Clinical Follow-up of 96 Patients Affected by Irritable Bowel Syndrome Treated with a Novel Multi-strain Symbiotic

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Abstract

Irritable bowel syndrome (IBS) is a very common chronic functional disorder of the lower gastrointestinal tract. It typically includes chronic and/or recurrent abdominal pain/discomfort, which can be relieved by defecation, and alteration of stool form or frequency.

Probiotics have been proposed as a therapeutic approach in several pathologic conditions of the gastrointestinal tract associated with dysbiosis, including IBS.

In this observational study we investigated the efficacy of a symbiotic formulation (SynGut™), composed of four probiotic strains and the prebiotic inulin, in the treatment of adult subjects affected by IBS. Seventy-one out of 96 patients reported an improvement of IBS symptoms, 19 of them reporting a substantial improvement. Two patients discontinued the treatment after a few days because of worsening of symptoms, but no serious adverse effects were reported. In the subgroup of patients (n = 18) who underwent faecal calprotectin dosage, this marker of gut inflammation was significantly decreased (127,3 vs 78,6, p < 0,0001) after two months of treatment respect to baseline. Our data confirm that this multi-strain symbiotic is well tolerated, and support the hypothesis that this symbiotic could improve IBS symptoms.

Further studies and randomized trials with larger patient populations are needed to confirm this positive effect with particular focus on strain-specific outcomes, usefulness of concomitant prebiotic and probiotic supplementation, dose optimization, and other relevant manufacturing specifications.

Keywords: Irritable bowel syndrome; Treatment; Probiotics; Prebiotics; Symbiotics

1. Introduction

Irritable bowel syndrome (IBS) is a chronic functional disorder of the lower gastrointestinal tract. It is one of the most common gastrointestinal conditions worldwide, predominantly affecting younger people (symptoms frequently date back to childhood) and women (female/male ratio of 2:1) (Ford
and Talley 2012). Its prevalence, according to a systematic review, ranges from 7% in South East Asia to 21% in South America; in Europe, it is estimated that IBS affects around 12% of the population (Lovell and Ford 2012).

It typically includes chronic/recurrent abdominal pain/discomfort, which can be relieved by defecation, and alteration of stool form or frequency. Abdominal bloating can also be associated (Ford and Talley 2012).

A patient without lower gastrointestinal alarm symptoms (which include weight loss, abdominal mass, rectal bleeding, heme positive stools or iron deficiency anemia, family history of colon cancer or age >50 years with no previous colon cancer screening), who shows longstanding typical symptoms of IBS can be diagnosed on clinical grounds with routine laboratory tests without the need of invasive investigative techniques (Ford and Talley 2012). Symptoms-based diagnostic criteria, known as “Rome criteria”, have been developed for this purpose and updated in 2006 (Longstreth et al. 2006) (Table 1). These criteria divide IBS patients according to the predominant stool form: patients are classified as constipation-predominant (IBS-C), diarrhea-predominant (IBS-D), or mixed (IBS-M). It must be underlined that not every patient can be classified according to these criteria (IBS-U, unclassified) and that stool form can change over time (Longstreth et al. 2006).

Table 1 Rome criteria for diagnosis of IBS (Longstreth et al. 2006).

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<tr>
<th>Diagnostic Criteria* for Irritable Bowel Syndrome</th>
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<td>Recurrent abdominal pain or discomfort** for at least 3 days per month in the last 3 months associated with 2 or more of the following:</td>
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<td>1. Improvement with defecation</td>
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<td>2. Onset associated with a change of frequency of stool</td>
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<td>3. Onset associated with a change in form (appearance) of stool</td>
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*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

**Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation for subject eligibility.

Quite often, as diagnosis remains uncertain, patients are referred to allergy clinics for a suspected food allergy/intolerance. Sometimes, IBS symptoms begin suddenly after a gastroenteritis and is therefore termed post-infectious IBS (PI-IBS) (Schwille-Kiuntke et al., 2011). PI-IBS has been reported after Campylobacter, Salmonella and Shigella infections of the gastroenteric tract (Spiller 2007). Biopsy specimens of the intestinal mucosa, obtained during a Campylobacter jejuni infection, showed an inflammatory infiltrate, with intraepithelial lymphocytes, calprotectin-positive macrophages and increase of enterochromaffin cells which in most cases persisted for the following six months (Spiller, 2007; Spiller et al., 2000). In these cases, it has also been documented an increase of interleukin (IL)-1β mRNAs and of mucosal permeability.
Recent studies have demonstrated mast cell infiltration in the colic mucosa, with degranulation in proximity of mucosal nerve terminations. This could contribute to abdominal pain in IBS patients (Barbara et al., 2004).

A direct association between IBS symptoms and psychological stress or psychiatric conditions has been observed (Mayer, Craske, and Naliboff 2001); given the frequent responsiveness of symptoms to neurotrophic therapies, IBS is often referred to as a "brain-gut disorder", although its pathophysiology remains uncertain (Mayer and Paulley 2008).

In a subject affected by IBS, accepting reported symptoms and distress as real while not minimizing them as a manifestation of anxiety and somatization, usually facilitates the establishment of a positive patient–doctor relationship and the patient’s compliance to proposed therapies (Mayer and Paulley 2008).

Currently available drugs for the management of IBS usually target the management of individual symptoms, such as constipation, diarrhea, and abdominal pain (Mayer and Paulley 2008).

The gut microbiota is a metabolically active complex ecosystem that plays an important role in health and in the pathogenesis of several diseases, not limited to the gastrointestinal tract (Whelan and Quigley 2013). Its composition varies significantly among individuals, being influenced by several factors including age, diet, and disease (Claesson et al. 2011). An increasing number of diseases is being associated to dysbiosis, from gastrointestinal diseases such as IBS and inflammatory bowel disease to extra-intestinal diseases such as obesity and diabetes (Shanahan 2013).

Probiotics are live micro-organisms which produce a health benefit when administered in certain amounts to the host (Sanders et al. 2013). Prebiotics are dietary non-digestible ingredients that selectively stimulate the growth and activity of one or a limited number of bacterial species of the intestinal flora. Symbiotic is a combination of probiotic and prebiotic. This formulation allows an increase in the survival of the probiotic organisms, because it immediately makes its substrate available for fermentation (Manzotti, Heffler, Fassio, et al. 2014; Manzotti, Heffler, and Fassio 2014).

In recent years, probiotics have been investigated in several pathologic conditions as an approach to modulate the gastrointestinal microbiota (O’Mahony et al. 2005; Rousseaux et al. 2007; Meltzer et al. 2004; Wald and Rakel; Astegiano et al. 2008; Mitsuyama and Sata 2008; Seksik et al. 2008; Guandalini, Cernat, and Moscoso 2014).

In this observational study we investigated the efficacy of a symbiotic formulation (SynGut™, Allergy Therapeutics Italia, Milan, Italy), composed of four probiotic strains (Bifidobacterium lactis W51, Lactobacillus acidophilus W22, Lactobacillus plantarum W21, Lactococcus lactis W19) and the prebiotic inulin, in the treatment of adult subjects affected by IBS.
2. Materials and Methods

The aim of this observational study was to evaluate the effect of the administration of a novel symbiotic multi-strain mixture for the management of IBS.

An industrial combination of *Bifidobacterium lactis* W51 ≥ 3.3x10^8 UFC/sachet, *Lactobacillus acidophilus* W22 ≥ 10^9 UFC/sachet, *Lactobacillus plantarum* W21 ≥ 3.3x10^8 UFC/sachet, *Lactococcus lactis* W19 ≥ 3.3x10^8 UFC/sachet and inulin 0.375 gr/sachet (*SynGut™*, marketed by Allergy Therapeutics Italia, Milan, Italy; manufactured by Winclove Probiotics, Amsterdam, The Netherlands) was used in this study. This content is in agreement with the guidelines of the Italian Ministry of Health on probiotics (Italian Ministry of Health, 2013).

A total of 96 adult subjects (54 females, mean age 34.8 years, range) affected by IBS according to Rome criteria (Longstreth et al. 2006), attending a single outpatient allergy clinic for a suspected food allergy/intolerance for the period of April 2013 to December 2015 were enrolled in the study. Each subject used 1 sachet per day for a period of two months. Patients were instructed to record improvement, persistence and/or worsening of IBS symptoms such as diarrhea, constipation, bloating, and abdominal pain/discomfort during the study period.

A follow-up evaluation took place at the end of the two-month period, and patients underwent an oral interview during which they were asked if they experienced worsening, no significant improvement, partial improvement or substantial improvement of their IBS symptoms.

In a subgroup of 18 patients, faecal calprotectin has been measured before and after symbiotic supplementation as a marker of gut inflammation (Däbritz, Musci, and Foell 2014). Statistics were conducted using Excel Microsoft Office.

3. Results

Of the 96 subjects evaluated, 94 took the symbiotic formulation once daily for two months, as the schedule prescribed, without reporting any adverse effect. Subjective evaluation of IBS symptoms after two months of *SynGut™* supplementation in our study population is showed in Figure 1.

Seventy-one patients reported an improvement of IBS symptoms, with 19 of them reporting a substantial improvement. Two patients discontinued the treatment after a few days because of worsening of symptoms, but no serious adverse effects were reported.

In the subgroup of patients (*n = 18*) who underwent faecal calprotectin dosage, this marker of gut inflammation was significantly decreased (127.3 vs 78.6, *p < 0.0001*) after two months of *SynGut™* supplementation in respect to the baseline (Figure 2).
**Fig. 1.** Subjective evaluation of IBS symptoms after 2 months of SynGut™ treatment.

**Fig. 2.** Faecal calprotectin dosage at baseline and after 2 months of SynGut™ treatment.
4. Discussion

Bacterial fermentation has been associated with many IBS symptoms such as flatulence, abdominal distension, and bloating. Moreover, qualitative changes in the microbiota have been described in IBS, but the contribution of the microbiota to the pathogenesis of IBS is not completely understood (Ford, Quigley, et al. 2014).

Nonetheless, recent studies have brought a greater understanding of probiotics mechanism of action in IBS. Some probiotics have considerable metabolic activity, including: capability of fermentation of nondigested carbohydrates and their conversion into short-chain fatty acids, modulation of the inflammatory response to some enteropathogens, vitamin synthesis and deconjugation of bile salts (Whelan and Quigley 2013). It has been demonstrated that some probiotics are capable of producing and secreting neurotransmitters and neuromodulators that modify some gastrointestinal functions, such as motility or visceral sensation. Finally, they can also modulate inflammation and enhance mucosal barrier function (Whelan and Quigley 2013).

Use of probiotics in patients affected by IBS has been investigated by several Authors (Moayyedi et al. 2010)(Kajander et al. 2005)(Kim et al. 2003)(Brigidi et al. 2001)(Brenner et al. 2009)(Whorwell et al. 2006), with encouraging results. A recent systematic review on the management of IBS by the Task Force on the Management of Functional Bowel Disorders of the American College of Gastroenterology (Ford, Moayyedi, et al. 2014) concluded that probiotics are effective in reducing IBS symptoms, bloating, and flatulence. In the same review, no recommendations were made regarding the use of prebiotics and symbiotics, due to the low number of trials available (2 for a total of 198 patients).

*Lactobacillus plantarum* (*L. plantarum* v299) has been tested in a recent clinical trial in patients affected by IBS; a four week treatment provided effective symptoms relief, with particular efficacy on bloating and abdominal pain (Ducrotté, Sawant, and Jayanthi 2012).

In the context of the same disease, *Lactobacillus acidophilus* (*L. acidophilus* SDC 2012, 2013) was associated with reduced scores for abdominal pain and discomfort after a four week treatment (Sinn et al. 2008).

At least two clinical trials assessed the efficacy of *Bifidobacterium lactis* in the management of IBS. In the first trial, *B. lactis* DN-173 010 was demonstrated to improve symptoms and gastrointestinal transit in 34 patients who were treated for four weeks (Agrawal et al. 2009). In the second trial, a *B. lactis*-enriched yoghurt, consumed twice daily for 8 weeks, was shown to improve symptoms in a group of 130 patients (Min et al. 2012).

In this observational study, a four-week dietary supplementation of *SynGut™* multi-strain symbiotic, composed of *Bifidobacterium lactis* W51, *Lactobacillus acidophilus* W22, *Lactobacillus plantarum* W21, *Lactococcus lactis* W19 and inulin, has been associated with an improvement of symptoms, with respect to the baseline, in 71 of the 96 adult IBS patients (Figure 1). Of these, 19 reported a substantial improvement, while 52 reported a partial improvement. Twenty-three
patients reported no improvement, while only 2 patients discontinued therapy after a few days because of a worsening of IBS symptoms (mainly constipation). No serious adverse effects were reported.

Faecal calprotectin dosage was performed to assess gut inflammation in a subgroup of the patients. In these subjects, faecal calprotectin was significantly decreased after two months of SynGut™ supplementation with respect to the baseline (Figure 2).

Our data, obtained from an observational study of 96 adult patients, confirms that the multi-strain symbiotic, composed of Bifidobacterium lactis W51, Lactobacillus acidophilus W22, Lactobacillus plantarum W21, Lactococcus lactis W19 and inulin, is well tolerated and supports the hypothesis that this symbiotic improves IBS symptoms. An increase of dosage or duration of the supplementation could be taken into account, at least for those patients who reported a partial improvement of symptoms with the standard dosage of one sachet/day for two months. As far as we known, possible explanation for the group of 23 patients who did not report any significant improvement of symptoms rely on the fact that IBS is multifactorial syndrome and that changes in the microbiota are just one of the involved pathogenic mechanisms.

The main limitations for this study include observational design without a control group and the lack of a standardized tool and/or scoring system for subjective evaluation of symptoms. Further studies and randomized trials with larger patient populations are needed to confirm this positive effect with particular focus on strain-specific outcomes, usefulness of concomitant prebiotic and probiotic supplementation, dose optimization, and other relevant manufacturing specifications.

Conflict of Interests

Filippo Fassio is a medical consultant for Allergy Therapeutics Italia s.r.l; Renato Rossi received consultancy fees from Allergy Therapeutics Italia s.r.l.

References


Seksis, Philippe, Xavier Dray, Harry Sokol, and Philippe Marteau. 2008. "Is There Any Place for Alimentary Probiotics, Prebiotics or Synbiotics, for Patients with Inflammatory Bowel Disease?" Molecular nutrition & food research 52(8):906–12.


http://dx.doi.org/10.1097/MOG.0b013e32835d7bba

http://dx.doi.org/10.1111/j.1572-0241.2006.00734.x