World Academy of Science, Engineering and Technology
International Journal of Medical and Health Sciences
Vol:17, No:7, 2023

Vancomycin and Rifaximin Combination Therapy for Diarrhoea Predominant Irritable Bowel Syndrome: An Observational Study

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***Abstract*—**Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by an alteration in bowel movements. There are three different types of IBS: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C) and IBS with mixed bowel habit (IBS-M). Antimicrobials are increasingly being used as treatment for all types of IBS. Due to this increased use and subsequent success, the gut microbiome as a factor in the etiology of IBS is becoming more apparent. Accepted standard treatment has focused on IBS-C and involves either vancomycin or rifaximin. Here, we report on a cohort of 18 patients treated with both vancomycin and rifaximin for IBS-D. These patients' records were reviewed retrospectively. In this cohort, patients were aged between 24-74 years (mean 44 years) and nine were female. At baseline all patients had diarrhea, four with mucus and one with blood. Other reported symptoms include abdominal pain (n = 11) bloating (n = 9), flatulence (n = 7), fatigue (n = 4) and nausea (n = 3). Patient's treatments were personalized according to their symptom severity and tolerability and were treated with a combination of rifaximin (500-3000 mg/d) and vancomycin (500 mg-1500 mg/d) for an ongoing period. Follow-ups were conducted between 2-32 weeks. Of all patients, 89% reported improvement of at least 1 symptom, one reported no change and one patient's symptoms got worse. The success of this combination treatment could be due to the different mechanisms of action undertaken by each medication. Vancomycin works by inhibiting the cell wall of the bacteria and rifaximin by inhibiting protein synthesis. This success in treatment validates the idea that IBS-D may be driven by a bacterial infection of the gastrointestinal microbiome. As IBS-D presents similarly to *Clostridium difficile* and symptom improvement can occur with the same treatment as *Clostridium difficile* of rifaximin and vancomycin, there is reason to suggest that the infectious agent could be an unidentified strain of *Clostridium*. Although these results offer some validity to the theory, more research is required.

Keywords*—Clostridium difficile* infection, diarrhea predominant irritable bowel syndrome, microbiome, vancomycin/rifaximin combination.

I. Introduction

IBS is a chronic gastrointestinal disorder that can be categorized into one of three groups based on the type of altered bowel movement: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C) and IBS with mixed bowel habit (IBS-M). The prevalence of each type differs based on region.

IBS affects approximately 11% of the global population [1]. IBS is diagnosed clinically with most predominant symptoms being abdominal pain, bloating and altered bowel movement [2]. All age groups suffer from IBS although the prevalence of IBS decreases for age groups over 50 years. Women are more likely to suffer from IBS than men and also report more symptoms.

Recently published clinical practice guidelines for pharmacologic treatment of IBS in American Gastroenterology Association indicated that there have been changing concepts of the treatment for IBS [3]. The contribution of the gut microbiome to the etiology of IBS is becoming increasingly recognized with increasing use of anti-microbial agents and this response suggests an infective component in IBS [4], [5]. Two randomized controlled trials showed that 10 days of rifaximin treatment reduced the symptoms in IBS patients [6], [7].

Previous studies on vancomycin and rifaximin used as monotherapy or combined have been conducted. A study by Basseri et al. using rifaximin alone showed that rifaximin was effective in treating travelers' diarrhea [2]. In another study, Fujikawa et al. [8] outlined vancomycin's ability to aid in opening the bowels and relieving IBS-C confirming our original description also observed by Celic et al. in 1995 [9]. In another study, Roshan et al. used a combination of vancomycin and rifaximin for IBS-C where 81% of participants noted significant improvement after 8 weeks [10]. Given the positive response in IBS-C, we studied similar combination in IBS-D. This study aimed to investigate the efficacy of personalized combination of vancomycin and rifaximin antibiotic treatments for IBS-D and evaluate the patients' clinical outcomes.

II. Method

A consecutive cohort of patients had their patient records reviewed retrospectively. This cohort was being treated with a combination of vancomycin and rifaximin for diarrhea predominant IBS. Patient demographics were identified as well as year of IBS diagnosis, baseline symptoms, amount and frequency of antibiotic treatment, symptoms at varying time points during treatment.

III. Results

We have conducted a study with 18 patients, aged between 25-74 years (mean 44 years) and 50% were female. The length of follow up ranged between 2 weeks to 32 weeks (Table I).

The patients have been given vancomycin and rifaximin

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together to treat their IBS-D. Out of those 18 patients, all of them have experienced diarrhea, 22% of the patients also experienced mucus and/or blood. Furthermore, 50% of the patients have experienced bloating and 60.5% of the cohort has experienced abdominal pain/cramps. Patients also reported experiencing nausea (n = 3), gurgling (n = 2), reflux (n = 1), and fatigue (n = 4).

TABLE I
IBS-D PATIENTS WHO RECEIVED VANCOMYCIN AND RIFAXIMIN

Demographics	Baseline					Dosage				Follow-up (weeks)	Response
						Vancomycin 250 mg		Rifaximin 500 mg			
	Diarrhea	Bloating	Abdominal pain/ Cramps	Flatulence	Other	Mane	Nocte	Mane	Nocte		
32 y, M	Mucus		✓			ii	ii	ii	ii	8	Formed BM. Decreased pain.
25 y, F	✓		✓	✓	Gurgling, urgency	i	ii	i		2	Improved food intolerance. Overall symptom improvement.
40 y, M	2/day		✓	✓	Restrictive diet	ii	ii	i		8	Complete resolution.
68 y, F	✓	✓	✓		Fatigue, brain fog	i	ii	i	ii	4	Reduced BM 1-3/day.
										8	2-3 BM/day. Abdominal pain, bloating, and brain fog persists.
38 y, M	2-3/day with mucus		✓	✓	Burping	i	ii	i		2	No wind, mucus, or burping. 1-2 formed BM/day.
47 y, F	Altered BM	✓	✓			i	i	i	i	8	80% improvement.
49 y, M	✓	✓				i	i	i	i	4	Improved BM.
67 y, F	4-12/day 3-4/night		✓	✓	Nausea	iii	iii	i	ii	8	3-4 formed BM/day. Abdominal pain and bloating improved.
74 y, M	Explosive					i	ii	i	i	8	Stopped rifaximin after a few days due to significant diarrhea. No response to vancomycin alone.
51 y, M	✓	✓				ii	ii	i		2	Symptoms improved.
51 y, F	✓	✓			Dietary sensitivity	i	ii	i	i	4	Less bloating. Normal BM.
32 y, M	3-4 BM/day with blood/ mucus					i	i	i	i	4	Symptoms reduced.
44 y, M	✓		✓		Chronic fatigue syndrome, brain fog	i	ii	i	ii	3	Improved cognition, concentration, energy, and mood.
										4	Formed BM daily.
42 y, F	Type 6 3+/day	✓				i	i	i	i	8	No change.
43 y, F	Explosive 2-3/week		✓	✓	Fatigue, severe headaches, restrictive diet	i	ii	i		12	2 formed BM/day, no abdominal pain, better focus, overall symptom improvement.
41 y, M	Type 6-7 8-9/day Incomplete emptying, occasional mucus/blood	✓	✓	✓	Reflux, heartburn, burping, nausea	ii	ii	ii	ii	20	5 formed BM/day. Reduced abdominal pain and bloating. Fatigue persists.
24 y, F	✓	✓	✓	✓	Fatigue, nausea	iii	iii	iii	iii	24	Formed BM 5-6/day Abdominal pain and bloating reduced.
32 y, F	✓	✓			Excessive belching, gurgling	i	i	i	i	32	Marginal improvement in all symptoms.

✓ : patient has reported this symptom; BM: Bowel movement; mg: milligram.

Treatment was varied based on symptom severity and tolerance with vancomycin prescription ranging 500 mg-1500 mg/day and rifaximin ranging 500-3000 mg/day.

Overall, 89% of patients reported improvement in one or more symptoms during the follow-up, 16.5% of patients reported better outcomes after just 2 weeks, 38% reported considerable reduction in symptoms after 8 weeks, while 16.5% have had significant reduction in symptoms and are now on the treatment for longer than 5 months.

IV. DISCUSSION

The use of the rifaximin and vancomycin combination for the treatment of IB-D resulted in the complete resolution of symptoms for 89% of the cohort. The role of these antibiotics

in improving the IBS symptoms of this cohort suggests that IBS-D may be infection driven. In this cohort, similar patient presentations to *Clostridium difficile*, as well as symptom improvement with the use of rifaximin and particularly, vancomycin, suggest that the infectious agent may be an unidentified *Clostridium*.

Multiple studies documented the role of innate immune dysfunction and consequent inflammatory processes in IBS, particularly in IBS-D [11]-[13]. Proinflammatory cytokines such as interleukins 6 and 8 were found to be slightly increased in the IBS population, supporting the hypothesis that IBS-D is an infection driven pathophysiology [14].

The mechanism of action for both vancomycin and rifaximin involves the inhibition of bacterial cell wall and protein synthesis, respectively [15], [16]. Rifaximin is a minimally absorbed antibiotic with activity against gram-negative enteric bacteria. However, rifaximin has been clinically trialed and found to have an effect in *Clostridium difficile* infected patients [17], [18]. Vancomycin is a poorly absorbable antibiotic with activity against gram-positive bacteria [19]. Vancomycin has been demonstrated to be efficacious in the treatment of *Clostridium difficile* and is currently standard of care [20]. Both oral rifaximin and vancomycin are relatively non-absorbable and therefore, result in limited systemic effects, allowing for a safe trial of treatment for IBS-D. Moreover, both antibiotics have been found to have effects on *Clostridium difficile* infection, supporting the clostridium-driven IBS-D hypothesis. Hence, these medications provide a safe and potentially efficacious alternative therapy for the treatment of IBS-D.

Although this study offers "real world" patient experience of the effects of the rifaximin/vancomycin combination on IBS-D, it has several limitations including the retrospective data collection, and the lack of standardization in the treatment regimen. Future research in this area should focus on prospective trials of the rifaximin/vancomycin combination in IBS-D patients with more objective response data.

However, these preliminary results offer an alternative etiology not previously considered and open the avenue for new research in the area.

ACKNOWLEDGMENT

We thank the patients who participated in the study.

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