IU/L (range 45–119), AST 27 IU/L (range 8–41), and GGT 46 IU/L (range 9–29). Surveillance magnetic resonance cholangiopancreatography (MRCP) scans in the 8 years following the diagnosis showed a normal liver with normal intrahepatic bile ducts. The hepatic common duct dilatation had also resolved. Magnetic resonance elastography results were within normal limits. Surveillance colonoscopies in each subsequent year showed only quiescent to mild chronic colitis on biopsy. As of September 2020, her colonoscopy and biopsies were normal as were her liver biochemistries: ALT 20 IU/L (range 10–35), ALP 51 IU/L (range 35–105), AST 26 IU/L (range 10–35), and GGT 22 IU/L (< 40).

Effect of oral vancomycin dose and brands

Over the course of her disease, the patient has been sensitive to changes in dose and manufacturer brand of oral vancomycin capsules. This is summarized graphically in Fig. 3. The capital letters on that graph refer to discrete clinical events as described in the following paragraphs. Of note, all the vancomycin described here was administered orally via capsules; no liquid form was used. The term "Vancocin" is used throughout to refer to the innovator product developed originally by Eli Lilly, licensed to ViroPharma and later to ANI Pharmaceuticals. Our understanding is that the ViroPharma and ANI generic brand products were identical to the innovator product, so are also referred to here as Vancocin to keep a clear distinction from non-innovator brands. Other generic brands of oral vancomycin capsules mentioned below are not the innovator product and are referred to simply as "generic vancomycin".

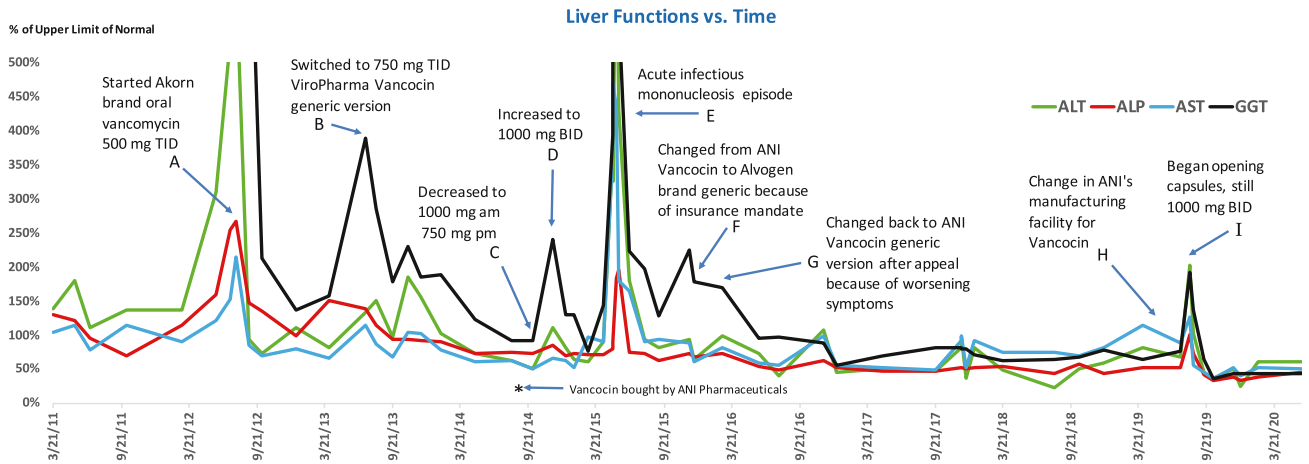

Fig. 3 Liver chemistries over time. Values are displayed as a percentage of the upper limit of normal. Each event is labeled by a capital letter for reference by the "Effect of oral vancomycin dose and brands" section of the text. *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *GGT* gamma glutamyl transpeptidase

In October 2012, generic oral vancomycin 500 mg TID was started in capsule form (35 mg/kg/day, Akorn Pharmaceuticals, Fig. 3, point A). By August 2013, transaminases had not yet completely normalized, so the dose was increased to 750 mg TID (40 mg/kg/day) (Fig. 3, point B). Because of a concern that some generic brands achieve different gut concentrations in some patients, she was switched to oral Vancocin (ViroPharma, Inc.). The patient's liver chemistries normalized except for mild gamma-glutamyltransferase (GGT) elevation of 55 IU/L (upper limit of normal 29 IU/L).

In October 2014, after 1 year of Vancocin 750 mg TID, her dose was reduced to 1000 mg in the morning and 750 mg in the evening. This dose change was followed by a spike in liver chemistries (Fig. 3, point C). In November 2014, her dose was then increased to 1000 mg BID (35 mg/kg/day; Fig. 3, point D) and her liver chemistries completely normalized. A few months later she incidentally had a transient elevation in liver chemistries from a bout of acute infectious mononucleosis (Fig. 3, point E).

In January 2016, the patient switched to Alvogen brand generic vancomycin capsules because insurance would not continue to cover Vancocin (Fig. 3, point F). Within 2 weeks, she experienced loose stools and elevations in liver chemistries. The following month she returned to Vancocin, the rights to which had been acquired by ANI Pharmaceuticals (Fig. 3, point G). Her stools and liver chemistries re-normalized.

In July 2019, while still taking Vancocin, she began experiencing loose stools and increases in liver chemistries (GGT 46–83 U/L, upper limit of normal < 60 U/L) and calprotectin (38.2–423.8 µg, upper limit of normal < 50 ug) (Fig. 3, point I). She increased her dose first to 750 mg TID and then to 1000 mg TID neither dose escalation improved her bowel symptoms nor liver chemistries. After learning that ANI Pharmaceuticals had changed its manufacturing facility location in the 2nd quarter of that year (Fig. 3, point H), and suspecting an issue with bioavailability in the gut caused by this change, possibly related to a change in capsulation, the patient began opening the capsules prior to ingesting. Within 2 weeks, her liver chemistries normalized and her GI symptoms fully resolved with her calprotectin dropping to 73.4 ug (ULN < 50 µg) and normalization in another 2 weeks. She returned to her normal dose of 1000 mg BID and continues to open the Vancocin capsules.

Discussion

In this patient with small-duct PSC, oral vancomycin 1000 mg BID via capsules led to resolution of diarrhea, weight loss and fatigue, normalization of liver chemistries, and normalization of colonoscopy findings. Surveillance MRCPs continued to show normal bile ducts and magnetic resonance elastography values continued to be within normal limits (Fig. 4). These effects have persisted up to the present, a total of 8 years. We observed that the particular formulation of vancomycin capsules impacted its effect on the liver chemistries and IBD symptoms; in one instance, this may have been related to gut availability, because opening the capsules resolved the problem.

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 key role [8]. There has been growing interest in developing drugs aimed at altering one or more gut microbiota targets [9, 19].

Patients with PSC and UC who are treated with oral vancomycin have been shown to improve both symptoms and liver biochemistries [11, 18, 20]. Vancomycin is a glycopeptide antibiotic with bactericidal activity against gram-positive bacteria. When orally administered, it has minimal systemic absorption; therefore, its effect presumably is confined to the intestinal lumen and perhaps mucosa. A study

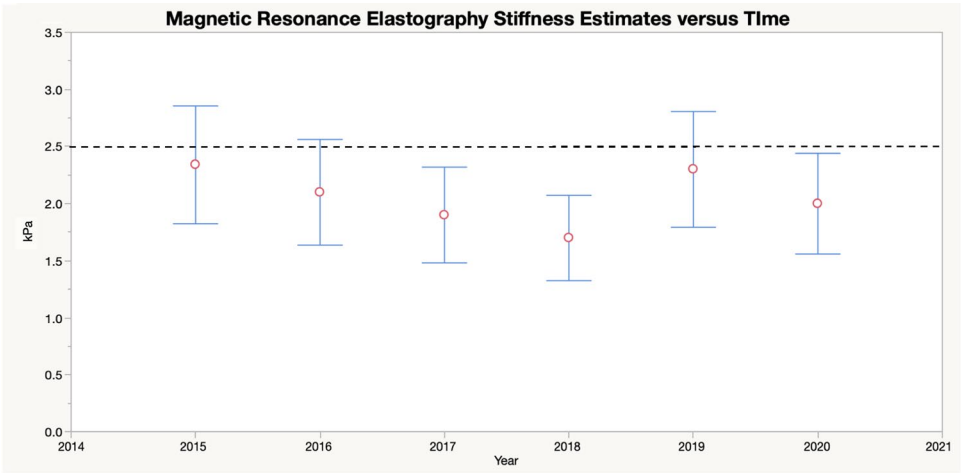

Fig. 4 Magnetic resonance elastography over time. The circles represent the measured liver stiffness expressed in kilo-Pascals (kPa). The error bars are not measurements; rather, they are estimates of the 95% confidence intervals based on a meta-analysis by Serai et al. [30]. The dotted line indicates the upper limit of normal

with 14 pediatric patients with PSC and active IBD treated with OVT showed significant improvement in GGT, ALT, and erythrocyte sedimentation rate values within 3 months of therapy [18]. OVT was also effective in the treatment of a pediatric patient with recurrent PSC after orthotopic liver transplantation, suggesting a disease mechanism with some causes external to the liver—potentially from the gut bacteria [21]. Recently, Ali et al. reported treatment of PSC patients with OVT was well tolerated and resulted in biochemical, cholangiographic, and histological improvement of the PSC and decreased inflammation of their IBD [11]. A dose of 500 mg TID for patients ≥ 30 kg was effective for most; dose was increased if liver chemistries did not normalize. In a recent retrospective study, Deneau et al. concluded that oral vancomycin did not improve outcomes compared to a control group [22]; however, the follow-up was short for biochemistries and histology (1 year), so statistical power was low for those outcomes. They did not consider MRCP or elastography improvement. There was no control for brand, and dose adjustment data were lacking.

The mechanism by which OVT leads to biochemical improvement is uncertain; several hypotheses have been proposed. The downregulation of tumor necrosis factor-alpha (TNF-α) production by monocytes may be a therapeutic effect of OVT in PSC [23]. Abarbanel et al. suggested an immunomodulatory mechanism evidenced by favorable changes in levels of regulatory T cells and transforming growth factor-β, an anti-inflammatory protein [24]. More recently, Nakamoto et al. showed that *Klebsiella pneumoniae* works cooperatively with *Proteus mirabilis* and *Enterococcus gallinarum* to disrupt the epithelial intestinal barrier, promote bacterial translocation, and eventually initiate a T helper 17 inflammatory response in the liver of gnotobiotic mice, exacerbating hepatobiliary injury [25]. Vaughn et al. showed that treatment of PSC-IBD subjects with OVT 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* [26].

In the present case, our patient's response seemed to be dependent on the dose and brand of vancomycin capsules. Notably, only Vancocin® worked consistently (with the recent exception discussed above), while two other brands of generic vancomycin capsules resulted in the return of gastrointestinal symptoms and re-elevations in liver chemistries. The cause is unclear. The manufacture of drugs from secretions of actinomycetes bacteria is a complex, delicate process [12]. Generic manufacturers may not have access to important proprietary nuances of biosynthesis as practiced by the innovator company. This could conceivably lead to reduced effects of the generic products for PSC/UC.

One possibility is variability in the therapeutic effects of the drug compound itself. Most studies of this have been done with parenteral administration, not oral. Vesga et al. tested three generic copies of Vancocin (the innovator) against two wild-type strains of *Staphylococcus aureus* in a neutropenic mouse thigh injection model; they found that all three generic products failed in vivo to kill *S. aureus*, whereas the innovator performed as expected [13]. They concluded that pharmaceutical equivalence does not imply therapeutic equivalence for vancomycin. However, these results were not replicable by Louie et al. [14]. Kim et al. found inferior in vivo pharmacokinetics and pharmacodynamics for five generic vancomycin products administered parenterally to mice, compared to Vancocin [27].

A second possibility is that some factor that affects bioavailability to the gut microbiome and/or intestinal mucosa differs between the brands; an obvious candidate would be capsule dissolution properties. Most bioavailability studies of OV focus on its presence in blood serum. This is of importance for consideration of possible toxicity, as well as of broader interest in understanding how peptide drugs are absorbed [28]. But bioavailability in the sense of action on the microbiome or mucosa is a distinct consideration that seems to have been little studied. Many PSC patients have IBD that might impact relevant gut conditions. Liquid formulations of oral vancomycin side-step the issue of capsule dissolution properties. In 2009, the FDA approved vancomycin hydrochloride generic capsules tested via in vitro bioequivalence testing, rather than in vivo testing. ViroPharma (the manufacturer of Vancocin at the time) challenged this action, claiming that because the active pharmaceutical ingredient is not well absorbed and is not highly soluble, Vancocin capsules do not fit the criteria for a waiver of in vivo bioequivalence testing [29]. Tests of in vivo therapeutic effects on liver chemistries and colonic symptoms are needed, specifically focused on oral administration.

Conclusion

Further investigation is needed to determine if different formulations and brands of vancomycin have different efficacy in PSC patients. This should include study of how capsule forms, as well as liquid forms, vary in bioavailability to the gut microbiome and mucosa. Optimal dosing regimens, perhaps patient-specific, also need to be determined. These factors may contribute to the variability of oral vancomycin trial results.

In our patient, oral vancomycin single-drug therapy, carefully controlled for dose and brand, led to profound improvement in her quality of life. Retrospective series and case reports have shown similar promise [10, 11, 18, 20]. Oral

vancomycin merits further study in randomized trials as a treatment for pediatric and adult PSC.

Compliance with ethical standards

Conflict of interest Cynthia W. Buness, Kevin M. Johnson, Ahmad Hassan Ali, Leina Alrabadi, Keith D. Lindor, Tamir Miloh, and Kenneth L. Cox, M.D. all declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from the patient for being included in the study.

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