

Saccharomyces boulardii in Maintenance Treatment of Crohn's Disease

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The possible role of *Saccharomyces boulardii*, a nonpathogenic yeast with beneficial effects on the human intestine, in the maintenance treatment of Crohn's disease has been evaluated. Thirty-two patients with Crohn's disease in clinical remission (CDAI < 150) were randomly treated for six months with either mesalamine 1 g three times a day or mesalamine 1 g two times a day plus a preparation of *Saccharomyces boulardii* 1 g daily. Clinical relapses as assessed by CDAI values were observed in 37.5% of patients receiving mesalamine alone and in 6.25% of patients in the group treated with mesalamine plus the probiotic agent. Our results suggest that *Saccharomyces boulardii* may represent a useful tool in the maintenance treatment of Crohn's disease. However, in view of the product's cost, further controlled studies are needed to confirm these preliminary data.

KEY WORDS: Crohn's disease; mesalamine; probiotics; relapses; *Saccharomyces boulardii*.

Crohn's disease is a chronic disorder with a high tendency to relapse. Most of the published controlled trials, as pointed out in two meta-analyses (1, 2), showed that 5-aminosalicylic acid (5-ASA, mesalamine) is significantly more effective than placebo in preventing relapses of the disease. However, negative results have also been reported (3), and all in all, clinical recurrences of Crohn's disease during maintenance treatment with mesalamine range from 28% to 34% at 6 months and from 34% to 58% at 12 months (3, 4). Therefore prevention of relapses remains a major issue in the treatment of Crohn's disease. Crohn's disease patients have an altered intestinal flora (5), and antimicrobial agents have been employed not only to treat complications arising from bacterial colonization (abscesses, fistulas, etc), but also to treat the disease itself (6, 7). Enteric flora can

be also modified by administration of microorganisms endowed with "beneficial" intestinal effects, the so-called probiotics (8).

Saccharomyces boulardii is a nonpathogenic yeast, reportedly able to protect the intestine against *Clostridium difficile* and cholera toxins (9, 10), clinically effective in preventing antibiotic-induced diarrhea (11), diarrhea associated with tube-feeding in critically ill patients (12), and recurrence of *Clostridium difficile* infection (13). In a pilot study, a preparation of *Saccharomyces boulardii* was found superior to placebo in promoting reduction of both frequency of bowel movements and Best index in a small group of patients with mildly active Crohn's disease (14).

The aim of the present study was to assess the possible therapeutic benefits of *Saccharomyces boulardii* in the maintenance treatment of inactive Crohn's disease.

MATERIALS AND METHODS

Thirty-two patients (20 men and 12 women) ages 23–49 were studied. Eligibility criteria were a firmly established diagnosis of Crohn's disease of the ileum, colon, or both obtained by endoscopic, radiological, and histological crite-

Manuscript received August 9, 1999; accepted December 30, 1999.

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TABLE 1. CHARACTERISTICS OF STUDY PATIENTS

	Group A	Group B
Sex (M/F)	9/7	11/5
Age (yr, range)	23-48	30-49
Disease duration (yr; mean \pm SD)	6.2 \pm 4.0	7.0 \pm 3.8
Disease location		
Ileum	5	4
Colon	1	0
Ileum + colon	11	12
Previous bowel resection	4	3
Duration of remission phase (weeks; mean \pm SD)	32 \pm 12	34 \pm 16
CDAI at study entry (mean \pm SD)	68 \pm 30	70 \pm 34

ria within the previous year, in remission. Remission was defined as Crohn's disease activity index (CDAI) <150 for at least three months.

Patients were excluded if they had Crohn's disease localized elsewhere, fistulas, active perianal or extraintestinal disease, allergy to salicylates or if they had been taking steroids during the previous month or immunosuppressive agents during the previous three months. Pregnant or lactating women were also excluded.

After giving informed consent, the patients were randomly allocated to one of the following maintenance treatments for six months: Group A (16 patients)—mesalazine 500 mg in a sustained-release preparation in ethylcellulose microgranules (Pentasa), two capsules three times a day or group B (16 patients)—*Saccharomyces boulardii* 500 mg two capsules in the morning + Pentasa 500 mg two capsules twice a day. Patients were seen at entry and after three and six months of treatment (or earlier if symptoms worsened) and CDAI was calculated. A clinical relapse was defined as CDAI > 150 with an increase of 100 points over the baseline values for more than two weeks. Statistical analysis was performed by Fisher's exact test.

RESULTS

All patients completed the study without reporting any side effects. The two treatment groups were found homogeneous as for gender, age, disease location, and history of previous bowel resection (Table 1). Clinical relapses at six months were observed in 6 of the 16 patients on standard mesalazine maintenance and in 1 of the 16 patients receiving also *Saccharomyces boulardii*. The difference is statistically different ($P = 0.04$).

DISCUSSION

In the present trial clinical relapses of Crohn's disease were observed to a significantly lesser extent in patients on maintenance treatment with mesalazine plus *Saccharomyces boulardii* (6.25%) than in subjects receiving mesalazine alone (37.5%). It

might be argued that in our study the rate of clinical recurrences of Crohn's disease at six months with mesalazine is higher than that reported by others (3, 4). On the other hand, it has been pointed out that relapses are more frequent in some subgroups of subjects, such as patients with a disease located in both ileum and colon, and with no previous ileal resection (4), who actually represent the majority of our study population (see Table 1). *Saccharomyces boulardii* is a nonpathogenic yeast that exerts trophic effects on the human intestinal mucosa (15), triggers endoluminal release of secretory IgA (16), and reduces antibiotic-induced and *Clostridium difficile*-associated diarrhea (9, 11, 17). *Saccharomyces boulardii* has similarities to another yeast, *Saccharomyces cerevisiae*, and, interestingly, antibodies against *Saccharomyces cerevisiae* (ASCA) are considered highly specific for Crohn's disease (18) and have been indicated as a possible subclinical marker of the disease in families (19).

The exact relationship (if any) between the presence of ASCA in Crohn's disease and the current, favorable results observed with *Saccharomyces boulardii* in maintaining the disease in remission needs to be further investigated. It must be pointed out that the clinical benefits of *Saccharomyces boulardii* administration were not represented by a mere reduction in diarrhea (a rather predictable effect with a probiotic), but also by an improvement in the other clinical parameters included in the CDAI Index (abdominal pain, general well being, hematocrit levels, etc). The product is well tolerated but is comparatively expensive and is not reimbursed by national health systems. Before advising routine use of *Saccharomyces boulardii* in the maintenance treatment of Crohn's disease, it is therefore mandatory to further confirm the present, preliminary data in larger, controlled clinical trials.

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