Oral Vancomycin and Gentamicin for Very Early Onset Inflammatory Bowel Disease

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ABSTRACT

Background: The pathogenesis of Inflammatory Bowel Disease (IBD) is complex and involves the contribution of genetic and environmental factors. Many patients with very early onset IBD (VEO-IBD) are difficult to treat. The current antibiotic medication that targets gram-negative and anaerobic bacteria provides only moderate efficacy in subsets of patients with IBD.

Methods: We report a case series of five children with mean age of IBD onset 1.6 years (range 6 months to 2.7 years) that were previously refractory to standard treatments who received oral vancomycin with or without gentamicin.

Results: Four out of five demonstrated substantial therapeutic effect, and the effect was sustained in three children over a follow up period of 12-33 months.

Conclusion: Our findings are consistent with model systems and suggest that randomized trials are required to establish whether a change in therapeutic paradigm, i.e. targeting gram-positive bacteria with non-absorbable antibiotics, may have therapeutic benefits.

INTRODUCTION

The pathogenesis of inflammatory bowel disease (IBD) is driven by both environmental and genetic factors [1]. Very Early Onset Inflammatory Bowel Disease (VEO-IBD) and Infantile IBD are subgroups of IBD diagnosed before the age of 6 and 2 years, respectively[2]; these are more often associated with monogenic etiologies. Poor response to conventional therapy has been noted in many defined monogenic disorders that can present with intestinal inflammation[2] but also in other patients with VEO-IBD[3]. Mechanisms involved in IBD include epithelial defects and innate and adaptive immune defects. These may lead to poor clearance of gut mucosal microbiota. In addition, inflammation itself can modify the microbiota. Indeed, multiple studies have identified a change in bacterial composition and diversity in patients with IBD. However, it is currently not clear whether dysbiosis in IBD is a cause or an effect - a consequence of inflammation. Irrespective of the sequence of events it is tempting to speculate that some patients may benefit from antibiotics that can revert dysbiosis. Current evidence suggests only moderate benefit of antibiotics and these are largely reserved for specific indications such as fistulizing Crohn's disease, pouchitis or *Clostridium difficile*. Further studies are needed to identify which bacteria need to be targeted since current antibiotics might even further reduce bacterial diversity and further imprint a colitogenic signature.

Vancomycin has been studied as therapy for primary sclerosing cholangitis (PSC). While children with PSC treated with vancomycin have been reported to incidentally also show improvement in concurrent IBD[4, 5], vancomycin has never been studied as exclusive therapy for VEO-IBD. Gentamicin is a nonabsorbable agent with efficacy against *E. coli* - an abundant pathogen in the mucosa and intracellular compartment in IBD which may have a potential pathogenetic role in IBD[6].

We report here our experience using oral vancomycin with or without gentamicin to treat five patients with VEO-IBD refractory to standard treatments. Cases are noted in brief and summarized in Table 1. Detailed case descriptions are presented in Supplementary Materials.

Approval for the study was granted by the Institutional Ethics Committees in each of the sites. Monogenic causes of the intestinal inflammation were investigated using whole exome sequencing or targeted panel sequencing using technologies as previously described[7].

CASE REPORTS

We present a group of 5 children with therapy refractory VEOIBD. Mean age of onset was 1.6 years (range 6 month to 2.7 years). No monogenic causes of intestinal inflammation were identified by routine phenotypic and immunological investigations or genetic tests. All patients had received previous treatment with multiple conventional anti-inflammatory and immunosuppressive medications. Stool testing for *Clostridium difficile* was negative in all children. Treatment with oral vancomycin alone in 1 and a combination of oral vancomycin and gentamicin in 4 lead to an initial improvement in 4 of the 5 children (80%) and sustained remission in 3 of the 5 patients (60%). The mean duration of followup was 23.7 months (range 12 to 33 months of remission). None of the patients experienced therapy-related side effects. Cases are summarized in **Table 1** and patient 3 is portrayed in **Figure 1**. Detailed case descriptions are presented in **Supplementary Materials**.

DISCUSSION

We report here for the first time successful treatment with oral vancomycin with or without gentamicin in patients with VEO-IBD. In three patients (patients 1-3) the response was dramatic and led to sustained remission without immunosuppressive maintenance treatment despite a

previous fulminant and therapy-resistant disease course. Response was temporal or absent in two additional patients: one responded dramatically but lost response upon discontinuation, and the other received vancomycin and gentamicin in conjunction with steroids and responded incompletely and transiently.

Patients with VEO-IBD comprise a heterogeneous group of diseases that is often difficult to treat. A growing minority of cases are now identified as monogenic disorders with well-defined pathogenetic defects [2]. A sizable proportion of these defects are related to immune dysfunction causing increased susceptibility to bacterial epithelial penetration or impaired bacterial clearance by intestinal immune cells. It thus stands to reason that these patients may benefit from therapy which targets bacteria that trigger intestinal inflammation.

Prior preliminary studies showed encouraging effects of oral vancomycin in ulcerative colitis. One underpowered double-blind controlled study of oral vancomycin as add-on treatment to intravenous steroids in 33 adult patients with acute severe colitis reported a lower numerical rate of short term colectomy in the vancomycin arm (11%) vs. placebo (47%; $P=0.057$)[8].

Vancomycin has been found in a few case series and one small controlled study to improve PSC[4, 5, 8-10]. Two of these studies were in children and reported that the IBD-related symptoms also improved in all patients; those patients who underwent repeat colonoscopy showed endoscopic resolution or improvement[4, 5].

As for gentamicin, one randomized controlled trial found that another aminoglycoside, tobramycin, increased remission rate in patients with acute flares of ulcerative colitis when administered orally as an adjunct to corticosteroids[11]. As Enterobacteriaceae such as *E. coli*

are expanded in IBD[6, 12] , antibiotics effective against *E. coli* could potentially have a therapeutic effect in IBD.

The fact that both vancomycin and gentamicin are not absorbed and act locally in the bowel lumen makes vancomycin with or without gentamicin an attractive intervention in young infants, as direct adverse events are negligible. While recent adult data suggests that some systemic absorption of oral vancomycin is not uncommon in the setting of *C. difficile* colitis, the limited available pediatric data has not demonstrated absorption [13, 14]. Nonetheless, the potential benefit of using gentamicin and/or vancomycin must be weighed against the risk of emerging resistant strains, such as vancomycin-resistant enterococci (VRE). We have not tested the patients for VRE; as treatment duration becomes more prolonged, we will need to address this potential issue and by testing we will learn more about the risk for VRE.

The study's shortcomings include its retrospective design, the small number of cases, and the non-uniform approach. However, the clear and unexpected therapeutic effects in patients with previously therapy-refractory disease observed in two centers suggest that this approach deserves further evaluation. Since the reported patients are the only patients we have treated with vancomycin for this indication to date, the data are unlikely to be a pure selection or reporting bias.

In conclusion, we report a case series of five patients with VEO-IBD treated with oral antibiotics - vancomycin with or without gentamicin - of whom four responded to the therapy. Our findings may represent a potential novel induction treatment in some cases of IBD. It should be further investigated in prospective randomized trials before it could be implemented in routine practice.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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FIGURE LEGENDS

Figure 1: Vancomycin induces sustained remission in a patient with previously therapy refractory very early onset IBD

Table 1: Vancomycin and gentamicin treatment of patients with therapy refractory VEO-IBD.

Patient	Gender	Age of diagnosis (age of symptoms)	Phenotype	Previous anti-inflammatory medication	Duration of antibiotic treatment	Effect of antibiotic treatment (follow up time)
1	M	7.5 mo (5 m)	CD-like Pancolitis	azithromycin-metronidazole, EEN, CS, salazopyrine, AZA, 6MP, IFX	Three 2-3 wk courses	Vancomycin & gentamicin - remission Remission sustained with no medication (33 months)
2	F	2.5 y (8m)	IBD-U Pancolitis PSC	5-ASA	Intermittent: 15 m vancomycin of which 3 m also gentamicin	Vancomycin & Gentamicin - remission Maintenance on vancomycin + salazopyrine
3	F	3y (2y)	IBD-U Pancolitis	EEN, 5-ASA, CS, AZA, MTX, IFX, metronidazole	15 m	Vancomycin – remission and maintenance (>1 year)
4	F	15 m (11 m)	UC-like Pancolitis	EEN, 5-ASA, salazopyrine	5 wk	Vancomycin & gentamicin - remission Reintroduction after cessation - unsuccessful
5	F	9 m (8 m)	IBD-U left-sided colitis	CS, 5-ASA, AZA	3 wk	Vancomycin & gentamicin - Unsuccessful

Abbreviations: 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; CD, Crohn's disease; UC, ulcerative colitis, IBD-U, inflammatory bowel disease unclassified; CS, corticosteroids; IFX, infliximab; EEN, polymeric/elemental diet; PSC, primary sclerosing cholangitis