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Research Article

Efficacy and Safety of Gelsectan for Post-Infectious Irritable Bowel Syndrome

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Abstract

Background-Aim: Acute infectious gastroenteritis is a known risk factor for Irritable Bowel Syndrome (IBS) development; namely post-infectious IBS (PI-IBS). We aimed to evaluate the efficacy and safety of Gelsectan, an agent with both film-forming protective properties and antioxidant actions on the intestinal mucosa, in patients with PI – IBS.

Methods: We prospectively recruited patients with diarrhea-predominant PI-IBS (group A) and patients with diarrhea predominant classical IBS (D-IBS) who were used as controls (group B). Diagnosis of IBS and PI-IBS was made according to the ROME IV and the Rome Foundation Working Team criteria. Patients received for 28 days, twice daily, a capsule containing Xyloglucan, Pea Protein and Grape Seed Extract and Xylo-oligosaccharides (Gelsectan, Devintec sagl). Response to treatment was defined as disappearance of diarrhea. The presence and intensity of abdominal pain and flatulence was measured on a 1 to 5 Likert scale.

Results: From September 2021 to December 2023, 135 patients in group A and 140 patients in group B received Gelsectan. At the end of treatment, 102 patients in group A (75.5%) and 87 patients in group B (62.1%) responded (p=0.016). The difference in both abdominal pain and flatulence were significantly higher in group A as compared to group B (p = 0.04 and p=0.06 respectively). No adverse effects were observed.

Conclusions: Agents with film-forming protective properties, such as Gelsectan, represent a new alternative therapeutic option for the management of patients with PI-IBS.

Keywords: Irritable Bowel Syndrome; Post-Infectious Irritable Bowel Syndrome; Gelsectan

Introduction

Irritable bowel syndrome (IBS) has a prevalence that ranges from 7% to 15% of the global population [1,2] and is probably the most common diagnosis in gastroenterology practice. The Rome IV criteria state that, in the absence of organic disease or biochemical abnormalities, it is characterized by mild to severe recurring abdominal pain and bloating linked to changes in bowel habits [3]. IBS's symptoms lead to high medical expenses, decreased productivity at work and in school, and a decline in the affected person's health-related quality of life [4].

It has been demonstrated that one of the biggest risk factors for the development of IBS is acute infectious gastroenteritis (bacterial, viral, and protozoal), a condition described for the first time in 1962 and referred to as post-infection IBS (PI-IBS) [5]. According to conservative estimates derived from mathematical modeling, the prevalence of PI-IBS in the general population may be 9%, which would represent more than half of all IBS cases in the US [6]. While there are some similarities between PI-IBS and diarrhea-dominant IBS, the former is known to have different pathophysiologic changes, since an increase in gut permeability is commonly seen in these cases possibly reflecting damage to the enterocytes [7].

At present, treatment options for PI-IBS are inadequate with no specific FDA-approved agents; therefore, current management strategies for this condition are based on expert opinion [8]. As with IBS in general, treatment is usually guided based on phenotype and predominant symptoms and includes dietary modifica-

tions and pharmacologic agents like mesalamine, corticosteroids, rifaximin and glutamine8. With multiple studies showing their potential advantages for IBS patients, probiotics and prebiotics have recently drawn a lot of attention as potent modulators of the intestinal flora [9,10], however, their merit for treatment of PI-IBS is not accepted as yet [11]. In the meantime, because the entry of pathogenic bacteria into the gastric lumen results in structural and/or functional changes, exposure to toxins may cause damage to the epithelium and enterocytes and therefore the administration of agents with mucosal protective properties could be of theoretical benefit to these patients [12].

Based on the above observations, we have designed a prospective study in order to evaluate the efficacy and safety of Gelsectan, an agent with both film-forming protective properties and antioxidant actions on the intestinal mucosa, in patients with PI-IBS.

Methods

Study design

Open-label, non-randomized, two-arm clinical study conducted at two tertiary medical institutions in Greece from September 2021 to December 2023.

Patient population

We prospectively recruited patients with diarrhea-predominant PI-IBS (group A) and patients with diarrhea predominant classical IBS (D-IBS) who were used as controls (group B). The consistency of stools was assessed using the 7-point Bristol Stool Scale [13]. Diarrhea predominant IBS and post IBS patients were those with loose or watery stools (Bristol scale 6–7) >25% and hard or lumpy stool <25%, in the absence of anti-diarrheal or laxative use.

Diagnosis of IBS was made according to the ROME IV criteria [3] as following

Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with two or more of the following criteria:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool.

The above-mentioned criteria have to be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

Diagnosis of post infectious IBS was made according to the Rome Foundation Working Team criteria [7] as following

- Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, with symptom onset at least 6 months before diagnosis, associated with ≥2 of the following:
  - Related to defecation
  - Associated with a change in frequency of stool
  - Associated with a change in form (appearance) of stool.
- Symptom development immediately following resolution of acute infectious gastroenteritis
- Infectious gastroenteritis defined by positive stool culture in a symptomatic individual or presence of ≥2 of the following acute symptoms (when stool culture not available):
  - Fever
  - Vomiting
  - Diarrhea
- Should not meet criteria for IBS prior to onset of acute illness.

Patients diagnosed with gastrointestinal disorders (e.g., inflammatory bowel disease) or those with a history of major gastrointestinal surgery (e.g., gastrectomy, gastrointestinal suture, or intestinal resection) were excluded. Patients who received antibiotics or antimicrobial agents within the past 3 months prior to providing consent were also excluded. Finally, patients who were pregnant, who had an oncology history (since these patients might exhibit diarrhea due to their underlying illness) and patients with alcohol dependence (due to the non-compliance shown by these patients) were also excluded.

Intervention

Patients received for 28 days, twice daily, a capsule containing Xyloglucan, Pea Protein, Grape Seed Extract and Xylo-oligosaccharides (Gelsectan, Devintec Sagl).

During the trial period, medications that could affect intestinal secretion or motility were prohibited.

Assessments were conducted at screening and on study days 1, and 28 (end of study). Patients were seen by their attending physician at the outpatient clinic of the two participating hospitals. General physical (vital signs), clinical (abdominal pain and bloating) and biochemical and haematological (creatinine, glucose, glutamic-pyruvic transaminase/alanine transaminase/aspartate transaminase, alkaline phosphatase, haemoglobin, and erythrocyte sedimentation rate, C reactive protein) assessments were performed.

Patients used a diary to document each day stools emissions, evolution of clinical symptoms, frequency and severity of unfavorable events, and use of rescue medication.

Only in non-responders or for diarrheal exacerbation was concurrent anti-diarrheal treatment given always with the investigators' permission.

Safety and tolerability were monitored during the entire study period. Any adverse event was reported and monitored during the 28 days of Gelsectan administration.

Study outcome

The primary outcome was response to treatment, defined as the disappearance of diarrhea, i.e. two or less non-watery stools emissions per day (stool of type 5 or less on the Bristol scale).

Secondary outcomes were changes in the presence and intensity of abdominal pain and flatulence, as these were measured on a 1 to 5 Likert scale (1: very good, 2: good, 3: acceptable, 4: poor, 5: very poor). These measurements were made in all patients immediately at the end of the 28-day administration of Gelsectan. At that point, patients' satisfaction was also measured with the TSQM V 9 Greek version questionnaire.

Ethics and registration

All study procedures were conducted in accordance with the ethical standards stipulated in the Declaration of Helsinki and approved by the ethics committee of the participating Hospital (Protocol Record 348/28-7-2021). The trial was also registered at ClinicalTrials.gov (Identifier: NCT05045768). All eligible patients provided written informed consent prior to the intervention.

Statistical analysis and sample size calculation

Results are reported using descriptive statistics. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as number (%). Statistical differences in mean values between treatment groups were assessed with the t-test. A 2-sided p value less than .05 was considered statistically significant. SPSS Statistics (version 26.0; IBM Corp, Armonk, New York, USA) was used for statistical analyses.

Sample size was calculated based on an expected difference in disappearance of diarrhea between treatment groups using 80% power and at 5% significance level. Since a responder was defined as a subject for which diarrhea disappeared at the defined experimental time, the sample size was calculated based on the following formula

- Expected responder rate for postinfectious irritable bowel syndrome group
- Expected responder rate for noninfective irritable bowel syndrome group
- Enrollment ratio
- Critical Z value for α
- Critical Z value for β
- Probability of type I error (0.05)
- Probability of type II error (0.2).

A sample size of at least 138 subjects per treatment arm for a total of 276 subjects, with an enrollment ratio of 1:1, is appropriate to detect an expected responder rate difference of 15% between postinfectious irritable bowel syndrome group and noninfective irritable bowel syndrome group when treated with Gelsectan. With a drop-out rate of 10%, the necessary sample size was calculated to be 306 subjects.

Results

Baseline characteristics of study population

During the study period, 351 patients were screened in the two participating centers. Fifty-three patients were excluded (4 were diagnosed with Crohn's disease, 1 with ulcerative colitis, 3 had a history of gastrointestinal surgery and the remaining 45 had received antibiotics or antimicrobial agents within the past 3 months prior to screening). Therefore, 298 were finally included in the study, namely 141 in group A and 157 in group B, who received Gelsectan for the treatment of their diarrhea. During the study period, 6 patients in group A and 17 patients in group B were lost to follow up; and therefore 135 patients in group A and 140 patients in group B completed the study and their results are analyzed here.

Patients' demographic and clinical characteristics at baseline for both groups are presented in Table 1. Mean (SD) age was 41.0 (7.8) years in group A and 38.5 (8.1) years in group B, and most patients were females.

Disappearance of diarrhea

After the end of the 28-day administration period, 102 patients of group A (75.5%) responded to treatment as compared to 87 patients of group B (62.1%) (p = 0.016). Precisely, mean (SD) number of stools per day and type of stool according to the Bristol scale at baseline were 4.6 (0.9) and 6.0 (0.8) for group A and 4.7 (1.1) and 5.7 (0.8) for group B respectively. The corresponding values post treatment were 2.5 (0.8) [p = 0.03] and 3.8 (0.7) [p = 0.06] for group A and 2.3 (0.9) [p = 0.04] and 3.4 (0.9) [p = 0.01] for group B.

Abdominal pain and flatulence

Mean (SD) severity scores for abdominal pain and flatulence at baseline were 3.6 (0.7) and 3.6 (0.8) for group A and 3.4 (0.8) and 3.5 (0.9) for group B respectively. The corresponding values post treatment were 1.9 (0.8) [p = 0.04] and 1.8 (0.7) [p = 0.07] for group A and 2.1 (0.9) [p = 0.04] and 2.3 (0.9) [p = 0.01] for group B (Table 2). The difference in both abdominal pain and flatulence were significantly higher in group A as compared to group B (p = 0.04 and p=0.06 respectively).

Adverse events

No adverse effects related to the study drug were observed in our patients receiving Gelsectan during the study period. Clinical laboratory tests and vital sign monitoring showed no values outside of normal norms.

Quality of life

The median (IQR) TSQM V9 questionnaire score after treatment was 54 [9] and 52 [8] in groups A and B respectively, demonstrating good quality of life following the administration of the study drug in both group of patients.

Discussion

In our study the administration of Gelsectan, an agent with both film-forming protective properties and antioxidant actions on the intestinal mucosa, alleviated symptoms in patients with both IBS and PI-IBS. Gelsectan containing Xyloglucan, Pea Protein and Grape Seed Extract and Xylo-oligosaccharides administered for 28 days, twice daily resulted in disappearance of diarrhea in 75.5% of patients with PI-IBS as compared to 62.1% of patients with classical IBS. The difference was statistically significant (p = 0.016).

IBS and/or PI-IBS with diarrhea do not yet have a conventional treatment protocol and therefore therapeutic alternatives include prescription drugs, over-the-counter pharmaceuticals, medicinal foods, lifestyle and nutritional changes, and psychiatric therapy [8]. However, the intricacy and diversity of the pathophysiology of IBS necessitate a range of therapeutic options, including nonpharmacological ones and for this reason therapies focusing on restoring mucosal barrier disruption and tight junction alterations have been tested lately [14]. The preclinical activities and clinical use of Gelsectan has been tested as a possible therapeutic approach in IBS with diarrhea, since a crucial characteristic of these patients is an altered intestinal barrier linked to immunological activation and clinical symptoms and film-forming mucosal protective agents in combination with antioxidants may offer a valuable nonpharmacological alternative for effective symptom control [15]. Xyloglucan has already been used for the treatment of acute diarrhea [16], while in a controlled clinical trial, Xyloglucan formulated with tyndallised Lactobacillus reuteri and Bifidobacterium brevis significantly reduced abdominal extension and flatulence in patients with functional bloating [17]. In addition, in a recent double-blind, randomized, cross-over clinical trial, 60 patients with D-IBS were randomly assigned to receive Gelsectan or placebo for 28 days, and were then crossed over to the alternative treatment. On day 28, a significantly higher proportion of patients starting treatment with Gelsectan than placebo (87 vs 0%; p = 0.0019) presented normal stools (Bristol Stool Form Scale type 3-4). On day 56, a significantly higher proportion of patients who crossed over to Gelsectan than placebo (93% vs 23%; p = 0.0001) presented normal stools[18]. Because of its mucin-like structure, Xyloglucan is thought to work by creating a physical barrier that shields the gut mucosa from pro-inflammatory substances (like food ingredients), bacteria, and allergens while also restoring the integrity of the intestinal epithelial barrier [16]. Our results, indeed, confirmed that Gelsectan was efficacious in the majority of patients with diarrhea predominant IBS and was even more efficacious in patients with diarrhea predominant PI-IBS.

Although several trials have tested possible therapies for classical IBS, therapeutic management of PI-IBS has been less extensively studied [11]. The Rome Foundation Working Team's current requirements for the diagnosis of PI-IBS are derived from the Rome IV criteria. These requirements, which must be met during the past three months with symptom onset at least six months prior to diagnosis and they were not included in the original Rome IV document because they were created after the publishing of the Rome IV criteria [7]. Acute infectious gastroenteritis is preferably identified by means of stool culture (however, it has to be taken into account that it is difficult to obtain one in subjects of the community), established molecular biology analyses (e.g., polymerase chain reaction) or by the presence of ≥2 of the following: fever, vomiting, or diarrhea [7]. In a patient who has never experienced IBS symptoms before, PI-IBS develops following the resolution of a gastrointestinal infection and the removal of the triggering pathogen [19]. IBS clinical features usually develop 6-18 months after the infectious gastroenteritis episode and PI-IBS patients are more likely than sporadic IBS patients to exhibit a diarrhea-predominant phenotype [20]. PI-IBS management strategies involve nonpharmacologic and pharmacologic therapies. Since there aren't much evidence-based suggestions for treating PI-IBS, the current recommendations are based on IBS treatment experience. Both intestinal barrier function and the gut microbiome have gained attention in the past few years as possible targets for alleviating symptoms in patients with PI-IBS presenting with diarrhea. The intricate interplay of the innate immune system inside the mucosa, mucus, the epithelial cell layer and its cell-cell junctions, and the microbiota results in the operation of the intestinal barrier. The epithelial tight junctions, where transmembrane proteins isolate the intestinal lumen from the paracellular space, are the primary means of determining ion permeability. As of right now, 26 distinct claudins-mostly barrier-forming claudins-have been found to control the ion and water permeability of the human intestine. But some of them, including claudin-2 and -15, are also channel builders. The latter type of tight junction proteins passively allow ions and water to pass through the epithelium and in this way can contribute to diarrhea [21]. In accordance with the above, a recent study has demonstrated that

PI-IBS patients experienced an increased macromolecule uptake by endocytosis following C. Jejuni infection, which resulted in low-grade inflammation and the release of pro-inflammatory cytokines [22]. Similarly, a recent study has shown that the administration of Gelsectan restored permeability in the ascendent colon in patients with diarrhea predominant IBS, since in these patients intestinal permeability was elevated compared with controls [23]. On the other hand, it is well known that the human gastrointestinal system has the highest concentration and diversity of the body's microbiota because of the nutrients' bioavailability. Five major bacterial phyla make up the healthy adult gastrointestinal microbiota: the phylums Firmicutes (synonym Bacillota) and Bacteroides (synonym Bacteroidota) dominate microbiota, with modest amounts of Actinobacteria (synonym Actinomycetota), Proteobacteria (synonym Pseudomonadota), and Verrucomicrobia [24]. The microbial diversity of the gut decreases during acute infectious gastroenteritis. The disturbance of the native microbiota can be explained in several ways. One would be directly during the interaction between the microbiota and the disease agent. Second, the host's mucosal immune response may cause the microbiota to change, or a combination of the two mechanisms mentioned may be responsible [25]. Considering the above data, the administration of an agent that enhances the mucosal barrier and at the same time restores the altered gut microbiome would be an attractive therapeutic approach in patients with diarrhea predominant PI-IBS. That is why we tested the administration of Gelsectan in patients with PI-IBS presenting with diarrhea and have shown for the first time that this is a safe and effective alternative in managing these patients.

Among the strengths of our study is the recruitment of a large number of patients with both classical IBS and PI-IBS. According to our knowledge our study is the first to show that an agent acting both through microbial restoration, and augmentation of barrier function is efficacious in patients with PI-IBS. Our study was adequately powered to show that Gelsectan alleviated diarrhea in a significantly bigger number of patients with PI-IBS as compared to patients with classical D-IBS. This is of particular importance since proof-of-concept clinical trials specific to the PI-IBS population are lacking. The short-term follow-up could be considered a limitation of our study, however, the majority of studies related to IBS drug therapies are characterized by such a limited monitoring time. Even though we defined classic D-IBS as a control group, the absence of a placebo group could be regarded as another drawback. However, adding a third group of patients would substantially increase the number of patients that should be recruited in the study. Moreover, we would like to test Gelsectans' efficacy in the subgroup of PI-IBS patients and to compare this efficacy to a population (D-IBS) in which Gelsectan has shown proven effectiveness.

	Group A	Group B	p value
Sex, male/female, n (%)	42 (29.8)/99 (70.2)	38 (24.2)/119 (75.8)	0.91
Age (years), mean (SD)	41.0 (7.8)	38.5 (8.1)	0.82
BMI (kg/m2), mean (SD)	21.3 (3.7)	22.9 (4.1)	0.99
Smoking, n (%)	39 (28.8)	40 (28.5)	0.94
Comorbidities:			
Heart disease, n (%)	8 (5.9)	11 (7.8)	0.65
Diabetes melitus, n (%)	1 (0.7)	3 (2.1)	0.81
Other, n (%)	5 (3.7)	6 (4.2)	0.72
Number of stools/day, mean (SD)	4.6 (0.9)	4.7 (1.1)	0.70
Type of stool (Bristol scale), mean (SD)	6.0 (0.8)	5.7 (0.8)	0.12

Table 1: Patients' baseline demographic and clinical characteristics in both groups.

	Abdominal pain		Flatulence	
	Group A	Group B	Group A	Group B
Baseline, Mean (SD)	3.6 (0.7)	3.4 (0.8)	3.6 (0.8)	3.5 (0.9)
Post-treatment Mean (SD)	1.9 (0.8)	2.1 (0.9)	1.8 (0.7)	2.3 (0.9)
p	0.04	0.04	0.07	0.01

Table 2: Abdominal pain and flatulence baseline and post-treatment values.

Conclusion

In conclusion, Gelsectan effectively and safely controlled diarrhea and alleviated clinical symptoms in patients with PI-IBS. Therefore, agents with film-forming protective properties, such as Gelsectan, represent a new alternative therapeutic option for the management of patients with PI-IBS.

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