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Profermin® in the treatment of IBS

An internal report on Nordisk Rebalance's open label clinical trial on IBS-D

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ABBREVIATIONS

AE	Adverse events
FSMP	Food for special medical purposes
IBS	Irritable Bowel Syndrome
IBS-D	Irritable Bowel Syndrome with predominant diarrhea
ITT	Intention to treat
Lp299v	Lactobacillus plantarum 299v

ABSTRACT

Background and aim

Profermin® is a food for special medical purposes developed for the dietary management of gastrointestinal diseases. The main ingredient is oats fermented by Lactobacillus plantarum 299v (Lp299v). In two studies, relatively small doses of oats fermented by Lp299v had a positive clinical effect on the flatulence and abdominal pain in patients suffering from irritable bowel syndrome (IBS). The aim of this open label clinical study was to assess i) whether a large daily dose of Profermin® has a clinically significant effect on diarrhea in the IBS subgroup suffering from IBS with predominant diarrhea (IBS-D), and ii) whether the large dose also has a clinically significant effect on other IBS symptoms concomitant to diarrhea.

Material and methods

The study included IBS-D patients of age 18 years or older. No medication interfering with bowel function was allowed. The intervention period with Profermin® was 12 weeks and the daily dose was 250 mL. Prior to the intervention patients registered their baseline symptoms and were instructed to

keep a diary throughout the intervention period describing the development in the severity of each of their symptoms. After completing or prematurely leaving the 12 weeks intervention, the patients were interviewed by the trial nurse, and based on baseline symptoms and the patients' diary entries, the patients categorized the effect on each of their symptoms as “very good”, “good”, “limited” or “no (effect)”. A clinically significant effect was defined as an effect characterized by the patient as very good or good. Patients were instructed to report adverse events (AE).

Results

17 IBS-D patients were included in the study. 8 (47 %) were females. All patients except two suffered from one or more of the following additional IBS symptoms: flatulence, abdominal pain, bloating and fatigue. In intention to treat (ITT) analyses a clinically significant effect on the diarrhea symptom was experienced by 13 patients (76 %) (95 % CI: 52 %-91 %). The clinically significant effect on other concomitant IBS symptoms varied from 20 % - 100 %. However, (11/11) 100 % (95 % CI: 77 % - 100 %) of the patients who obtained a significant clinical effect on diarrhea also experienced a significant clinical effect on their concomitant IBS symptoms. No AE were reported.

Conclusion

Profermin® is safe and induces a clinically significant effect on diarrhea in IBS. Profermin® also induces a significant clinical effect on other IBS symptoms in patients who obtain a clinically significant effect on diarrhea.

INTRODUCTION

Irritable bowel syndrome (IBS) is a wide spread disease in the industrialized world affecting 10 % of the population in Europe and 14 % in USA[1, 2]. IBS is an exclusion diagnosis with a wide range of symptoms including the 3 main symptoms, according to which IBS may be divided into 3 subcategories: i) constipation (IBS-C), ii) diarrhea (IBS-D) and iii) alternating constipation and diarrhea (IBS-A). No generally acknowledged treatments are available. There is an unmet need for IBS treatments as i) the symptoms can be severe and strongly reduce quality of life and ii) the patients' many unsuccessful contacts with the health system are costly.

It has been demonstrated in two studies that oats fermented by Lactobacillus plantarum 299v (Lp299v) have a positive clinically effect on flatulence and abdominal pain in IBS patients[3, 4]. However, the studies showed no positive effects on diarrhea in IBS. This might be due to the use of relative low doses of fermented oats and Lp299v ($2x10^{10}$ cfu and 3.6 g fermented oats).

Profermin® is a food for special medical purposes (FSMP) and consists of fermented oats, Lp299v, barley malt, lecithin (phosphatidylcholine) and water. The primary aim of the present study was to investigate the effect of the dietary management on diarrhea in IBS with 250 mL daily doses of Profermin®. 250 mL Profermin® contains about 10 times higher amounts of fermented oats and Lp299v compared to the daily amounts used in the two previous studies. Also, the aim was to elucidate the effect on additional IBS symptoms in patients with IBS-D.

MATERIAL AND METHODS

The study was conducted between 2009 and 2011 on a population of 17 IBS-D patients. It was an open label study, in which the dietary management with a 250 mL daily dose of Profermin® was tested on diarrhea and concomitant symptoms in IBS.

Patient recruitment; inclusion and exclusion

Dietary management of gastrointestinal diseases with FSMPs was described on the homepage of Nordisk Rebalance, and patients who were interested in participating in a study with a new FSMP were encouraged to contact the study nurse by e-mail or by phone. Patients were eligible if they had been diagnosed with IBS by their GP or by a gastroenterologist, if they were 18 years or above and if their primary IBS symptom was diarrhea. Treatment with antibiotics 14 days before inclusion and during the study was not allowed. Similarly, systemic treatment with steroids or medication affecting the bowel function was not allowed. Included patients stated where and when they had been diagnosed with IBS and gave informed consent. The patients were instructed to register their baseline symptoms and to keep a diary on i) the development in their symptoms, ii) their intake of Profermin® and iii) any experienced AE. It was the patient's own decision how the development of the symptoms was described in the diary.

Reasons for exclusion after inclusion were withdrawal of consent, protocol violations, side effects rendering discontinuation necessary and medical treatment with antibiotics or other drugs interfering with the gastrointestinal function.

Outcome measures

The primary endpoint was to assess whether a daily intake of 250 mL Profermin® can induce a clinically significant positive effect on diarrhea in IBS. The secondary endpoint was to assess whether the daily intake of Profermin® has a clinically significant positive effect on IBS symptoms additional to diarrhea in each patient.

Based on the baseline symptoms and diary entries the patients categorized the effect on each of their symptoms as “very good”, “good”, “limited” or “no (effect)”. A clinically significant positive effect

was defined as an effect characterized by the patient as "very good" or "good". No clinically significant effect was defined as an effect characterized by the patient as "limited" or "no (effect)".

Description of the intervention

Profermin® is manufactured as previously described[5]. Profermin® is packed in 250 mL cartons. The product is tested for pH and colony forming units (CFU) of Enterobacteriaceae, yeasts/moulds and Lp299v. The pH must be between 3.6 and 4.2 and the CFU of Enterobacteriaceae, yeasts/moulds must each be less than 100/mL. The CFU of L. plantarum is about 10^9/mL. The energy content of 100 mL Profermin® is 58 kcal (240 kJ), from 1.6 g protein, 9.8 g carbohydrate and 0.9 g fat. The daily Profermin® dose was 250 mL. The patients were instructed to drink the Profermin® as the first meal of the day and to register the intake in their diary on a daily basis.

Ethics, approvals and patient consent

Since Profermin® is a FSMP and not a medicinal product, no authorization by the Danish Medicines Agency was required. All patients gave informed consent according to the Helsinki declaration. The study was not registered on www.clinicaltrials.gov since this was not required in relation to FSMP trials at the time when the study was initiated. The trial has been cleared with The Ethical Committees of the Copenhagen Region.

Statistical analysis

The principle of intention to treat (ITT) was used in the data analysis. Data for patients who dropped out or were excluded were therefore included in the analysis using the principle of last value carried forward - i.e. the value determined by the patient in the interview with the trial nurse shortly after the premature termination of the patient's participation in the study. Confidence intervals were calculated according to the modified Wald method.

RESULTS

The patients

41 IBS patients were screened and 17 IBS-D patients – 8 females - were included in the study. All patients except two (M1 and M4) suffered from one or more of the following additional IBS-D symptoms: Flatulence, abdominal pain, bloating and fatigue (Table 1). Sex, ages, symptoms and mean ages are shown in Table 1. Based on the interviews compliance was estimated to be > 95 %. Three patients experienced no or only a limited effect and dropped out after 4 weeks of intervention.

Patient		Effect on	Effect on other IBS symptoms				*Weeks in*
No.	Age	diarrhea	Flatulence	Abdominal pain	Bloating	Fatigue	*treatment*
W1	20	+++		+++			12
W2	21	+++	+++	+++		+++	12
W3	20	+		+	+		4
W4	44	++			++		4
W5	78	+++				+++	12
W6	58	+++		+++			12
W7	64	0		0	0		4
W8	24	0		0	0		4
M1	75	+++					12
M2	65	+++				+++	12
M3	50	+++				+++	12
M4	65	++					12
M5	48	+++				+++	12
M6	45	+		+	+		12
M7	18	+++				+++	12
M8	32	+++		+++			12
M9	54	+++		+++		+++	12

Table 1 Clinical effect on IBS symptoms after intervention with Profermin in 8 female (W1, W2 etc.) and 9 male (M1, M2 etc.) IBS patients

Mean age (years): Women 41.1, SD +/- 23.2; Men (years) 50.2 SD +/- 17.6

+++ = very good effect; ++ = good effect; + = limited effect; 0 = no effect

Primary endpoint

11 patients experienced a “very good effect” on diarrhea and 2 experienced a “good effect”, i.e. (13/17) 76 % (95 % CI: 52 %-91 %) experienced a clinically significant effect on diarrhea. Two patients experienced a “limited effect” and 2 patients “no effect”, i.e. (4/17) 24 % (95 % CI: 9 %-48 %) experienced no significant clinical effect on diarrhea.

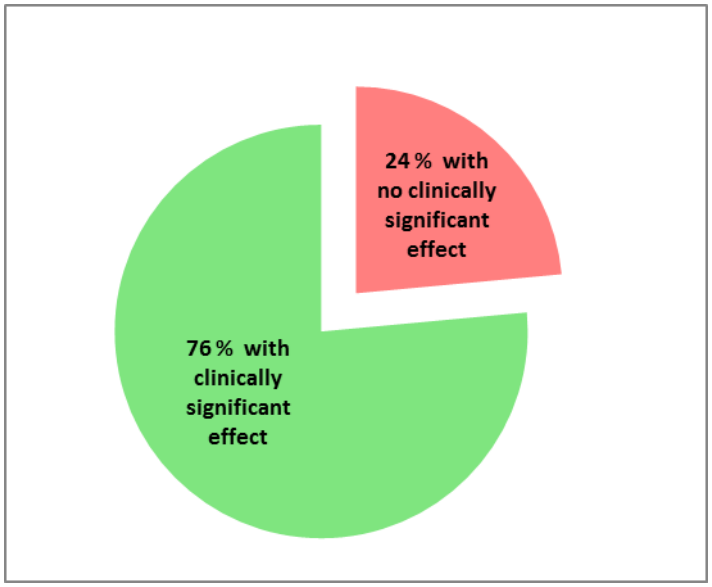

Figure 1. Effect on diarrhea in ITT analysis; percentages of clinically significant significant effect and no clinically significant effect.

Secondary endpoint

The analysis of the effect of Profermin® intervention on IBS symptoms concomitant to diarrhea may be carried out using two different approaches. When the “effect on other IBS symptoms” in Table 1 is analysed vertically, treatment effects are (1/1) 100 % on flatulence, (5/9) 56 % on abdominal pain, (1/5) 20 % on bloating and (7/7) 100 % on fatigue. However, a most interesting approach is to analyse Table 1 horizontally. In this analysis, patients who experienced a clinically significant effect are separated from patients who experienced no clinical effect. Following, patients of each group are clustered (Table 2, A and B).

A	Patient	Effect on	Effect on other IBS symptoms			
	No.	diarrhea	*Flatulence*	*Abdominal pain*	*Bloating*	*Fatigue*
	W1	+++		+++		
	W2	+++	+++	+++		+++
	W4	++			++	
	W5	+++				+++
	W6	+++		+++		
	M1	+++				
	M2	+++				+++
	M3	+++				+++
	M4	++				
	M5	+++				+++
	M7	+++				+++
	M8	+++		+++		
	M9	+++		+++		+++

B	Patient	Effect on	Effect on other IBS symptoms			
	No.	diarrhea	*Flatulence*	*Abdominal pain*	*Bloating*	*Fatigue*
	W3	+		+	+	
	W7	0		0	0	
	W8	0		0	0	
	M6	+		+	+	

Table 2 A and B. Patients grouped according to significant clinical treatment effect on diarrhea (A) or no clinical treatment effect on diarrhea (B). '+++ = very good effect; ++ = good effect; + = limited effect; 0 = no effect

11 of the 13 patients who experienced a significant clinical effect on diarrhea had other concomitant IBS symptoms (Table 2A). Of the 11 patients (11/11) 100 % (95 % CI: 70 % - 100 %) experienced a significant clinical effect on all their concomitant IBS symptoms. Correspondently, of the four patients who experienced no significant clinical effect on diarrhea (4/4) 100 % (95 % CI: 45 % - 100 %) experienced no significant clinical effect on their concomitant IBS symptoms (Table 2B).

Descriptions of exclusions and drop outs

No patients were excluded, but 4 patients dropped out after 4 weeks due to unsatisfactory effect.

Safety and tolerability

No AE's were reported.

DISCUSSION

In this study, we showed that 76 % (95 % CI: 52 %-91 %) of the IBS-D patients treated with Profermin® experienced a clinically significant effect on diarrhea. Interestingly, we also observed a significant clinical effect on concomitant IBS symptoms in patients where a significant clinical effect was obtained on diarrhea. Furthermore, no significant clinical effect on concomitant IBS symptoms was observed in patients where Profermin® showed no clinically significant effect on diarrhea. These results suggest that multiple IBS symptoms in these patients may have a common cause.

Three out of four patients who did not respond to Profermin® decided to drop out after 4 weeks. This reaction is understandable since additional 8 weeks with intervention seemed to be futile.

Two clinical studies by Nobaek et al. and Niedzielin et al.[4, 5] show clinical effect of fermented oats and Lp299v on flatulence and abdominal pain in IBS. No clinical effect was shown on diarrhea. A predominant symptom of the inflammatory bowel disease ulcerative colitis is diarrhea. Since we have shown clinical effect in ulcerative colitis using Profermin® containing high doses of fermented oats and Lp299v[6, 7], we decided to study the effect on IBS-D of dietary treatment using significantly larger daily doses of fermented oats and Lp299v compared to the amounts used in the two IBS studies. The daily dose of 250 mL of Profermin® used in this study provides about 10 times the daily amount used by Nobaek et al. and Niedzielin. Our results strongly support that fermented oats and Lp299v have a clinically significant effect in IBS in particular in relatively large doses.

No AE were observed, which support results concerning safety from other clinical studies with Profermin®[6, 7].

This study has limitations in terms of a relatively small number of patients and an open label design without a control product.

Conclusion

Profermin® is safe, well tolerated and induces a clinically significant effect on diarrhea in IBS. Furthermore, Profermin® has a clinical significant effect on concomitant IBS symptoms in IBS patients who obtain a clinically effect on diarrhea.

Conflicts of interests:

Aleksander Krag has acted as consultant to Nordisk Rebalance. Hans Israelsen, Jørgen Villumsen and Bjørn von Ryberg are employees of Nordisk Rebalance.

Author contributions:

Hans Israelsen and Jørgen Villumsen conceived and performed the study and developed the overall design. Hans Israelsen, Bjørn von Ryberg and Aleksander Krag drafted the paper and all authors participated in the critical revision for important intellectual content and approved the final version.

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