A meta-analysis of the benefit of probiotics in maintaining remission of human ulcerative colitis: evidence for prevention of disease relapse and maintenance of remission

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Abstract

Introduction: Probiotics are living microorganisms that, upon ingestion in specific numbers, exert health benefits beyond those of basic nutrition. They are used for preventing relapse of ulcerative colitis but there is not enough evidence to prove their effectiveness. The aim of the study was to evaluate the efficacy of probiotics in preventing relapse of ulcerative colitis and compare their efficacy with mesalazine as a standard treatment for ulcerative colitis.
Material and methods: PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched for studies investigating the efficacy of probiotics in maintaining remission of ulcerative colitis. Relapse rate was the key outcome of interest. Data were searched within the time period of 1966 to January 2008.
Results: Two controlled trials which determined the efficacy of probiotics and 4 which compared the efficacy of probiotics with mesalazine in preventing relapse of ulcerative colitis met our criteria and were included in the meta-analysis. Pooling of 2 trials for the efficacy of probiotics yielded a significant odds ratio of 0.0269 [95% confidence interval (CI) 0.0049-0.1478, P<0.0001). The odds ratio for 4 studies which compared the efficacy of probiotics with mesalazine was 0.99 (95% CI 0.67-1.48, P=0.9419), a non-significant odds ratio.
Conclusions: Probiotics are effective in maintaining remission and their effect in preventing relapse is comparable with mesalazine.

Key words: ulcerative colitis, probiotics, maintaining remission, relapse, mesalazine, meta-analysis.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory process, which diffusely affects the superficial mucosa of the colon [1]. Although the aetiology of UC is unknown, genetic and environmental factors are thought to be involved in the pathophysiology of UC [2-6]. The role of intestinal microorganisms in inflammatory bowel disease cannot be ignored. It has been found that inflammation is more frequent in areas with the highest bacterial concentration and in active UC viable enteric bacteria invade

mucosal ulcers, which results in fistula. A germ-free environment attenuates or prevents inflammation in many transgenic or knockout mutant murine models of colitis [7]. Thus, change of the luminal contents with antibiotics or probiotics may be a potentially effective therapeutic option [8, 9]. Our recent meta-analysis studies demonstrated the effectiveness of antibiotics in inducing remission in UC [10] and Crohn's disease (CD) [11] and probiotics in the management of pouchitis [12] but failed to demonstrate the efficacy of probiotics in maintaining remission and preventing clinical and endoscopic recurrence in CD [13].

Probiotics are living microorganisms such as lactic acid bacilli, *Lactobacillus*, *Bifidobacterium*, *Escherichia coli Nissle* 1917, *Clostridium butyricum*, *Streptococcus salivarius* thermophilus, and the nonpathogenic yeast *Saccharomyces boulardii*. Classically, the natural history of UC includes periods of disease flare-up and remission, and treatment in UC is directed towards inducing and maintaining remission of symptoms and mucosal inflammation. Once remission is achieved with any of the therapeutic schemes available, up to 70% of the patients given no treatment are expected to relapse within a 1-year period [14, 15]. Aminosalicylates are well established for maintaining remission in patients with UC [16] but their use was limited by side effects. Currently, probiotics are suggested for maintaining remission in UC and preventing relapse of inactive disease [14, 17]. There have been no reports of severe adverse events with the use of probiotics in humans in the context of clinical trials [18].

Because of the potential benefits and safety of probiotics, we considered performing a meta-analysis of the efficacy of probiotics in preventing relapse and comparing the efficacy of them with mesalazine as a standard treatment for maintaining remission in patients with UC.

Material and methods

PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched for studies investigating the efficacy of probiotics in maintaining remission in patients with UC. Data were collected from 1966 to 2008 (up to January). The search terms were: "probiotic" and "ulcerative colitis". The search was limited to English language. The reference list from retrieved articles was also reviewed for additional applicable studies. Relapse rate was the key outcome of interest. Relapse was defined as the appearance of UC symptoms and/or signs which needed additional medical treatment or any increase in colitis activity index (CAI) to more than 4 points.

Three reviewers independently examined the title and abstract of each article to eliminate duplicates, case studies, and uncontrolled trials. Studies that did not determine our desirable outcome (relapse rate) and those whose target groups were not patients with UC (patients with CD or pouchitis) were excluded from the meta-analysis.

Data from selected studies were extracted in the form of 2 × 2 tables. All included studies were pooled and weighted. The data were analyzed using StatsDirect ver. 2.6.2. Odds ratio (OR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenszel method. The Breslow-Day test was used to test for heterogeneity. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using a L'Abbé plot, as an aid to explore the heterogeneity of effect estimates. Funnel plot analysis was used as a publication bias indicator.

Results

The electronic searches yielded 739 items: 209 from PubMed, 2 from Cochrane Central, and 528 from Embase. Of those, 10 trials were scrutinized in the full text. Six reports were considered eligible and thus included in the meta-analysis (Figure 1) [14, 17-21].

The final comparison included 2 randomized controlled trials [17, 18] which compared the efficacy of probiotics against placebo and 4 randomized controlled trials [14, 19-21] which compared the efficacy of probiotics against mesalazine for maintaining remission in patients with UC.

Two controlled trials represented 55 patients with UC who were randomized to receive probiotics or placebo [17, 18]. Patients' characteristics, type and dosage of probiotic, duration of treatment, treatment before the study and relapse rate are shown in Table I. Relapse rate in the probiotic group was 23.1% (6 of 26) and in the placebo group was 92% (23 of 25). The summary OR (fixed effects) for relapse of disease under probiotic therapy in two trials [17, 18] was 0.0269 with a 95% CI of 0.0049-0.1478, a significant OR ($P<0.0001$, Figure 2A). The Breslow-Day test for heterogeneity ($P=0.6267$) indicated that the studies are not significantly heterogeneous (Figure 2B) and the fixed effects meta-analysis for individual and summary of OR was applied. Regression of normalized effect versus precision for included studies for "relapse with probiotic therapy" cannot be calculated because of too few strata.

Four controlled trials represented 533 patients with UC who were randomized to receive probiotics or mesalazine [14, 19-21]. Patients' characteristics, type and dosage of probiotic, mesalazine dosage, duration of treatment, treatment before the study and relapse rate are shown in Table II. Relapse occurred in 31.8% (84 of 264) of the probiotic group and 32.7% (88 of 269) of the mesalazine group. The characteristics of these four studies are shown in Table II. The summary OR for relapse of disease among probiotics intake vs. mesalazine therapy in

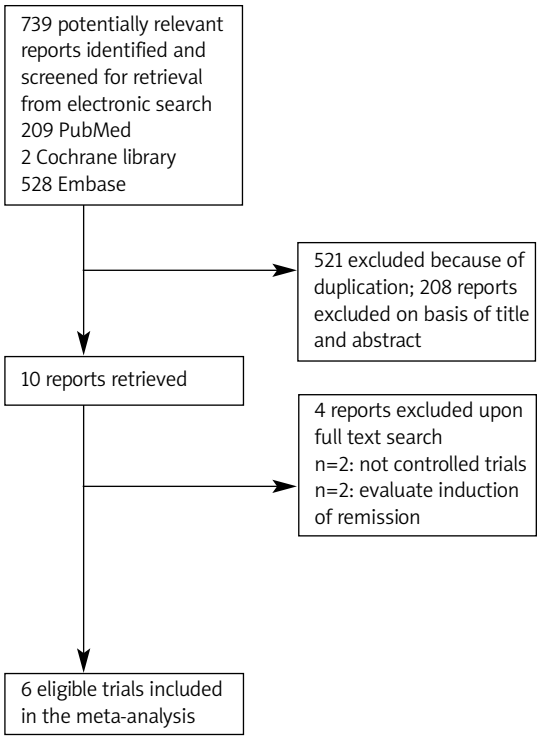

Figure 1. Flow diagram of the study selection process

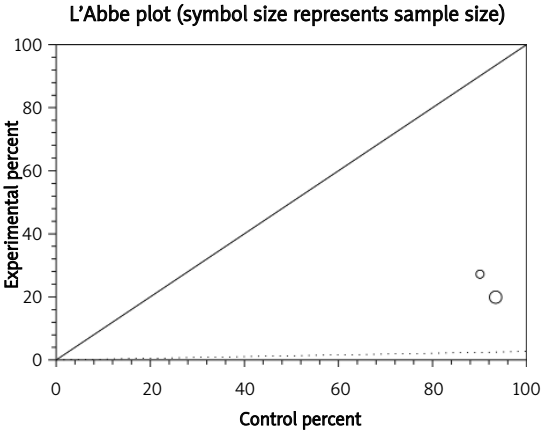

Figure 2B. Heterogeneity indicators for the outcome of "relapse" for studies including probiotic therapy compared to placebo

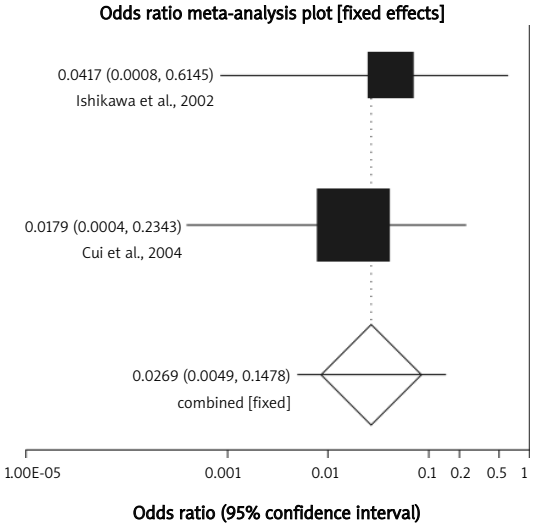

Figure 2A. Individual and pooled odds ratios for the outcome of "relapse" in the studies considering probiotic therapy compared to placebo

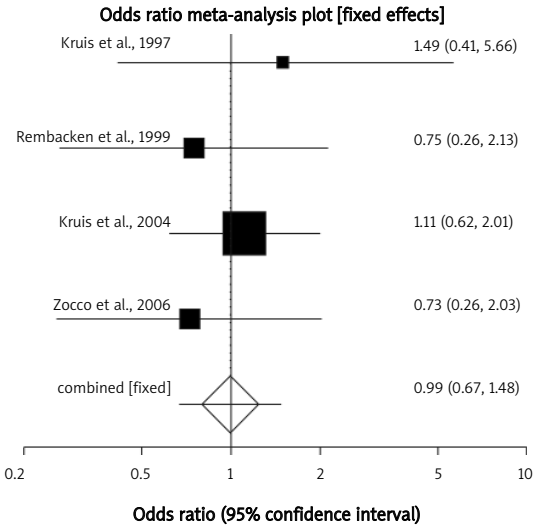

Figure 3A. Individual and pooled odds ratios for the outcome of "relapse" in the studies considering probiotic therapy compared to mesalazine

four trials [14, 19-21] was 0.99 with a 95% CI of 0.67 to 1.48, a non-significant OR (P=0.9419, Figure 3A). The Breslow-Day test for heterogeneity (P=0.6957) indicated that the studies were homogeneous and could be combined and the fixed effects meta-analysis for individual and summary of OR was applied (Figure 3B). Regression of normalized effect versus precision for included studies for "relapse with probiotic therapy" was –0.465895 (95% CI –6.734089 to 5.8023, P=0.7794), and Kendall's test on standardized effect vs. variance indicated tau =0.333333, P=0.75 (Figure 3C).

Discussion

The present meta-analysis showed that probiotics are effective in maintaining remission and their effect in preventing relapse is comparable with mesalazine. It has been well established that the composition of gut microflora in IBD patients changes to increased pathogenic bacteria and decreased bifidobacteria and lactobacilli. This imbalance between aggressive and beneficial bacterial species results in the development of chronic intestinal inflammation and thus positive effects of probiotics seem rational [22, 23]. Three main mechanisms for beneficial effects

Table I. Characteristics of studies comparing probiotics with placebo

Trial		Ishikawa et al., 2002 [17]	Cui et al., 2004 [18]
Patient characteristic	mean age [years]	ND	ND
	sex [M/F]	11/10	ND
Probiotic name		*Bifidobacteria* – fermented milk	bifid triple viable capsule
Name of bacteria in probiotic		*Bifidobacterium breve* *Bifidobacterium bifidum* *Lactobacillus acidophilus*	*Bifidobacteria* *Lactobacillus acidophilus* *Streptococcus faecalis*
Dosage		1×10^{10} viable bacteria/day	1.26 g/day
Treatment duration (months)		12	2
Treatment before the study		prednisolone salazosulfapyridine	glucocorticoid sulphasalazine
Relapse	/probiotic	3/11	3/15
	/placebo	9/10	14/15

Table II. Characteristics of studies comparing probiotics with mesalazine

Trial		Kruis et al., 1997 [9]	Rembacken et al., 1999 [20]	Kruis et al., 2004 [21]	Zocco et al., 2006 [15]
Patient characteristic	sex [M/F]	55/48	61/55	118/104	70/55
	mean age [years]	43.5	40	41.5	33.5
Probiotic name		*Escherichia coli* preparation	*Escherichia coli* preparation	*Escherichia coli* preparation	*Lactobacillus* GG
Name of of bacteria in probiotic		*Escherichia coli* Nissle 1917	*Escherichia coli* Nissle 1917	*Escherichia coli* Nissle 1917	*Lactobacillus* GG
Probiotic dosage		5×10^{10} viable bacteria/day	1×10^{11} viable bacteria/day	5×10^{10} viable bacteria/day	18×10^{9} viable bacteria/day
Mesalazine dosage (mg/day)		1500	1200	1500	2400
Treatment duration (months)		3	12	12	12
Treatment before the study		salicylates steroids	salicylates steroids azathioprine	ND	ND
Relapse	/mesalazine	6/53	32/44	38/112	12/60
	/probiotic	8/50	26/39	40/110	10/65

of probiotics can be illustrated including alteration of the enteric microbiota, modulation of the host immune response, and enhancement of the barrier function through interactions with epithelial and immune cells in the gut [23].

The results of our recent meta-analysis showed that probiotics are not more beneficial than placebo for maintaining remission and preventing clinical and endoscopic relapses in patients with CD [13]. It should not be forgotten that the type of probiotics varies and this issue might influence the efficacy of probiotics. In most of the trials included in that meta-analysis, lactobacillus was the main bacteria of the probiotic preparation,

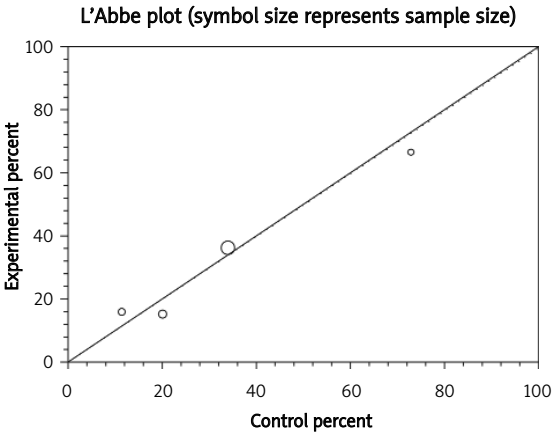

Figure 3B. Heterogeneity indicators for the outcome of "relapse" for studies considering probiotic therapy compared to mesalazine

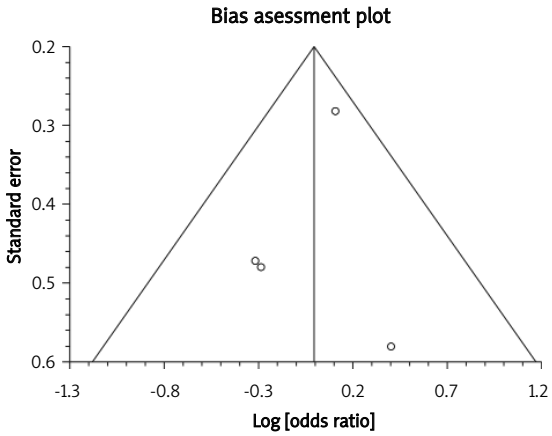

Figure 3C. Publication bias indicators for the outcome of "relapse" for studies including probiotic therapy compared to mesalazine

while in the present meta-analysis bifidobacterium was the major component. Thus, the different results obtained from these two meta-analyses may be due to different probiotic preparations used for treatment. Moreover, the dominant bacterial flora in patients with UC differs from those diagnosed with CD, and this implicates that a different strategy targeting bacterial flora should be used for these patients [24, 25]. It is also important to remember that the efficacy of one probiotic may not be the same in all patients or in the same patient with different types of disease. Responsiveness to treatment is dependent on several variables, including characteristics of the host (age, sex, lifestyle, compliance), the lesions (site, extent, type of gross lesions), previous history (presence, number and type of resections), and risk factors (smoking, appendectomy, familial history of inflammatory bowel disease) [26].

The collected studies evaluating the efficacy of probiotics in maintaining remission in patients with UC indicate a benefit of probiotics in prevention of disease relapse equal to that of mesalazine as a standard treatment. This positive effect of probiotics is most commonly mediated through antagonistic activity against pathogenic bacteria either by inhibition of adherence and translocation or by production of antibacterial substances, modulation of intestinal cytokine production, anti-inflammatory properties, and improvement of gut permeability [27, 28].

Comparing mesalazine and probiotics, probiotics are known to have fewer side effects, more tolerability and better compliance of the patients. Therefore, considering the similar efficacy in preventing relapse shown by both types of treatment, probiotics seem to be an appropriate alternative to mesalazine or a supplement in maintaining remission in patients with UC. The role of probiotics in the maintenance treatment of UC needs to be further assessed by larger controlled trials in future.

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