Probiotic treatments for induction and maintenance of remission in inflammatory bowel diseases: a meta-analysis of randomized controlled trials

Mikihiro Fujiya · Nobuhiro Ueno · Yutaka Kohgo

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Abstract Probiotics have been used for the treatment of inflammatory bowel diseases (IBD). However, the effects of probiotics on the induction and maintenance of remission in ulcerative colitis (UC) or Crohn's disease (CD) still remain controversial. This systematic review verified the findings of high-quality randomized controlled trials (RCTs) which investigated the therapeutic effects of probiotics on IBD. After the quality assessment, 20 RCTs which investigated the effects of probiotics on the induction or maintenance of remission in IBD were identified. From the results of the validation of these RCTs, beneficial effects of probiotic treatments to improve the response rate and remission rate on the remission induction therapies [risk ratio (RR) 1.81; 95 % confidence interval (CI) 1.40–2.35 and RR 1.56; 95 % CI 0.95–2.56, respectively] were verified. Furthermore, probiotic treatments exhibited effects equal to mesalazine on the maintenance of remission in UC (RR 1.00; 95 % CI 0.79–1.26). In contrast, no significant effect of probiotic treatments was shown in either the induction or maintenance of remission in CD. Because there were many variations in the conditions among these studies, a further analysis evaluating the effects of probiotic treatments in IBD is needed to clarify the optimal probiotics and treatment regimens for each condition or population in IBD patients.

Keywords Probiotics · Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Lactobacillus · Bifidobacterium · *Escherichia coli* · Ileal pouch

Introduction

Inflammatory bowel disease (IBD) is a chronic and refractory intestinal inflammation which mainly comprises ulcerative colitis and Crohn's disease, and whose causes are still unclear. The pathogenesis of IBD is thought to be associated with genetic susceptibility, an impairment of intestinal epithelial cells and host immune dysfunctions, as well as an imbalance of commensal bacteria [1, 2], because the mammalian intestine possesses more than 2,000 species of bacterial organisms that are indispensable partners for developing intestinal tissue and maintaining its homeostasis [3–5].

Probiotics, which are defined as “live microorganisms which confer a health benefit on the host, when administered in adequate amounts” [6], have potential effects on human health, as well as the treatment of intestinal disorders such as IBD. Indeed, the beneficial effects of probiotics were proposed more than 100 years ago [7, 8]. Recent advances in this field have proposed several mechanisms by which probiotics may improve intestinal disorders, including inhibiting the growth of pathogenic bacteria [9–17], enhancing the intestinal barrier function [18–24] and modulating the host immune responses [25–40]. Based on the results of etiological and pre-clinical studies of the effects of probiotics, many clinical trials have been conducted, and have suggested that probiotics are potentially useful in the treatment in IBD patients. However, the data from these studies were based on various subjects using different genera, species, strains and doses of probiotics [41, 42]. The sample sizes of these studies have been relatively small, so there has been no definitive evidence. The present review systematically evaluates the effects of probiotic treatments on IBD based on existing randomized controlled trials (RCTs).

M. Fujiya (✉) · N. Ueno · Y. Kohgo
Division of Gastroenterology and Hematology/Oncology,
Department of Medicine, Asahikawa Medical University, 2-1
Midorigaoka-higashi, Asahikawa, Hokkaido 078-8510, Japan
e-mail: fjym@asahikawa-med.ac.jp

Methods

Retrieval strategy and quality assessment

A meta-analysis was conducted to evaluate the effects of probiotic treatment on IBD. The data from PubMed (1997 to August 2013) and the Cochrane Controlled Trials Register (1997 to August 2013) were searched. The keywords used were: probiotics, inflammatory bowel disease, ulcerative colitis, Crohn's disease, *Escherichia coli*, *Lactobacillus* and *Bifidobacterium*. The language was limited to studies published in English. The retrieval results were reviewed by two evaluators. The evaluators were not blinded to the study drug, authors, institutions or journals when reviewing the studies. All of the randomized controlled studies that compared probiotics with standard treatments used for IBD or placebo were collected. Both adult and pediatric studies were included. All IBD patients were diagnosed based on the definite diagnostic standards in all of the included studies. Reviews, case reports, and abstracts and presentations of meetings were excluded.

The risk of bias was evaluated in accordance with the Cochrane Handbook for Systematic Reviews of Interventions, using the following parameters: adequacy of random sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data and selective outcome reporting [43]. The Jadad score was also used to evaluate the quality of each RCT. Briefly, the details of randomization, blinding procedure and information on withdrawals were evaluated. One point was awarded for the specification of each criterion (Table 1). High-quality RCTs which scored three points or more were included in this review [44]. A funnel plot was generated to assess the possibility of publication bias [45].

Data collection and bias assessment

The interventions used for treatment and control, disease severities, administration procedures, number of enrolled patients and observation intervals were extracted from each study. In the articles associated with remission induction therapy for IBD, the remission or response rates of the probiotic treatment and control groups were extracted, regardless of whether the data were part of the primary or secondary endpoint. Similarly, the relapse rates of the diseases were extracted from the articles associated with maintenance therapy for IBD. An intention-to-treat analysis was chosen for the total number of patients enrolled in each group. A forest plot analysis was used to verify the relative strength of the treatment effects in multiple quantitative scientific studies. The inter-study

heterogeneity was tested and quantified using the Cochran Q statistic and the I^2 statistic, respectively. Funnel plots were used to obtain evidence of publication bias when two or more studies were included.

Statistical analysis

The relative risk and 95 % confidence interval (95 % CI) were calculated based on the data. The statistical analysis was performed with the Cochrane Collaboration's Revman 5.0 software program. The inter-study heterogeneity was tested using the Cochran Q test, with the significance level set at $P < 0.1$, and was quantified by using the I^2 statistic. If there was any obvious inter-study heterogeneity ($I^2 > 50\%$), the random effects model was chosen; if not, the fixed effects model was chosen.

Results

Evaluation of the selected studies

A total of 1004 subjects were retrieved. After screening the titles, abstracts or full text and excluding reviews, case reports, uncontrolled tests and basic research studies, 27 studies were selected. Thereafter, seven studies were excluded because of a low Jadad score (<3) (Table 1). The characteristics of the 20 studies included are shown in Table 2. Of these 20 studies, three were conducted on the response rate to probiotic treatment, four studies examined the remission induction rate and two studies evaluated both the response and remission induction rates of UC patients, five studies focused on the maintenance therapy for UC, two studies on the maintenance therapy for an ileal pouch (Table 3), one study was performed on the remission induction therapy for CD and four studies examined the effects of probiotics on the maintenance therapy for CD (Table 4).

The effects of probiotic treatment on induction of remission in UC

Five studies which investigated the effects of probiotic treatment on the induction of remission described a response rate as an endpoint (Table 2). The VSL#3 preparation was used as the probiotic treatment in two studies [46, 47]. *Bifidobacteria*-fermented milk, *Bifidobacterium longum*/Synergy 1 and *Lactobacillus reuteri* ATCC 55730 were used as the probiotic treatments in the other three studies [48–50]. Four studies used a placebo as the control intervention [46, 48–50], and the other study used

Table 1 The risk of bias in the included studies

References	Random sequence generation	Allocation concealment	Blind participants, personnel and outcome assessors of outcome	Incomplete outcome data	Selective reporting	Jadad score
[55]	Unclear	Unclear	High	High	High	4
[51]	Unclear	Unclear	Low	High	High	3
[62]	High	High	High	High	High	5
[59]	High	High	High	High	High	5
[60]	High	High	High	High	High	5
[48]	Unclear	Unclear	High	Low	High	3
[52]	Unclear	Unclear	Low	High	High	3
[56]	Unclear	Unclear	High	High	High	4
[50]	High	High	High	High	High	5
[63]	Unclear	Unclear	High	High	High	5
[57]	Unclear	Unclear	Low	High	High	3
[64]	High	High	High	High	High	5
[65]	High	High	High	High	High	5
[53]	High	High	High	High	High	5
[46]	High	High	High	High	High	5
[54]	High	High	High	High	High	5
[47]	High	High	High	High	High	5
[61]	High	High	High	High	High	5
[58]	High	High	Low	High	High	4
[49]	High	High	High	High	High	5

balsalazide with the probiotic treatment or placebo [47]. The treatments were orally administered in four studies [46–48, 50] and anally in one study [49]. The observation intervals were 12 weeks in two studies [46, 48], 8 weeks in two studies [47, 49] and 4 weeks in one study [50].

Three studies revealed a significant improvement in the response rate [46, 47, 49]. Of these three studies, one study proposed that the probiotic effect was exerted in a concentration-dependent manner [46]. The other two studies [48, 50] showed no significant improvements, but both had investigated small sample sizes (Table 3). Because the inter-study heterogeneity of these five studies was very low ($P = 0.43$, $I^2 = 0\%$), a fixed-effects model was applied to analyze the effects of the probiotic. These five reports included a total of 362 patients. Of these 362 patients, probiotic treatments were used in 184 patients, and 178 patients were treated with a placebo with or without conventional therapies. The total response rate of the probiotic treatment group was 51.1 % (94/184), while that in the placebo group was 28.7 % (51/178). The risk ratio (RR) of all patients was 1.81, and the 95 % confidence interval (CI) was 1.40–2.35 (Fig. 1a). The analysis therefore showed that the probiotic treatments were useful for decreasing the severity of the active UC in comparison to the placebo. Funnel plots of these studies showed a symmetrical distribution, thus suggesting low publication bias (Fig. 2a).

Six studies which investigated the effects of probiotic treatment on the induction of remission described the remission induction rate as an endpoint (Table 2). One study was excluded because all patients received steroid therapy [51]. In the remaining five studies, VSL#3 was used as the probiotic treatment in two studies [52, 53]. Bifidobacteria-fermented milk, *E. coli* strain Nissle 1917 and *L. reuteri* ATCC 55730 were used as the probiotic treatments in the other three studies [48, 49, 54]. Three studies used a placebo as the control intervention [48, 49, 54] and the other two studies used conventional therapies with the probiotic treatment or placebo [52, 53]. The medications were orally administered in three studies [48, 52, 53] and anally administered in two studies [49, 54]. The observation interval was 12 weeks in one study [48], 8 weeks in three studies [49, 52, 54] and 4 weeks in one study [53].

One study [53] revealed a significant improvement in the remission induction rate, while the other four studies [48, 49, 52, 54] individually showed no significant improvements (Table 3). Because the inter-study heterogeneity of these five studies was high ($P = 0.048$, $I^2 = 58.4\%$), a random-effects model was applied for the analysis of the effects of the probiotic on improving the remission induction rate. These reports included a total of 230 patients. Among these patients, probiotic treatments were used in 140 patients, and 90 patients were treated with

Table 2 The characteristics of the included studies

References	Probiotics	Disease	Severity	Administration procedures	No. in each treatment group	Treatment intervention	No. in the control group	Control intervention	Assessment	Observation period
Remission induction in UC										
[51]	<i>E. coli</i> (serotype O6:K5:H1)	UC	All severities	Oral	57	<i>E. coli</i> (serotype O6:K5:H1)	59	Mesalazine	Remission induction rate	12 weeks
[48]	Bifidobacteria-fermented milk	UC	Mild to moderate	Oral	10	Bifidobacteria-fermented milk	9	Placebo	Remission induction and response rate	12 weeks
[52]	VSL#3	UC	Mild to moderate	Oral	30	VSL#3 + balsalazide	30	Placebo + balsalazide	Remission induction rate	8 weeks
[50]	<i>B. longum</i> /Synergy 1	UC	All severities	Oral	10	<i>B. longum</i> /Synergy 1	10	Placebo	Response rate	4 weeks
[53]	VSL#3	UC	All severities	Oral	14	VSL#3 + conventional therapy	15	Placebo + conventional therapy	Remission induction rate	4 weeks
[46]	VSL#3	UC	Mild to moderate	Oral	77	VSL#3	70	Placebo	Response rate	12 weeks
[54]	<i>E. coli</i> strain Nissle 1917	UC	Moderate	Enema	68	<i>E. coli</i> strain Nissle 1917	20	Placebo	Remission induction rate	8 weeks
[47]	VSL#3	UC	Mild to moderate	Oral	71	VSL#3 + conventional therapy	73	Placebo + conventional therapy	Response rate	8 weeks
[49]	<i>L. reuteri</i> ATCC 55730	UC	All severities	Enema	16	<i>L. reuteri</i> ATCC 55730	15	Placebo	Remission induction and response rate	8 weeks
Maintenance of remission in UC										
[55]	<i>E. coli</i> Nissle	UC	All severities	Oral	50	<i>E. coli</i> Nissle	53	Mesalazine	Relapse rate	3 weeks
[51]	<i>E. coli</i> (serotype O6:K5:H1)	UC	All severities	Oral	39	<i>E. coli</i> (serotype O6:K5:H1)	44	Mesalazine	Relapse rate	12 months
[56]	<i>E. coli</i> Nissle 1917	UC	All severities	Oral	110	<i>E. coli</i> Nissle 1917	112	Mesalazine	Relapse rate	12 months
[57]	Lactobacillus GG	UC	All severities	Oral	65	Lactobacillus GG	60	Mesalazine	Relapse rate	12 months

Table 2 continued

References	Probiotics	Disease	Severity	Administration procedures	No. in each treatment group	Treatment intervention	No. in the control group	Control intervention	Assessment	Observation period
[58]	<i>L. acidophilus</i> La-5 and <i>B. animalis</i> subsp. lactis BB-12 (Probio-Tec AB-25)	UC	All severities	Oral	20	Probio-Tec AB-25	12	Placebo	Relapse rate	12 months
Maintenance of remission in the ileal pouch										
[59]	VSL#3	Pouchitis	All severities	Oral	20	VSL#3	20	Placebo	Occurrence of pouchitis	12 months
[60]	VSL#3	Pouchitis	All severities	Oral	20	VSL#3	16	Placebo	Relapse rate	12 months
Remission induction in CD										
[61]	<i>B. longum</i> and Synergy 1.	CD	All severities	Oral	13	<i>B. longum</i> and Synergy 1. + conventional therapy	11	Placebo + conventional therapy	Remission induction rate	6 months
Maintenance of the remission in CD										
[62]	Lactobacillus GG	CD	All severities	Oral	23	Lactobacillus GG	22	Placebo	Relapse rate	12 months
[63]	Lactobacillus GG	CD	All severities	Oral	39	Lactobacillus GG	36	Placebo	Relapse rate	24 months
[64]	<i>L. johnsonii</i> LA1	CD	All severities	Oral	43	<i>L. johnsonii</i> LA1	47	Placebo	Relapse rate	6 months
[65]	<i>L. johnsonii</i> LA1	CD	All severities	Oral	34	<i>L. johnsonii</i> LA1	36	Placebo	Relapse rate	12 weeks

Table 3 Data included in the studies of treatment of UC

References	No. of treated subjects	No. of responders in the treated cases	No. of control subjects	No. of responders in control cases	RR	95 % CI
A. Remission induction in UC (Response rates)						
Kato et al. [48]	10	7	10	4	1.75	0.74–4.14
Furrie et al. [50]	10	5	10	3	1.67	0.54–5.17
Sood et al. [46]	77	25	70	7	3.25	1.50–7.03
Tursi et al. [47]	71	41	73	29	1.45	1.03–2.05
Oliva et al. [49]	16	16	15	8	1.88	1.17–3.01
References	No. of treated subjects	No. of treated cases that achieved remission	No. of control subjects	No. of control cases that achieved remission	RR	95 % CI
B. Remission induction in UC (Remission rates)						
Kato et al. [48]	10	4	10	3	1.33	0.40–4.49
Tursi et al. [52]	30	24	30	21	1.14	0.85–1.53
Miele et al. [53]	14	13	15	4	3.48	1.49–8.16
Matthes et al. [54]	70	29	20	7	1.18	0.61–2.29
Oliva et al. [49]	16	5	15	0	10.33	0.62–171.78
References	No. of treated subjects	No. of relapses in treated cases	No. of control subjects	No. of relapses in control cases	RR	95 % CI
C. Maintenance of remission in UC						
Kruis et al. [55]	50	8	53	6	1.43	0.48–4.24
Rembacken et al. [51]	39	26	44	32	0.92	0.69–1.22
Kruis et al. [56]	162	40	165	38	1.07	0.75–1.53
Zocco et al. [57]	65	10	60	12	0.77	0.36–1.65
Wildt et al. [58]	20	15	12	11	0.82	0.60–1.11
References	No. of treated subjects	No. of relapses in treated cases	No. of control subjects	No. of relapses in control cases	RR	95 % CI
D. Maintenance of remission in the ileal pouch						
Gionchetti et al. [59]	20	2	20	8	0.25	0.06–1.03
Mimura et al. [60]	20	3	16	15	0.16	0.06–0.46

No. number, RR relative risk, 95 % CI 95 % confidence interval

a placebo with or without conventional therapies. The total remission induction rate of the probiotics therapy group was 53.6 % (75/140) and that of the non-probiotics therapy group was 38.9 % (35/90). The RR in all patients was 1.56, and the 95 % CI was 0.95–2.59 (Fig. 1b). Therefore, probiotic treatment tended to be, but was not significantly, effective for improving the remission induction rate. Funnel plots of these studies showed a symmetrical distribution, suggesting low publication bias (Fig. 2b).

The effects of probiotic treatment on maintenance of remission of UC

Five studies investigated the effects of probiotic treatment on the maintenance of remission (Table 2). *Escherichia coli* Nissle was used as probiotic treatment in two studies [55,

56]. *Escherichia coli* (serotype O6:K5:H1), *Lactobacillus* GG and Probio-Tec AB-25 (*Lactobacillus acidophilus* La-5 and *Bifidobacterium animalis* subsp. lactis BB-1) were used as probiotic treatments in the other three studies [51, 57, 58]. Medications were orally administered in all studies. The observation intervals were 12 months in four studies [51, 56–58] and 3 weeks in one study [55]. Mesalazine was used as a control intervention in four studies. One study used placebo as a control intervention, and showed no significant effect of probiotic treatment on the prevention of relapse in UC. The four that used mesalazine as a control intervention were included in a subsequent analysis. Because the inter-study heterogeneity of the four studies was very low ($P = 0.7075$, $I^2 = 0\%$), a fixed-effects model was applied for the analysis of the probiotic effects. These reports included a total of 638 patients. Among these 638 patients, probiotic treatments were used in 316 patients,

Fig. 1 Forest plots of the response, remission induction and relapse rates of the probiotic group versus the control group in UC. Forest plots of the fixed-effects comparison of probiotics vs. placebo for the response rate (a), remission induction rate (b), relapse rate during the remission stage of UC (c) and remission in the ileal pouch in

postoperative UC patients (d) are shown. For each comparison, the results of tests for heterogeneity are shown, in addition to the Z statistic and associated P value for the strength of the observed effect

Fig. 2 The results of the inverted funnel plot analysis of the response, remission induction and relapse rates in UC patients. The inverted funnel plot analysis of the relative response rate (a), remission rate

(b), and relapse rate in the remission stage of UC (c), and remission in the ileal pouch in postoperative UC patients (d) between the probiotics group and placebo group are shown

and 322 patients were treated with standard therapy (mesalazine). The total relapse rate of the probiotics therapy group was 25.0 % (84/336) and that in the mesalazine group was 26.3 % (88/334). The RR in all patients was 1.00, and the 95 % CI was 0.79–1.26 (Fig. 1c). Therefore, probiotic treatment could prevent the relapse of UC as effectively as the administration of mesalazine. Funnel plots of these studies showed a symmetrical distribution, suggesting low publication bias (Fig. 2c).

The effects of probiotic treatment on maintenance of remission in the ileal pouch

Two studies investigated the effects of probiotic treatment on the maintenance of remission in the ileal pouch [59, 60] (Table 2). Oral administration of VSL#3 was used as a

probiotic treatment, a placebo was used as a control intervention and the observation interval was 12 months in both of these studies. Because the inter-study heterogeneity of these two studies was very low ($P = 0.62$, $I^2 = 0\%$), a fixed-effects model was applied for the analysis of the probiotic effects. These reports included a total of 76 patients. Among the 76 patients, probiotic treatments were used in 40 patients, and 36 patients were treated by standard therapy (mesalazine). The total relapse rate of the probiotics therapy group was 26.5 % (5/40) and that of the non-probiotics therapy group was 29.6 % (23/36). The RR in all patients was 0.19, and the 95 % CI was 0.08–0.44 (Fig. 1d). Therefore, probiotic treatment helps to prevent pouchitis in postoperative UC. The funnel plot of these studies showed a symmetrical distribution; however, it is difficult to determine the grade of the publication bias because only two studies were analyzed (Fig. 2d).

The effects of probiotic treatment on induction of remission of CD

Only one study investigated the effects of probiotic treatment on the induction of remission in CD [61] (Table 2). Patients were administered conventional CD therapies with *B. longum* and Synergy 1 or placebo. The study showed that 62 % of patients in the probiotic treatment group (8 of 13) and 45 % of those in the placebo group (5 of 11) achieved remission. The RR was 1.35, and the 95 % CI was 0.62–1.94, indicating that the additional administration of *B. longum* and Synergy 1 did not significantly improve the remission induction rate in CD patients.

The effects of probiotic treatment on maintenance of remission in CD patients

Four studies investigated the effects of probiotic treatment on the maintenance of remission in CD patients [62–65] (Table 2). Two studies used *Lactobacillus* GG as a probiotic treatment [62, 63] and the other two used *Lactobacillus johnsonii* LA1 [64, 65]. The medication was orally administered and a placebo was used as a control intervention in all four studies. The observation intervals were 3 months [65], 6 months [64], 12 months [62] and 24 months [63] in these studies. Because the inter-study heterogeneity of these four studies was very low ($P = 0.245$, $I^2 = 27.9\%$), a fixed-effects model was applied for the analysis of the probiotic effects. These reports included a total of 180 patients. Among the 180 patients, probiotic treatments were used in 139 patients, and 141 patients were treated with a placebo. The total relapse rate of the probiotics therapy group was 26.5 % (35/139) and that of the non-probiotics therapy group was 29.6 % (29/141). The RR in all patients was 1.18, and the 95 % CI was 0.81–1.70 (Fig. 3a). Therefore, probiotic treatment did not contribute to preventing the relapse in postoperative CD patients. Funnel plots of these studies did not show a symmetrical distribution, and thus a publication bias may have been present (Fig. 3b).

Discussion

This systematic review assessed the effects of probiotics on the treatment of UC and CD using a meta-analysis. In UC, the analysis revealed that probiotic treatment was useful for relieving the disease activity, increasing the remission induction rate, and preventing the relapse of disease in UC patients as effectively as the administration of mesalazine, and could decrease the development of pouchitis in postoperative UC patients. These results indicate that probiotic

treatment is useful in UC in both the active and remission phases.

The present review identified nine RCTs which investigated the effects of probiotics on the induction of remission. Of the nine studies, five investigated the response rate to probiotic treatment in UC. A forest plot analysis, which is used to verify the relative strength of treatment effects in multiple quantitative scientific studies, found that there was significant efficacy of probiotic treatment for improving the activity of UC (RR 1.18, 95 % CI 1.40–2.35). Furthermore, in five studies which examined the remission induction rate, probiotic treatment tended to improve the remission induction rate (RR 1.56, 95 % CI 0.95–2.59). The analysis in this review suggests that probiotic treatments provide a sufficient benefit for the induction of remission in UC. In contrast, Mallon et al. [66] showed in their systematic review of four RCTs published from 1999 to 2005 that probiotic treatment was not useful as a remission induction therapy in UC. However, most of the studies included in their review were small in size [48, 50–52], and thus may have lacked the power to detect a statistically significant difference. Compared with their review, the present systematic review included a much larger number of patients, because five more studies published after 2005 were identified [46, 47, 49, 53, 54], and we verified the efficacy of probiotic treatments in inducing remission in UC.

The present review also identified five RCTs that investigated the effects of probiotics on the maintenance of UC [51, 55–58]. One study used a placebo as a control intervention [58], and four studies compared the effects of probiotic treatment with mesalazine [51, 55–57]. A forest plot analysis of these four studies showed no difference between the effects of probiotic treatments and mesalazine administration on the maintenance of remission in UC (RR 1.00, 95 % CI 0.79–1.26), validating that probiotic treatment is useful for maintaining remission in patients with quiescent UC. In addition, the present review also identified two studies that investigated the effects of probiotic treatment on the maintenance of remission in the ileal pouch of postoperative UC patients, and revealed a significant benefit of probiotic treatment in the prevention of pouchitis (RR 0.19, 95 % CI 0.08–0.44). Naidoo et al. previously reviewed four studies and showed that there was insufficient evidence to draw conclusions about the efficacy of probiotics for maintenance of remission in UC [66]. Their review included studies that used either mesalazine or placebo as a control intervention. This variation between our study and theirs was thought to be the cause of their failure to draw a conclusion. The present review thus excluded a study that used a placebo as a control intervention [58] and analyzed the other four studies [51, 55–57], and we were able to verify the efficacy of probiotic

Fig. 3 Forest plots and the results of the inverted funnel plot analysis of the relative relapse rates in CD. Forest plots of the fixed-effects comparison of probiotics vs. placebo for the response rate (**a**), and the

results of the inverted funnel plot analysis of the relative relapse rate in the remission stage in CD patients (**b**) are shown

treatments for the maintenance of remission in UC patients. Sang et al. [67] also suggested in their systematic review that probiotic treatments were more effective than placebo for maintaining remission in ulcerative colitis, despite the fact that low-quality studies were included. Consequently, such RCTs suggest that there is a significant effect of probiotic treatment on the induction and maintenance of remission in UC, despite variations in the design and treatment interventions among the studies (Table 2).

While the results of the present review and other studies suggested a beneficial effect of probiotic treatments on the induction and maintenance of remission in UC, there are some limitations to these studies, including variations in the inclusion and exclusion criteria, the treatment and control interventions, schedules and concentrations of the probiotics, observation intervals, procedures used to assess the disease activity, concomitant medications, the ethnicity of the patients and the lifestyles of the enrolled patients. Therefore, the optimal probiotic treatment for UC patients in the active and quiescent phases needs to be investigated in further RCTs.

In CD patients, one RCT which investigated the effects of probiotics on the induction of remission and four RCTs which investigated the effects on the maintenance of remission in CD patients were identified. All of the studies showed no significant effects on either the induction or maintenance of remission in CD. The forest plot verified no beneficial effect of the probiotic treatments on the maintenance of remission in CD. Rolfe et al. [68] reviewed seven studies, including abstracts, of maintenance therapy in CD by *Lactobacillus* administration. The meta-analysis indicated that *Lactobacillus* administration was not effective for the maintenance of remission in CD patients. Shen et al. [69] also reviewed six controlled studies, including original articles, as well as abstracts and meeting reports, of maintenance therapy in CD by *Lactobacillus* administration and obtained the same conclusion. Another two meta-analyses investigated the effects of probiotics on maintenance therapy for postoperative CD, and concluded that probiotics were not superior to placebo for any outcome measured [70, 71]. Taken together, these studies indicate that probiotic treatments appear to be insufficient to induce

an effect on either the induction or maintenance of remission in CD.

In summary, the present study identified 20 high-quality RCTs which investigated the effects of probiotics on the induction or maintenance of remission in IBD. From the results of the validation of these RCTs, probiotic treatment is a practical option for UC patients as both remission induction and maintenance therapy, but such treatment is not effective in CD patients. Because there were many variations in the conditions among the studies, future studies on the value of probiotic treatment in IBD should consider the effects of different probiotics and different regimens, together with the specific patient populations which are most likely to benefit from probiotic treatment.

Disclosures Conflict of Interest: The authors declare that they have no conflict of interest.

Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

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