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Randomized Controlled Trial

Safety and efficacy of purified clinoptilolite-tuff treatment in patients with irritable bowel syndrome with diarrhea: Randomized controlled trial

Clinoptilolite-tuff treatment in IBS-D

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder with poor response to treatment. IBS with predominant diarrhea (IBS-D) is accompanied by abdominal pain as well as high stool frequency and urgency. Purified clinoptilolite-tuff which is approved by the Food and Drug Administration for use as dietary supplement with the brand name G-PUR® has previously shown therapeutic potential in other indications based on its physical adsorption capacity.

AIM

To assess whether symptoms of IBS-D can be ameliorated by oral treatment with purified clinoptilolite-tuff (PCT).

METHODS

In this randomized, placebo-controlled, double-blind pilot study, 30 patients with IBS-D diagnosis based on Rome IV criteria were enrolled. Following a 4-week run-in phase, 14 patients were randomized to receive a 12-week treatment with G-PUR® 2 g three times daily and 16 patients received placebo. The relief from IBS-D symptoms as measured by the proportion of responders according to the *Subject's Global Assessment (SGA) of Relief* was assessed as primary outcome. For the secondary outcomes validated IBS-D associated symptom questionnaires, exploratory biomarkers and microbiome data were collected.

RESULTS

The proportions of *SGA of Relief* responders after 12 wk were comparable in both groups, 21% in the G-PUR® and 25% in the placebo group, after 4 wk of treatment 36% of patients in the G-PUR® group vs. 0% in placebo group reported complete or considerable relief. An improvement in daily abdominal pain was noted in 94% vs. 83% (P = 0.0353), and the median number of days with diarrhea per week decreased by 2.4

vs. 0.3 days in the G-PUR® and placebo group, respectively. Positive trends were observed in proportion of Bristol Stool Form Scale (BSFS) 50% responders, combined abdominal-pain and stool-consistency response, and Perceived Stress Questionnaire (PSQ) score. Only 64% in the G-PUR® group compared to 86% in the placebo group required rescue medication intake during the study. Stool microbiome studies showed a minor increase in diversity in the G-PUR® group, but not in the placebo group. No PCT related serious adverse events were reported.

CONCLUSION

In this randomized, double-blind, placebo-controlled study, the purified clinoptilolite-tuff product G-PUR® demonstrated safety and clinical benefit towards some symptoms of IBS-D, representing a promising novel treatment option for these patients.

Key Words: Irritable bowel syndrome; Diarrhea; Functional gastrointestinal disorder; Clinoptilolite; Zeolite; Treatment

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Core Tip: The purified clinoptilolite-tuff product G-PUR® could show an improvement in abdominal symptoms and stool abnormalities in patients with irritable bowel syndrome with predominant diarrhea (IBS-D). Additionally, it reduced the use of rescue medication and tended to enrich gut microbiome diversity compared to placebo, while showing no safety concerns. Hence, the purified clinoptilolite-tuff product G-PUR® represents a promising novel treatment option for patients with IBS-D.

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder of high global prevalence with a substantial impact on quality of life associated with abdominal pain and altered bowel habits. According to the Rome IV criteria, IBS is characterized by recurrent abdominalgia occurring at least once a week over the period of three months together with at least two of the following criteria: pain related to defecation, change in stool frequency or change in form/appearance of stool, with the onset of symptoms at least 6 mo prior to diagnosis. IBS can be divided into IBS subgroups with predominant constipation (IBS-C), diarrhea (IBS-D), mixed bowel habits (IBS-M) or unclassified (IBS-U) subtype[1, 2]. The prevalence of IBS in the literature ranges between 1-45%, reflecting the geographical and methodological variety. IBS affects at least twice as many women as men, occurring in women primarily in the late teenage years to the mid-forties[3].

While no underlying morphologic correlation has yet been identified in IBS, the multifactorial biopsychosocial model postulates a contribution of genetic predisposition, history of gastrointestinal infections with possible increase in gut permeability and activation of the immune system, malabsorption of bile acids, neuropsychological disorders, and the bidirectional brain-gut axis[4-6]. The therapeutic approach is empirical and aims to reduce symptoms of IBS.

Several natural mineral adsorbents, *e.g.* dioctahedral smectite, spherical carbon, bentonite or zeolites have been investigated in patients with IBS and have shown variable degrees of effectiveness in alleviating symptoms[7-11]. Clinoptilolite, a commonly found mineral from the group of natural zeolites, is characterized by high ad/absorptive capacity, and the ability to support ion exchange, and to act as a molecular sieve, owing to its microporous crystalline structure with multiple microcavities[12, 13]. A number of clinical studies have evaluated the potential of clinoptilolite-based products in relieving symptoms of gastric discomfort, such as diarrhea[14], gastric hyperacidity,[15, 16] or veisalgia[17]. Furthermore, clinoptilolite has shown benefit in enhancing the intestinal wall integrity as indicated by decreased concentrations of the tight-junction modulator zonulin, and reduction of inflammation-

associated markers, such as α1-antitrypsin, high-sensitivity C-reactive protein, and a trend towards beneficial microbiome changes[10, 18].

In a pilot study with clinoptilolite in IBS patients, significant decreases in clinical parameters such as pain, distension, or bowel habits were reported. Despite the pronounced placebo effect seen in this study, clinoptilolite showed a trend towards an augmented clinical benefit[19]. Based on these encouraging results, we aimed to determine the clinical effectiveness and safety of PCT product G-PUR® in patients with diarrhea-associated IBS (IBS-D) symptoms in a randomized controlled trial.

MATERIALS AND METHODS

Trial design

We conducted a randomized, placebo-controlled, double-blind, parallel-arm study to evaluate the safety and clinical efficacy of a 12-week oral treatment with G-PUR® 2 g three times daily or matching placebo in a cohort of 30 patients with IBS-D diagnosis based on Rome IV criteria[2]. Glock Health, Science and Research GmbH acted as sponsor of this multicenter study and was responsible for the design and report of this study. The study protocol was approved by the Ethics Committee of the Medical University of Vienna (No. 1295/2019), Ethics Committee of Upper Austria (No. 1208/2019), and the Austrian Federal Office for Safety in Health Care (BASG) and is registered at clinicaltrials.gov (NCT04138186). This study was conducted at the Department of Clinical Pharmacology at the Medical University of Vienna and Klinikum Wels-Grieskirchen, Department of Internal Medicine in accordance with the Declaration of Helsinki and the ISO 14155 guideline. All study participants provided written informed consent before any study-specific procedures were performed. The clinical investigation was initiated in September 2019 and completed in February 2021.

Patient population

Eligible patients had to be between 18-75 years of age and fulfill the Rome IV criteria for IBS-D, i.e. more than 25% of the bowel movements graded as the *Bristol Stool Form Scale (BSFS)* type 6 or 7 (equivalent to mild/severe diarrhea) and less than 25% of bowel

movements graded as type 1 or 2 (equivalent to mild/severe constipation)[20]. Moreover, patients had to have moderate to severe abdominal pain as defined by an IBS Symptoms Severity Scale (IBS-SSS) score >175 and stable eating habits one month prior to randomization. Patients >50 years of age had to have an unremarkable colonoscopy within the preceding 5 years. Patients were excluded if they failed to record >50% of daily diary entries during screening/run-in phase, had rectal bleeding in the absence of documented bleeding hemorrhoids or anal fissures, had a history of major gastrointestinal surgery, or had been or were being treated with antibiotic medicines, including rifaximin, used pro- or antikinetic agents (except as a rescue medication, see below), tricyclic antidepressants or immunosuppressive therapy. Patients with a history of positive tests for ova, parasites, or *Clostridioides difficile* infection had to undergo repeated testing with negative results during the screening/run-in phase.

Investigational medical device

G-PUR® is a purified clinoptilolite-tuff (PCT), prepared from a high-grade raw material with low heavy metal content, sourced from a mine in the eastern Slovak Republic[21, 22] and has been marketed in the United States as a dietary supplement since 2016. G-PUR® has been successfully applied in different therapeutic indications[23, 24]. The patented purification process is technically based on ion exchange mechanisms of the clinoptilolite mineral, micronization and terminal heating, which results in the removal of all natural impurities and a homogeneous, very fine-grained particle size[25]. The production process is thoroughly quality assured meeting all required regulatory standards. The purified product has been evaluated by independent laboratories and conforms with the safety requirements for human consumption. Besides the very high clinoptilolite content in the purified product (>75%), other mineral phases like cristobalite, feldspars, accessory biotite and quartz are contents of G-PUR®. The almost completely inert product is characterized by a high adsorption capacity for a variety of toxins, heavy metals, and other undesirable substances[26-28]. G-PUR® is not absorbed or metabolized in the gastrointestinal tract and therefore excreted unchanged *via* stool. The therapeutic potential is based on the physical adsorption capacity of G-PUR® [23, 24].

For this clinical investigation, G-PUR® was provided in hard-gelatine Capsugel® AAA capsules, each containing 400 mg of PCT. Colloidal silicon dioxide (Aerosil®) was added as an excipient at a concentration of 0.5% to enhance flowability and enable accurate filling of the capsules. Placebo was provided in identical-looking capsules, each containing 400 mg maltodextrin and 0.5% magnesium stearate as excipient.

Randomization and blinding

Randomization was performed by Assign Data Management and Biostatistics (ADMB). Based on the randomization list, blinding was performed centrally by NUVISAN Pharma Services. The randomization list was prepared by computer software (random permuted blocks with confidential block size) using a 1:1 ratio. One sealed randomization list was stored at ADMB and was not to be opened until after database lock. Patients fulfilling all eligibility criteria as confirmed at Visit 3 were enrolled into the clinical investigation and randomized. Enrolled patients were allocated to the next highest randomization number (medication kit identification number). Investigational site staff, including the investigator, and patients were blinded to treatment allocation.

Trial procedures

Eligible patients underwent a 4-week screening/run-in phase, followed by a 12-week double-blind treatment phase and a 2-week withdrawal phase. The total study duration per patient was 18–21 wk and included 7 study visits. Patients also had to complete at least 14 days of baseline diary entries over the 28-day screening/run-in phase. Throughout the double-blind 12-week treatment phase and the 2-week withdrawal phase, a limited use of loperamide and hyoscine butylbromide was allowed as rescue medication. Following the run-in phase, patients were randomized to receive five G-PUR® capsules or identical-looking placebo capsules, three times a day before meals with a minimum of 200 mL tap water. The total daily dose of PCT in the treatment arm was 6 g. Due to the high adsorption capacity and the possible risk of interaction between the PCT product G-PUR® and other medicines, participants were instructed to

allow for a minimum 2-hour window between G-PUR® and other oral medication intake. Throughout the entire study duration, patients were supported by health care professionals and psychological therapists.

According to the guidelines by the European Medicines Agency (EMA)[29] and the Food and Drug Administration (FDA)[30], abdominal pain based on an 11-point numerical rating scale as well as stool consistency according to the Bristol Stool Form Scale (BSFS) should be assessed daily to determine the effect of medicine treatment in patients with IBS-D. Accordingly, patients kept daily diaries of abdominal pain, bloating, urgency, stress, stool frequency, stool consistency, treatment adherence, and use of any concomitant or rescue medications using an electronic patient-reported outcome (ePRO) system throughout the study. At the end of the treatment phase, i.e., at Visit 6, ePRO diary usability was evaluated.

Outcomes

The primary objective of this clinical investigation was to assess the relief from IBS-D symptoms after a 12-week treatment with G-PUR® 2 g three times daily *vs* placebo as measured by the *Subject's Global Assessment (SGA) of Relief* questionnaire[31]. The secondary objectives were to assess the safety and tolerability of treatment with G-PUR®, impact of treatment on additional IBS-related symptoms, bowel habits, health-related quality of life, psychological status (i.e., anxiety, depression, and stress), patient satisfaction with ePRO diary, and additional exploratory parameters including microbiome analysis.

The primary endpoint of this clinical investigation was the proportion of responders according to the *SGA of Relief* [31] using the last 4 post-randomization assessments in the treatment period or, if fewer than 4 post-randomization SGAs were available, on all post-randomization *SGA of Relief* questionnaires. Patients were considered responders if they answered "considerably relieved" or "completely relieved" at least 50% of the time or at least "somewhat relieved" 100% of the time.

The following variables were assessed as secondary endpoints: 1) *SGA of Relief* estimated by time point, absolute change in *SGA of Relief* compared to baseline and relationship between *SGA of Relief* by treatment groups in a logistic regression model with *Irritable Bowel Syndrome Severity Scoring System (IBS-SSS), Hospital Anxiety and Depression Scale (HADS)*, pain intensity, stool frequency, and stool consistency at Visit 3 as independent variables; 2) incidence of (serious) adverse events; 3) daily intensity of abdominal pain using an 11-point numerical rating scale (NRS), including the proportion of *abdominal-pain responders*, with *abdominal-pain response* defined as an at least 30% improvement in abdominal pain on at least 50% of days with available *ePRO diary* entries, compared to the patient's worst abdominal pain reported in the screening/run-in phase (baseline abdominal pain), additional analyses of *abdominal-pain response*, defined as an at least a) 40%, 50%, or 60% improvement in abdominal pain on at least 50% of days, b) 30%, 40%, 50%, or 60% improvement in abdominal pain on at least 40% of days or 30%, 40%, 50%, or 60% improvement in abdominal pain on at least 30% of days, with available ePRO entries compared to the patient's worst baseline abdominal pain or proportion of days with an at least 30% improvement in abdominal pain compared to the patient's worst baseline abdominal pain; 4) daily intensity of bloating using an 11-point NRS; 5) daily intensity of urgency using an 11-point NRS; 6) daily stress level using an 11-point NRS; 7) daily stool frequency; 8) daily stool consistency using the *Bristol Stool Form Scale (BSFS)*[32], including the proportion of *BSFS responders*, with BSFS response defined as an at least 50% reduction in the number of days per week with at least one *BSFS* type 6 or 7 stool ('diarrhea') compared to the screening/run-in phase ('baseline diarrhea'), daily proportion of patients with *BSFS* type 6 or 7 (i.e., diarrhea) and number of days per week with diarrhea; 9) proportion of patients with a combined *abdominal-pain and BSFS response*; 10) patient compliance with daily *ePRO diary* reporting; 11) *ePRO diary* usability; 12) gastrointestinal symptoms using the *IBS-SSS*[33] during each study visit assessing the proportion of patients with a ≥50 reduction in the *IBS-SSS* score and number of pain-free days using the *IBS-SSS;* 13) quality of life using the *12-item Short Form Survey (SF-12)* questionnaire[34]; 14) anxiety

and depression using the *HADS*[35]; 15) stress response using the *Perceived Stress Questionnaire (PSQ)*[36]; *16)* use of rescue medication. In addition, the following variables were analyzed: 17) *VAS of Treatment Expectation and Relief*[37]; *18) Freiburger Ernährungsfragebogen*[38] ; *19) Global Physical Activity Questionnaire (GPAQ)*[39].

The following variables were assessed as exploratory endpoints before and after 12 wk of treatment: 20.) indoleamine-2,3-dioxygenase (IDO)[40] and zonulin[41] in capillary blood, 21.) bile acid[42], human beta defensin 2 (HBD2)[43], gluten[44], and zonulin[45] in stool, 22.) microbiome in stool (Next-generation sequencing, myBioma GmbH).

Safety analysis included adverse events and adverse device effects, device deficiency, laboratory results and aluminum levels.

Statistical analysis

No formal sample size calculation was performed owing to the exploratory pilot study design. Overall, 30 patients were randomized to treatment with either G-PUR® or placebo. Analyses were performed using Statistical Analysis Software (SAS) 9.3 or higher. The Full Analysis Set analysis is provided in this publication including data from all patients who were randomized. Patients were analyzed in the treatment group they were randomized to, regardless of the actual treatment received. For the inferential analysis of the primary endpoint the rate of responders according to SGA was compared in an intention to treat analysis between the two treatment groups using Fisher's exact test. A two-sided significance level of 5% was applied. For all secondary efficacy endpoints, categorical variables were compared between treatment groups using Fisher's exact test. Continuous variables were compared using a Wilcoxon rank-sum test (Mann–Whitney U test). In general, the last available post-randomization assessment during the treatment period were used to compare secondary efficacy parameters between treatment groups. Data were summarized by treatment group and, where appropriate, by visit. Descriptive statistics (number of observations, mean, standard deviation, minimum, median, and maximum) were provided for continuous variables. Frequency counts and percentages were presented for categorical variables.

Five patients who were withdrawn from the study prematurely were not included in this assessment of adherence and efficacy. Logistic regression analysis for parameters *SGA of Relief* and IBS-SSS, HADS, NRS, stool frequency, consistency included only patients with available results for all relevant independent variables (n = 27).

RESULTS

Patient population

We screened 44 patients in order to include 30 trial participants, of whom 14 were randomized into the G-PUR® arm and 16 received placebo (Figure 1). The two study groups were similar regarding their demographic and baseline characteristics but patients in the G-PUR® group had a slightly longer disease duration. The median age of the study population was 34 years (range, 20–73) and 21 of the 30 patients (70%) were women. Baseline patient demographics and concomitant medications are summarized in Table 1, medical history in Table 2. At baseline, analgesic and antipyretic medications were used by two patients (14%) in the G-PUR® arm and 8 patients (50%) in the placebo arm; the use of medicines for functional gastrointestinal disorder was comparable in both groups.

Primary outcome

After 12 wk of treatment the proportion of responders according to the SGA *of Relief* was 21% (n = 3) in the G-PUR® group and 25% (n = 4) in the placebo group (P = 1.0; Table 3).

Secondary outcomes

A between-group difference in *SGA of Relief* was obvious after 4 wk of treatment, with 36% of patients in the G-PUR® group reporting complete or considerable relief, compared to 0% in the placebo group (Figure 2). Consistent with this observation, the median proportion of days with an at least 30% improvement in abdominal pain compared to the patient's worst abdominal pain at baseline was higher in the G-PUR® group (94%) than in the placebo group (83%, P = 0.0353). This was also seen for abdominal-pain response, where 93% of patients (n = 13) in the G-PUR® group were

classified responders, compared with 81% (n = 13) in the placebo group (P = 0.6015). Although not statistically significant, the proportion of BSFS responders was more pronounced in the G-PUR® group. However, the median number of days with diarrhea per week decreased by 2.4 days in the G-PUR® group and by only 0.3 days in the placebo group.

Quality of life as assessed using the SF-12, anxiety and depression evaluated using the HADS, and IBS-SSS scores showed no absolute differences between groups. The significant difference between groups at the end of the study is likely related to the less favorable baseline PCS-12 in the placebo group. Overall, 7/11 patients (64%) in the G-PUR® group and 12/14 patients (86%) in the placebo group reported intake of rescue medication during the trial. In the analysis of perceived stress level, the change in total PSQ score was not different between groups. When score items were analyzed separately, 'tension' was significantly relieved in patients receiving G-PUR® (P = 0.0399 *vs* placebo). Main secondary outcomes are summarized in Table 3.

In the exploratory biomarker analysis, IDO and zonulin levels in capillary blood and levels of bile acid, HBD2, and zonulin in stool were not altered during the observation period. Microbiome studies in stool showed a mild increase in diversity in the G-PUR® group, but not in the placebo group. Although these effects were minor, this finding was further supported by the spatial changes of beta diversity seen in the G-PUR® but not in the placebo group (Figures 3-5).

Safety analysis

G-PUR® was well tolerated throughout the study. Only 2 of the 69 adverse events (AE) in the G-PUR® group, i.e., mild mucosal dryness and mild abdominal distension, were considered treatment-related adverse device events (ADE). With an overall exposure of 805 treatment days in the G-PUR® group, this corresponds to an ADE rate per patient year of 0.9, which was similar to placebo (0.7 per patient year). The AE rate per patient year differed between groups, with 31 events per patient year in the G-PUR® group and 90 in the placebo group. With many of the reported AE related to the patients' IBS symptoms, this large between-group difference in AE frequency may be at least in part

related to the effects of treatment. Because G-PUR® contains alumino-silicates, the release of aluminum has been a potential source of concern. In this study, an elevation in aluminum levels above normal limits was not seen in any of the patients of the entire cohort. In the G-PUR® group, the proportion of patients with aluminum levels below the reference range increased from 14% (n = 2) at baseline to 40% (n = 4) at the end of treatment. In the placebo group, this proportion was 13% (n = 2) at baseline and 0% (n = 0) at the end of treatment.

DISCUSSION

This study provides evidence for the effectiveness and safety of the purified clinoptilolite-tuff product G-PUR® in the treatment of IBS-D. While no consistent change in *SGA of Relief* in response to G-PUR® was demonstrable, the favorable results of G-PUR® were seen in the reduction of cardinal symptoms of IBS-D, i.e., abdominal pain and improvement in stool consistency compared to placebo. This is further supported by symptom improvements over time and lower use of rescue medications in the G-PUR® than in the placebo group. Importantly, the proportion of days with an at least 30% improvement in abdominal pain was significantly higher in the G-PUR® group compared to placebo. The particular attention and patient support in this study by health care professionals and psychological therapists might have contributed to the strong placebo effect and has reduced disease-associated anxiety in both groups. While the PSQ total score improved in the G-PUR® group, it deteriorated in the placebo group, with the between-group difference in change over time trending towards significance (P = 0.0843). This advantage of G-PUR® was driven mainly by the 'tension' subscore, whose absolute change differed significantly between groups (P = 0.0399), and to a lesser extent by the 'joy' and 'demands' subscores.

The comparison of IBS treatment efficacy is generally difficult because there have been only few head-to-head randomized controlled trials (RCT). The fluctuations of IBS symptoms over time and the scale of the placebo effect complicates endpoint assessment at scheduled time points. Hence, our primary endpoint of symptom relief at

week 12 does not necessarily cover the wide range of symptoms associated with IBS-D, and it cannot be used to describe a continuous clinical improvement over the treatment period.

In a clinical trial micro-activation-zeolite improved IBS-associated symptoms of abdominal discomfort with stool frequency and stool consistency to the same extent as placebo, indicating a pronounced placebo effect[10]. A recent randomized trial in 190 IBS patients[46] found some improvement for abdominal pain, discomfort, and IBS severity after an 8-week treatment with small-intestinal-release peppermint oil. However, the main outcomes including abdominal pain response or overall symptom relief were not significant when using endpoints recommended by FDA and EMA. Similarly, another study assessing peppermint oil treatment in IBS patients based on IBS-SSS endpoint did not lead to significant result[47].

In this trial, G-PUR® was administered over a period of 12 wk. The daily dose of 6 g G-PUR® was well tolerated and there were no clinical or laboratory safety signals throughout the study. The overall rate of AE was lower in the G-PUR® group than in the placebo group, and the low ADE rate per patient year was at placebo level. Although G-PUR® is an aluminum-containing substance, no elevation in serum aluminum levels were observed in patients in this trial. This is related to the fact that within the product's mineral phases, aluminum is not mobile but tightly bound, building up the silicate mineral crystal lattice[21]. Interestingly, the proportion of patients in whom aluminum was below the reference range at the end of the study increased in the G-PUR® group. This may also be related to the ability of clinoptilolite to adsorb metal ions in the gastrointestinal tract.

Currently, various pharmacological and non-pharmacological therapeutic interventions are available for the management of IBS-D. The treatment is individualized for the patients' needs and predominant symptoms by their physician, considering the risk-benefit ratio for each strategy. Loperamide, which was used as rescue therapy in the present trial, is often used as first-line agent to treat diarrhea in IBS-D. However, despite its widespread clinical use, it is worth noting that loperamide is not effective against

IBS-associated abdominal pain and bloating[48-50]. Similarly, eluxadoline, a mixed opioid receptor drug, can reduce visceral hypersensitivity and prolong the gastrointestinal transit time, but the effects on abdominal pain relief are modest[51, 52]. In a recent meta-analysis of established traditional therapies in IBS, tricyclic antidepressants are recommended for treatment of abdominal pain, but careful dosing is warranted based on the side-effect profile[53, 54].

Dietary and lifestyle changes constitute an important non-pharmacological approach in treating IBS symptoms. A recent meta-analysis showed that patients receiving a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) in RCTs experienced a statistically significant reduction in pain and bloating compared to patients receiving a traditional diet[55]. Overall, the exclusion of foods high in FODMAP may reduce IBS symptoms and can be recommended to affected patients, but there is still a need for higher-quality evidence to guide management[56]. Similarly, supplements such as vitamin D have shown modest effects compared to placebo[57-59]. PCT has been shown to be an effective sorbent for gluten derived from food sources[27], which could also contribute to its supposed benefit.

In research concerning functional disorders, treatment effects are generally assessed *via* patient-reported outcomes, which renders the objective evaluation difficult. A strength of this study is that it was designed to meet all of the essential methodological quality criteria for functional gastrointestinal research[60], including a randomized, placebo-controlled, double-blind design, the use of the Rome IV criteria for enrolment, the selection of patients with moderate to severe IBS based on the IBS-SSS, the prohibition of a wide range of concomitant medications, a treatment duration of 12 wk, the use of validated symptom scores, and the formal documentation of safety data. Despite the limitation of small sample size, the clinical benefit of PCT could be demonstrated in various clinical meaningful endpoints.

The gut microbiome analysis of the patients revealed a trend towards greater alpha and beta microbial diversity in the treatment group, which has been associated with a healthy gut microbiome and improved symptoms. This change has not been observed

in the placebo group. Larger cohorts would be needed to identify a causal relation to the change in abundance of a single or several bacteria species. A pilot study with 41 patients who received 3g of zeolite or microcrystalline cellulose twice daily showed that zeolite may lower intestinal inflammation of IBS patients. A positive effect on the gut microbiome was in line with our results[10]. Alterations in gut microbiome may impact the intestinal immune, barrier and neuromuscular junction functions, and cause imbalance in the bidirectionally communicating gut-brain axis, however, the exact composition of a healthy microbiome remains unclear[61, 62].

CONCLUSION

In conclusion, this randomized placebo-controlled, double-blind pilot study provides evidence that the PCT product G-PUR® can be safely used over a prolonged period of 12 wk, also in the treatment of patients with IBS-D. A favorable result of G-PUR® was detectable for some symptoms of IBS, i.e., abdominal pain and stool consistency. Further, a lower use of rescue medication in the G-PUR® than in the placebo group, and a trend towards greater microbial diversity generally associated with a healthy gut microbiome was observed.

ARTICLE HIGHLIGHTS

Research background

10

Irritable bowel syndrome with diarrhea (IBS-D) is a highly prevalent chronic gastrointestinal disorder with substantial impact on quality of life. Despite the advance in the available treatment, there is a need for effective therapy options with a favourable safety profile.

Research motivation

Previous studies have shown positive effects of clinoptilolite-tuff G-PUR® in multiple indications, especially for its adsorption capacity for a variety of toxins, heavy metals,

and other undesirable substances. Thus, clinoptilolite-tuff might be an effective therapy in IBS-D.

Research objectives

The primary objective of this clinical investigation was to assess the relief from IBS-D symptoms after a 12-week treatment with G-PUR®. The main secondary objectives were to assess the safety and tolerability of treatment with G-PUR®, the impact of treatment on IBS-related symptoms, quality of life, and additional exploratory parameters including microbiome analysis.

Research methods

We performed a randomized, placebo-controlled, double-blind pilot study on 30 patients with IBS-D. Over a treatment period of 12 wk, 14 patients received 2 g G-PUR® three times daily and 16 patients received placebo. The proportion of responders according to the *Subject's Global Assessment (SGA) of Relief,* validated IBS-D associated symptom questionnaires, exploratory biomarkers and microbiome data were collected and analyzed.

Research results

After 12 wk of treatment, the proportions of *SGA of Relief* responders were comparable in both groups (21% in the G-PUR® and 25% in the placebo group), while after 4 wk of treatment 36% of patients in the G-PUR® group vs. 0% in placebo group reported complete or considerable relief. An improvement in daily abdominal pain, diarrhea-free days, abdominal-pain and stool-consistency response was seen in the G-PUR® group compared to placebo.

Research conclusions

In this randomized, double-blind, placebo-controlled study, the purified clinoptilolite-tuff product G-PUR® demonstrated safety and clinical benefit towards some symptoms of IBS-D, representing a promising novel treatment option for these patients.

Research perspectives

Further research is needed to evaluate clinical efficacy of clinoptilolite-tuff product G-PUR® in larger cohorts.

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