International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 6 (6): 826-835, 2010
ISSN 1811-7775

A Review and Meta-analysis of the Efficacy of Antibiotics and Probiotics in Management of Pouchitis

[1,2]S. Nikfar, [3]M. Darvish-Damavandi and [4]M. Abdollahi
[1]Department of Pharmacoeconomics and Pharmaceutical Administration,
Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[2]Food and Drug Laboratory Research Center,
Ministry of Health and Medical Education, Tehran 1417614411, Iran
[3]Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore
[4]Mohammad Abdollahi, Faculty of Pharmacy and Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences, Tehran 1417614411, Iran

Abstract: Pouchitis is the most frequent long-term complication of Ileal Pouch-Anal Anastomosies (IPAA) surgery for Ulcerative Colitis (UC) which is a nonspecific inflammation of the ileal reservoir. Its clinical frequency varies depending on the definition and the follow up but is approximately 50% after a decade. Antibiotics and probiotics are currently the most widely accepted treatment in pouchitis patients. Objective of this study was to meta-analyze efficacy of probiotics and antibiotics in the management of pouchitis. All databases specially Pubmed, Web of Science, Scopus, Cochrane and Google Scholar were searched between 1965 and December 2009 and relevant controlled clinical trials were extracted, reviewed and validated according to the study protocol. The outcome of interest was defined by a Pouchitis Disease Activity Index (PDAI)<7. Thirteen clinical trials were included in the meta-analysis. Pooling of the results from eight trials yielded a Relative Risk (RR) of 5.33 with a 95% CI of 2.12-13.35 and a significant RR (p = 0.0004) in all kind of probiotics treatment group in comparison with the placebo group. Summary RR for clinical improvement in six trials was 14.17 with a 95% CI of 1.19-168.93 (p = 0.036) in efficacy of VSL#3 (all doses) comparing to placebo and slightly more effective for VSL#3 (6 g day^{-1}) comparing to placebo with RR of 20.35 with a 95% CI of 6.16-67.22 (p<0.0001). Efficacy of antibiotics comparing to placebo showed a summary RR of 2.68 with a 95% CI of 0.4-17.99 and p = 0.3107 for clinical improvement in three trials. The summary RR for efficacy of ciprofloxacin comparing to metronidazole was 0.68 with a 95% CI of 0.44-1.06 (p = 0.8913). In conclusion, alongside the benefit of probiotics and antibiotics in the management of pouchitis, effects of probiotics and antibiotics on pouchitis vary according to different mixtures of microorganisms strains in probiotics and different spectrums of antibiotics.

Key words: Pouchitis, probiotic, antibiotic, microorganisms

INTRODUCTION

Pouchitis is the most frequent long-term complication of Ileal Pouch-Anal Anastomosies (IPAA) surgery for Ulcerative Colitis (UC) which is a nonspecific inflammation of the ileal reservoir. Its clinical frequency varies depending on the definition and the follow up but is approximately 50% after a decade (Ruseler-van Embden *et al*., 1994; Stochi and Pemberton, 2001).

Although, the exact etiology of pouchitis remains largely unknown, some studies have identified that reduced counts of lactobacilli and bifidobacteria within the pouch and subsequent dysregulation of inflammatory response may contribute to the development of this syndrome (Gosselink *et al*., 2004a; Ohge *et al*., 2005).

The Pouchitis Disease Activity Index (PDAI) was proposed by Sandborn *et al*. (1994) as a tool for objective and reproducible scoring of signs and symptoms of pouchitis in diagnosis of disease. According to PDAI, active pouchitis is defined as a score ≥ 7 and remission is defined as a score <7.

Therapeutic approaches include several pharmacological agents that seem helpful for the treatment of pouchitis. Given the association, antibiotics and probiotics are currently the most widely accepted treatment in pouchitis patients (Elahi *et al*., 2009; Rahimi *et al*., 2006, 2007a).

Corresponding Author: Mohammad Abdollahi, Faculty of Pharmacy and Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences, Tehran 1417614411, Iran
Tel: +98-21-66959104 Fax: +98-21-66959104

Acute or chronic types of pouchitis can usually be treated effectively with antibiotics, making these agents the mainstay of treatment (Elahi *et al*., 2009). Clinical experiences have demonstrated that most patients with pouchitis respond to antibiotic therapy, most often with metronidazole or ciprofloxacin. Metronidazole has been the most commonly used drug and the majority of patients show an initial response at a dose of 750-1500 mg day^{-1}. Moreover, ciprofloxacin may have better efficacy and less toxicity compared with metronidazole in treatment of acute pouchitis (Madden *et al*., 1994; Sandborn, 1994; Shen *et al*., 2001). While the majority of patients with pouchitis respond to a two-week treatment course with a single antibiotic, some may have refractory disease, requiring combination antibiotic therapy (Mimura *et al*., 2002). However, relatively few randomized controlled antibiotic trials have been performed.

Besides antibiotic therapy, probiotics are being researched as a prevention of pouchitis episodes. When the inflammation reduced or eliminated, the problem of maintaining remission remains. In recent years a series of placebo controlled randomized clinical trials have been conducted demonstrating that the modification of bacteria flora using probiotic bacteria preparation may be highly effective (Elahi *et al*., 2008; Furrie *et al*., 2005; Kruis *et al*., 1997; Pochapin, 2000; Rahimi *et al*., 2008a,b; Sen *et al*., 2002). They comprise a variety of bacterial species including Lactobacilli, Bifidiobacteria and streptococci as well as non pathogenic *Esherichia coli* (Gionchetti *et al*., 2003). Although, the mechanism of action of probiotics has not been fully elucidated, clinical and preclinical studies have shown that probiotics have anti-inflammatory effects (Gionchetti *et al*., 2003; Gionchetti *et al*., 2000; Mimura *et al*., 2004). Most randomized control trial, on the use of probiotics are limited by small sample sizes, making it possible that a true positive effect of therapy has not been detected because of low power. There is no comparative meta-analysis on the efficacy of probiotics and antibiotics for management of pouchitis. Meta-analysis technique is a statistical procedure for combining data from multiple studies and is necessary because only summary statistics are available in the literature to assess the magnitude and the benefits from use of antibiotics or probiotics in management of pouchitis. Our previous meta-analysis showed effectiveness of antibiotics and probiotics in IBD and Irritable Bowel Syndrome (IBS) (Nikfar *et al.,* 2008; Rahimi *et al*., 2006, 2007a, 2008a, b; Rezaie *et al*., 2010). In our last meta-analysis, we found that use of antibiotics in pouchitis is beneficial. In the present work, the effect of both probiotics and antibiotics in patients who had undergone IPAA is reviewed and meta-analyzed.

Data sources and meta-analysis: The search terms clinical trials, antibiotics, probiotics, pouchitis and IPAA were searched in all relevant databases especially Pubmed, Web of Science, Scopus, Cochrane and Google Scholar for studies reported use of probiotics or antibiotics in treatment of IPAA from 1965 up to December 2009. A total of 892 results were examined. Primary outcomes included clinical improvement and remission in IPAA by use of probiotics and antibiotics. The definition was varied from study to study; therefore, PDAI score ≥ 7 was defined as an endpoint to harmonize studies. After primary search, data which were duplicate, reviews, case study, or low quality studies were excluded.

Assessment of trial quality: The methodological quality of included trials was assessed using the Jadad score, which judges of the descriptions of randomization, blinding and dropouts (withdrawals) in the trials (Table 1). This is summarized as follow: a: whether randomized or not (yes = 1 point, No = 0); b: whether randomization was described appropriately or not (yes = 1 point, No = 0); c: double blind (yes = 1 point, No = 0); d: was the double blinding described appropriately (yes = 1 point, No = 0); e: whether withdrawals and dropouts described or not (yes = 1 point, No = 0). The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3 (Jadad, 1998).

Statistical analysis: Data from selected studies were extracted in the form of 2×2 tables. Included studies were weighted and pooled. The data were analyzed using Statsdirect software version 2.7.7. Relative risk (RR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenszel and Der Simonian-Laird method. The Cochran Q test was used to test heterogeneity. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L'Abbe plot as an aid to explore the heterogeneity of effect estimates. Funnel plot analysis was used as publication bias indicator.

Table 1: Jadad quality score of randomized, controlled trials included in the meta-analysis

Study	Randomization	Blinding	Withdrawal and dropout	Total score
Gosselink *et al*. (2004a)	1	0	0	1
Gionchetti *et al*. (2000)	3	0	2	1
Kuisma *et al*. (2003)	4	1	2	1
Mimura *et al*. (2004)	5	1	2	2
Madden *et al*. (1994)	4	1	2	1
Sambuelli *et al*. (2002)	4	1	2	1
Shen *et al*. (2001)	2	0	0	2
Gionchetti *et al*. (2002)	4	0	2	2
Gionchetti *et al*. (2003)	4	0	2	2
Shen *et al*. (2005)	5	1	2	2
Kuhbacher *et al*. (2006)	3	0	2	1
Isaacs *et al*. (2007)	3	0	2	1
Gosselink *et al*. (2004b)	3	1	0	2

RESULTS

We reviewed total of 892 abstract and titles were found and reviewed in first step (Fig. 1), of which, 864 were excluded on the basis of title and abstract irrelevancy or duplication. Therefore, 28 studies were scrutinized in full text, of which, 13 were considered eligible and met inclusion criteria for systematic review of probiotics and antibiotics for pouchitis and included in this analysis. Of excluded studies, one was case report, 9 were open study and were not randomized properly, one was pilot study and the other 4 has no placebo control in their treatment or they used mezalasine as concomitant therapy.

The quality of eligible studies was assessed by Jadad score. Seven out of 13 studies received Jadad score ≥ 4. Four studies received Jaded score 3 and other two studies had score of 2 and 1, respectively (Gosselink *et al*., 2004a; Shen *et al*., 2001).

The included trials covered 128 patients for probiotic arm, 62 for antibiotic arm and 213 patients for placebo. Among included patients, 172 were women (42.7%) and 231 were men (57.3%). Patients characteristics, type and dosage forms, duration of treatment and outcomes for each study are shown in Table 2-7.

Efficacy of all types of probiotics comparing to placebo: The summary RR for clinical improvement in eight trials (Gionchetti *et al*., 2000, 2002, 2003; Gosselink *et al*., 2004b; Kuhbacher *et al*., 2006; Kuisma *et al*., 2003; Mimura *et al*., 2004; Shen *et al*., 2005) was 5.33 with a 95% CI of 2.12-13.35 and a significant RR (p = 0.0004, Fig. 2a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p<0.0001, Fig. 2b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for clinical improvement among all types of probiotics vs. placebo therapy was 1.797054 (95% CI = 0.608753 to 2.985355, p = 0.0101) and Kendall's test on standardized effect vs. variance indicated tau b = 0.777778, p = 0.012 (Fig. 2c).

Efficacy of VSL#3 (all doses) comparing to placebo: Summary RR for clinical improvement in six trials (Gionchetti *et al*., 2000, 2002, 2003; Kuhbacher *et al*., 2006; Mimura *et al*., 2004; Shen *et al*., 2005) was 14.17 with a 95% CI of 1-19-168.93 and a significant RR (p = 0.036, Fig. 3a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p<0.0001, Fig. 3b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for

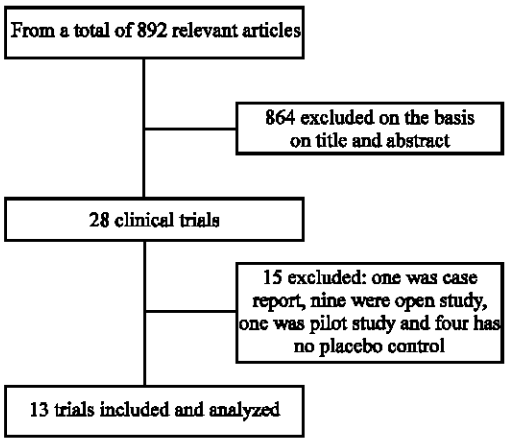

Fig. 1: Algorithm of the study selection and inclusion in meta-analysis

Table 2: Outcomes of clinical trials on probiotic

Study	Type of study	Condition	Concomitant therapy	Control group	Change in PDAI from baseline		Percentage of improvement: Patients	Control	AEs
Gionchetti *et al*. (2000)	RCT	Chronic pouchitis in remission	Rifaximine 1 g plus ciprofloxacin 500 mg bid	Placebo	0 to 2		85% 17/20	0% 0/20	No side effect
					Control	Patients			
Kuisma *et al*. (2003)	RCT	Acute active pouchitis		Placebo	8.4±0.7 to 8±0.7	8±0.8 to 8±1.1	2/10 20%	1/10 10%	No side effect
Mimura *et al*. (2004)	RCT	Maintenance of antibiotic induced remission		placebo placebo	3 comes to 2 for vsl and 11 for		85% 17/20 side effect	6% 1/16	1 Patients has
Gionchetti *et al*. (2002)	RCT	Maintenance of antibiotic induced remission in acute active pouchitis		Placebo		-	17/20 85%	0/20 0%	-
					Control	Patients			2 patients
Shen *et al*. (2005)	OL	Relapsing antibiotic dependant pouchitis after IPAA		Discontinue treatment or no treatment	3.17±1.49 to 2.83 ±1.43	2.67±0.52 to 0.33 ±0.52	6/6 100%	0/25 0%	complained of melena, bowel movement and constipation
					Control	Patients			
Gionchetti *et al*. (2003)	RCT	Chronic pouchitis after UC		Placebo	0 to 1.5	0 to 0	18/20 90%	12/20 60%	No side effect
Kuhbacher *et al*. (2006)	RCT	Recurrent or chronic active pouchitis		Placebo		baseline was 3	10/10 100%	0/5 0%	-
Gosselink *et al*. (2004b)	RCT	Pouchitis after IPAA		No treatment		-	38/42 90%	39/85 46%	-

RCT: Randomized clinical trial; OL: Open label; AEs: Adverse effects

Table 3: Patient's characteristic of trials on probiotics

Study	Mean age		Sex M/F		No. of patients	Type of probiotic	Dosage	Duration	Follow up	
Gionchetti *et al.* (2000)	33.5		23/17		40	VSL #3	6 g day 1 (500 billions)	36 weeks	16 weeks	
	Patient	Control	Patient	Control						
	---	---	---	---		Lactobacillus				
Kuisma *et al.* (2003)	46.4	48.24	7/3	4/6	20	Rhamnosus GG	4 capsule (10^{10} cfu day^{-1})	12 weeks		
			Patient	Control						
Mimura *et al.* (2004)	36		12/8	8/8	36	VSL #3	6 g (1800 billions bacteria)/day	48 weeks	48 weeks	
Gionchetti *et al.* (2002)					40	VSL #3	3 g (1.8×10^{12} bacteria)/day	36 weeks		
	Patient	Control	Patient	Control						
Shen *et al.* (2005)	40.0 ±11.5	42.9±13.4	4/2	14/11	6	VSL #3	6 g (1800 billions bacteria)/day	7 weeks	60±20 weeks	
	Patient	Control	Patient	Control						
Gionchetti *et al.* (2003)	31.8	34.2	11/9	12/8	40	VSL #3	3 g (900 billions bacteria)/day	48 weeks		
Kuhbacher *et al.* (2006)	34		9/6		15	VSL #3	6 g (1800 billions bacteria)/day	8 weeks	48 weeks	
	Patient	Control	Patient	Control					Patient	Control
	---	---	---	---		Lactobacillus			---	---
Gosselink *et al.* (2004b)	38	35	27/14	46/39	127	Rhamnosus GG	1.4×10^{10} cfu day 1	28 weeks	32 months	68 months

CFU (Colony Forming Unit): A measure of viable bacterial or fungal numbers

Table 4: Patients' characteristics of trials on antibiotics

Study	Mean age		Sex M/F		No. of patients		Type of antibiotic	Dosage	Duration	Follow up
Madden *et al.* (1994)					21		Metronidazole	400 mg tid	2 weeks cross over 2 weeks	
	Patient	Control	Patient	Control	Patient	Control				
	---	---	---	---	---	---				
Sambuelli *et al.* (2002)	38	31	8/6	10/2	14	12	metronidazole	500 mg bid	6 weeks	
Isaacs *et al.* (2007)					18		rifaximin	1200 mg/daily	4 weeks	

Table 5: Outcomes of trials on antibiotic

	Type of study	Condition	Concomitant therapy	Control group	Change in PDAI from baseline		Percentage of improvement		Aes
							Patients	Control	
Madden *et al.* (1994)	RCT	Chronic active pouchitis		Placebo			8/11 73%	1/10 10%	6/11 (55%) in metronidaxole group
					Control	Patients			
			Budenoside		---	---			
Sambuelli *et al.* (2002)	RCT	Acute and chronic pouchitis	enema 2 mg/100 mL at bedtime	Placebo	11 to 6	12 to 5	7/14 50%	7/12 58%	57% in metronidaxole group and 25% in budenoside group
Isaacs *et al.* (2007)	RCT	Active acute or chronic pouchitis		Placebo	-1.6 Change from baseline		2/8 25%	0/10 0%	

RCT: Randomized clinical trial; OL: Open label; AEs: Adverse effect

Table 6: Patients characteristics of studies comparing ciprofloxacin and metronidazole

Study	Mean age	Sex M/F	No. of patients	Ciprofloxacin dosage	Matronidazole dosage	Duration	Follow up
Gosselink *et al.* (2004a)	37	6/7	13	500 mg bid	500 mg bid	2 weeks	5 Years
Shen *et al.* (2001)	41.4±13.3	9/7	16	500 mg bid	20 mg/kg/day	2 weeks	

Table 7: Outcomes of studies comparison ciprofloxacin with metronidazole

Study	Type of study	Condition	Change in PDAI from baseline		Percentage of improvement		AEs
			Metronidazole group	Ciprofloxacin group	Metronidazole group	Ciprofloxacin group	
Gosselink *et al.* (2004a)	OL	Beginning of pouchitis	11 to 5	10 to 2.5	3/7 42%	4/6 66%	33% in metronidazole group
Shen *et al.* (2001)	RCT	Acute antibiotic responsive pouchitis	9.9±2.2 to 6.9±1.2	9.9±2.2 to 3.8±1.7	6/9 67%	7/7 100%	33% in metronidazole group

RCT: Randomized clinical trial; OL: Open label; AEs: Adverse effect

clinical improvement among VSL#3 (all doses) vs. placebo therapy was 2.532234 (95% CI = 1.931703 to 3.132765, p = 0.0003) and Kendall's test on standardized effect vs. variance indicated tau b = 0.857143, p = 0.0323 (Fig. 3c).

Efficacy of VSL#3 (6 g day^{-1}) comparing to placebo: Summary RR for clinical improvement in four trials (Gionchetti *et al.*, 2000; Kuhbacher *et al.*, 2006; Mimura *et al.*, 2004; Shen *et al.*, 2005) was 20.35 with a 95% CI of 6.16-67.22 and a significant RR (p<0.0001, Fig. 4a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (p = 0.8303, Fig. 4b) and could be combined, thus the fixed effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for clinical improvement among VSL#3 (6 g day^{-1}) vs. placebo therapy was 1.784746 (95% CI = -4.965545 to 8.535037, p = 0.3732) and Kendall's test on standardized effect vs. variance indicated tau = 1, p = 0.0833 (Fig. 4c).

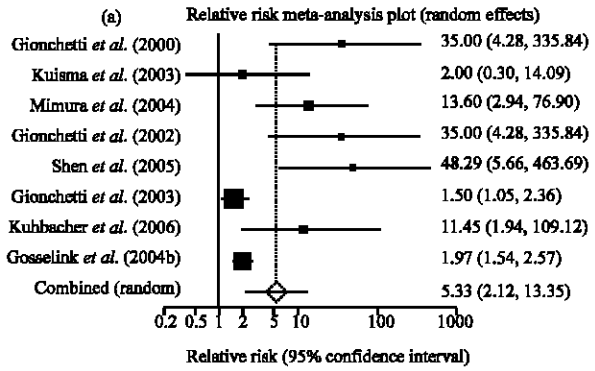

Fig. 2a: Individual and pooled relative risk for the outcome of clinical improvement in the studies considering all types of probiotics vs. placebo therapy

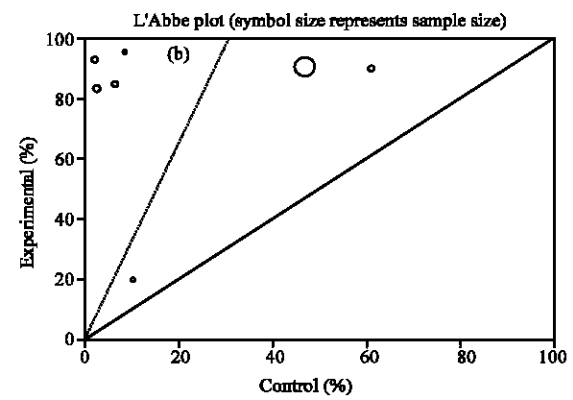

Fig. 2b: Heterogeneity indicators for the outcome of clinical improvement in the studies considering all types of probiotics vs. placebo therapy

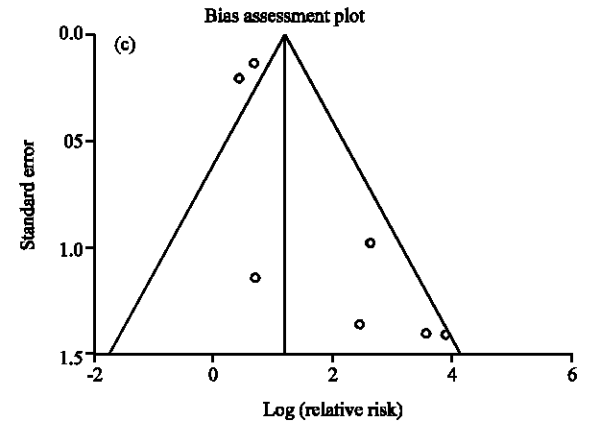

Fig. 2c: Publication bias indicators for the outcome of clinical improvement in the studies considering all types of probiotics vs. placebo therapy

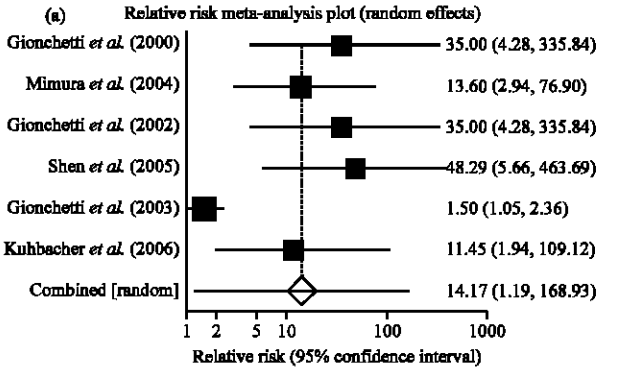

Fig. 3a: Individual and pooled relative risk for the outcome of clinical improvement in the studies considering VSL#3 (all doses) vs. placebo therapy

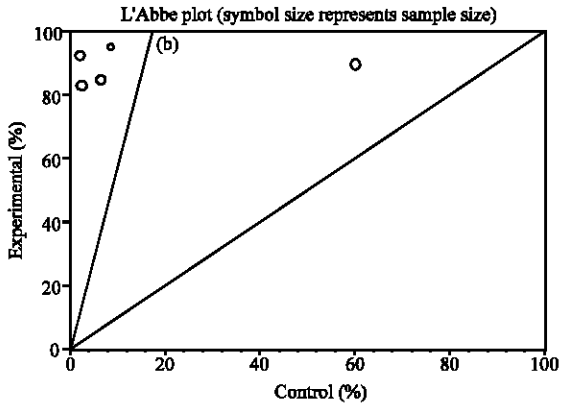

Fig. 3b: Heterogeneity indicators for the outcome of clinical improvement in the studies considering VSL#3 (all doses) vs. placebo therapy

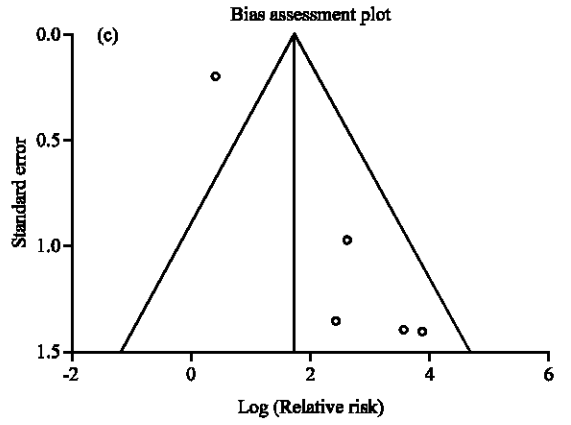

Fig. 3c: Publication bias indicators for the outcome of clinical improvement in the studies considering VSL#3 (all doses) vs. placebo therapy

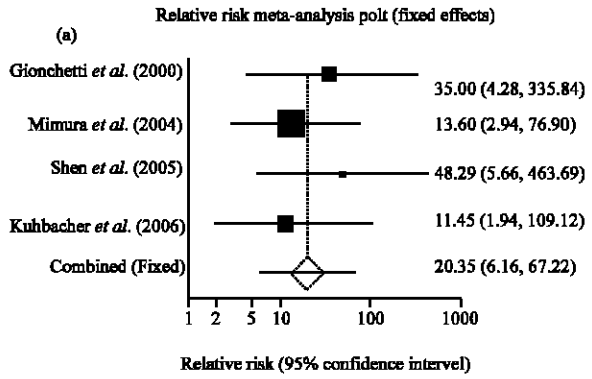

Fig. 4a: Individual and pooled relative risk for the outcome of clinical improvement in the studies considering VSL#3 (6 g day^{-1}) vs. placebo therapy

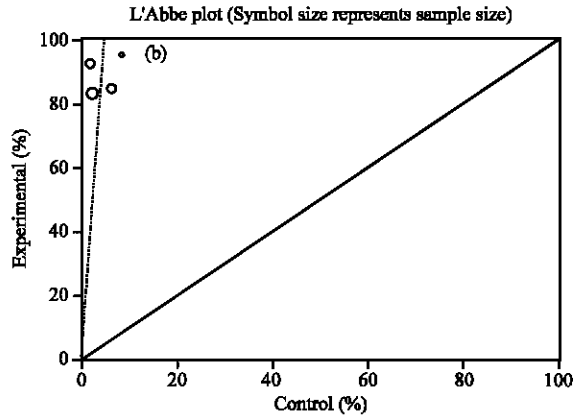

Fig. 4b: Heterogeneity indicators for the outcome of clinical improvement in the studies considering VSL#3 (6 g day^{-1}) vs. placebo therapy

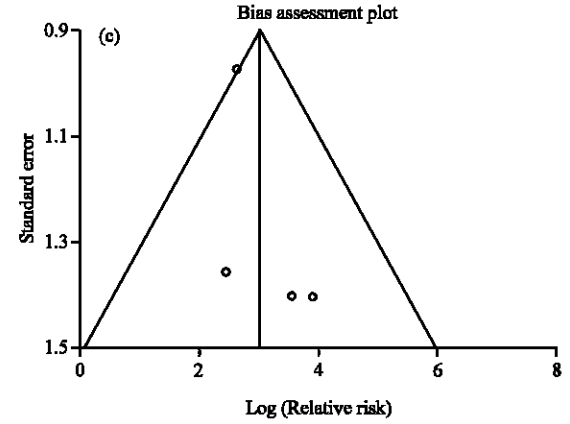

Fig. 4c: Publication bias indicators for the outcome of clinical improvement in the studies considering VSL#3 (6 g day^{-1}) vs. placebo therapy

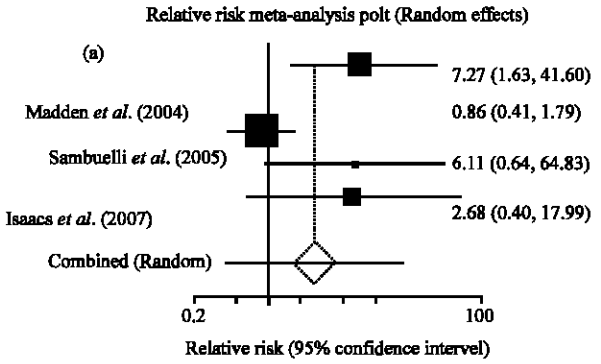

Fig. 5a: Individual and pooled relative risk for the outcome of clinical improvement in the studies considering antibiotics vs. placebo therapy

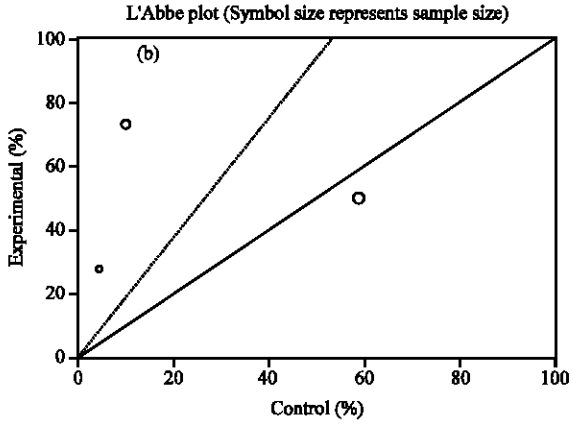

Fig. 5b: Heterogeneity indicators for the outcome of clinical improvement in the studies considering antibiotics vs. placebo therapy

Efficacy of antibiotics comparing to placebo: Summary RR for clinical improvement in three trials (Isaacs *et al.*, 2007; Madden *et al.*, 1994; Sambuelli *et al.*, 2002) was 2.68 with a 95% CI of 0.4-17.99 and a non significant RR (p = 0.3107, Fig. 5a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (p = 0.0269, Fig. 5b) and could not be combined, thus the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for clinical improvement among antibiotics vs. placebo therapy could not be calculated because of too few strata.

Efficacy of ciprofloxacin comparing to metronidazole: The summary RR for clinical improvement in two trials (Gosselink *et al.*, 2004a; Shen *et al.*, 2001) was 0.68 with a 95% CI of 0.44-1.06 and a non significant RR (p = 0.8913, Fig. 6a). The Cochrane Q test for heterogeneity indicated

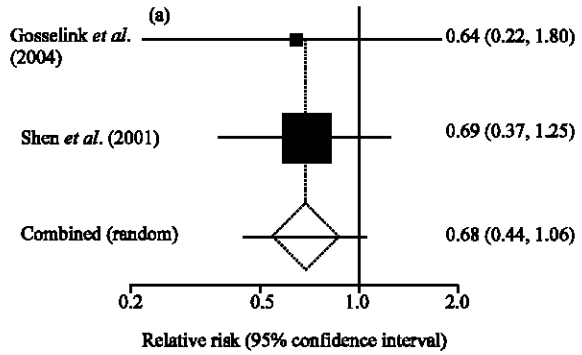

Fig. 6a: Individual and pooled relative risk for the outcome of clinical improvement in the studies considering ciprofloxacin vs. metronidazole therapy

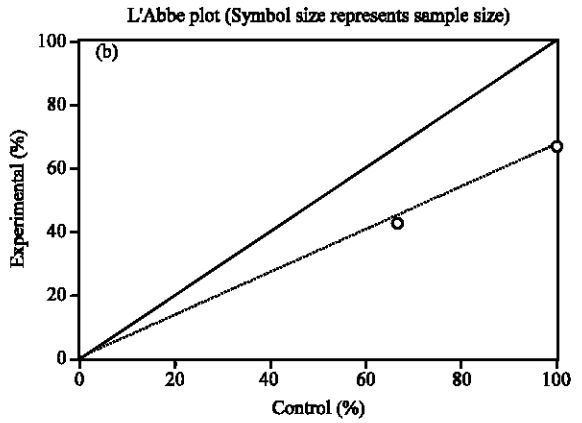

Fig. 6b: Heterogeneity indicators for the outcome of clinical improvement in the studies considering ciprofloxacin vs. metronidazole therapy

that the studies are not heterogeneous ($p = 0.0269$, Fig. 6b) and could be combined but because of few included studies, the random effects for individual and summary of RR was applied. Regression of normalized effect vs. precision for all included studies for clinical improvement among antibiotics vs. placebo therapy could not be calculated because of too few strata.

DISCUSSION

The results of this study indicate that antibiotics are not significantly more effective than placebo in management of pouchitis whereas high dose of probiotics are significantly efficient. Among antibiotics tested, ciprofloxacin was better than metronidazole while among probiotics, VSL#3, 6 g day^{-1} was more efficient than lactobacillus or even VSL#3, 3 g day^{-1} in maintenance of remission in pouchitis.

Thus, treatment is toward reducing fecal concentrations of bacteria through use of bacteria to alter the relative balance of anaerobes or other bacteria (Sandborn *et al*., 2000). Results also indicated that studies on all types of probiotics vs. placebo were heterogeneous and could not be combined. Besides, publication bias existed; we could say that this efficacy is relatively significant and homogenous and could be combined for use of VSL#3 especially in dose of 6 g day^{-1}. It has been proved that probiotics can directly or indirectly affect endogenous flora and immune system that shifts the balance between aggressive and regulator factors in response to mucosal flora toward suppressive activity (Ulisse *et al*., 2001). Pronio et al showed that treatment with VSL#3 is associated with expansion of both CD4-CD25 and CD4-LAP-regulatory T cell in filtrating the laminar propria or on the induction of nitric oxide synthesis (Pronio *et al*., 2008). In an open study in 2007, oral administration of high dose of VSL#3 which is effective in treatment of active pouchitis, was found to be related in increasing of fecal concentration of bifidiobacteria, Lactobacillus and Thermophilus (Gionchetti *et al*., 2000, 2007; Venturi *et al*., 1999) or due to increasing cytokine IL-10 and decreasing cytokine IL-1, TNF-α and INF-g (Hart *et al*., 2004; Ulisse *et al*., 2001). Considering the effectiveness of immunologic modifiers agents on IBD (Rahimi *et al*., 2007b, c), some of actions of probiotics especially VSL#3 can be well explained. Among probiotics, only high dose (6 g day) of VSL#3 acted more effectively in patients especially with severe inflammation. In contrast, treatment with L-rhamnosus GG alone didn't results in any clinical improvement of pouch inflammation (Kuisma *et al*., 2003). L-rhammosus seems to act mainly via its effect on antagonizing pathogens directly through release of antimicrobial compounds or reducing the gut pH by lactic acid production (Langhendries *et al*., 1995) competing to binding to receptor site with potential pathogens and competing with pathogens (Fujiwara *et al*., 1997; Kailasapathy and Chin, 2000) for available nutrients and other growth factors (Rolfe, 2000). Thus the idea that action of VSL on regulation of inflammation factors is more responsible for its efficacy is supported.

This meta-analysis also showed that antibiotic therapy in overall is not statistically effective in treatment of pouchitis. In addition, studies of single antibiotic therapy were heterogeneous and could not be combined. It has been demonstrated that metronidazole as a commonly-used antibiotic in the examined trials was not much effective than placebo in terms of endoscopic inflammation changes (Madden *et al*., 1994). However, comparison of ciprofloxacin with metronidazole was

homogenous and indicated that ciprofloxacin which eradicates two kinds of pathogens without disturbing majority of anaerobic bacteria is preferable to metronidazole with greater improvement in symptoms, endoscopic scores and reduction in total of PDAI. Moreover, several studies indicate adverse effect of metronidazole that is estimated about 30% when compared to 0% for ciprofloxacin (Shen *et al*., 2001). This result was also confirmed by our previous report (Elahi *et al*., 2009). Combination of ciprofloxacin with rifaximine resulted in significant improvement in clinical symptoms, endoscopic and histological activity (Abdelrazeq *et al*., 2005). This could propose the idea that combining of different kinds of antibiotic for acute pouchitis is more helpful than single therapy that has also support of other studies even for probiotics (Doherty *et al*., 2010; Elahi *et al*., 2008; Van-Gossum *et al*., 2007).

Although in the recent years, several review articles about usage of antibiotic and probiotic in pouchitis have been reported but global approval cannot be obtained yet because of limitations of various clinical trials and lack of meta-analysis. Considering different effects of probiotics containing different mixtures of microorganisms strains and antibiotics with different broad spectrums on pouchitis, there is still a need for performing studies to evaluate the flora of pouch and some randomized placebo control clinical trials about antibiotic combination therapy and antibiotic-probiotic combination therapy with defined endpoint in both acute and chronic pouchitis with clear patient's characteristics.

ACKNOWLEDGMENT

This study was in part supported by Tehran University of Medical Science.

REFERENCES

Abdelrazeq, A.S., S.M. Kelly, J.N. Lund and S.H. Leveson, 2005. Rifaximin-ciprofloxacin combination therapy is effective in chronic active refractory pouchitis. Colorectal Dis., 7: 182-186.

Doherty, G.A., G.C. Bennett, A.S. Cheifetz and A.C. Moss, 2010. Meta-analysis: Targeting the intestinal microbiota in prophylaxis for post-operative Crohn's disease. Aliment. Pharmacol. Ther., 31: 802-809.

Elahi, B., S. Nikfar, S. Derakhshani, M. Vafaie and M. Abdollahi, 2008. On the benefit of probiotics in the management of pouchitis in patients underwent ileal pouch anal anastomosis: A meta-analysis of controlled clinical trials. Dig. Dis. Sci., 53: 1278-1284.

Elahi, B., S. Nikfar, S. Derakhshani, M. Vafaie and M. Abdollahi, 2009. Benefit of antibiotic therapy on pouchitis after ileal pouch anal anastomosis: A systematic review and meta-analysis of clinical trials. Central Eur. J. Med., 4: 164-170.

Fujiwara, S., H. Hashiba, T. Hirota and J.F. Forstner, 1997. Proteinaceous factor(s) in culture supernatant fluids of bifidobacteria which prevents the binding of enterotoxigenic *Escherichia coli* to gangliotetraosylceramide. Applied Environ. Microbiol., 63: 506-512.

Furrie, E., S. Macfarlane, A. Kennedy, J.H. Cummings, S.V. Walsh, D.A. O'neil and G.T. Macfarlane, 2005. Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: A randomised controlled pilot trial. Gut, 54: 242-249.

Gionchetti, P., F. Rizzello, A. Venturi, P. Brigidi and D. Matteuzzi, *et al*., 2000. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: A double-blind, placebocontrolled trial. Gastroenterology, 119: 305-309.

Gionchetti, P., C. Amadini, F. Rizzello, A. Venturi and V. Palmonari *et al*., 2002. Probiotics-role in inflammatory bowel disease. Dig. Liver Dis., 34: 58-62.

Gionchetti, P., F. Rizzello, U. Helwig, A. Venturi and K.M. Lammers *et al*., 2003. Prophylaxis of pouchitis onset with probiotic therapy: A double-blind, placebo-controlled trial. Gastroenterology, 124: 1202-1209.

Gionchetti, P., F. Rizzello, C. Morselli, G. Poggioli and R. Tambasco *et al*., 2007. High-dose probiotics for the treatment of active pouchitis. Dis. Colon Rectum, 50: 2075-2082.

Gosselink, M.P., W.R. Schouten, L.M. Van-Lieshout, W.C. Hop, J.D. Laman and J.G. Ruseler-van Embden, 2004a. Eradication of pathogenic bacteria and restoration of normal pouch flora: Comparison of metronidazole and ciprofloxacin in the treatment of pouchitis. Dis. Colon Rectum, 47: 1519-1525.

Gosselink, M.P., W.R. Schouten, L.M.C. Van-Lieshout, W.C.J. Hop, J.D. Laman and J.G.H. Ruseler-Van Embden, 2004b. Delay of the first onset of pouchitis by oral intake of the probiotic strain *lactobacillus rhamnosus* GG. Dis. Colon Rectum, 47: 876-884.

Hart, A.L., K. Lammers, P. Brigidi, B. Vitali and F. Rizzello *et al*., 2004. Modulation of human dendritic cell phenotype and function by probiotic bacteria. Gut, 53: 1602-1609.

Isaacs, K.L., R.S. Sandler, M. Abreu, M.F. Picco and S.B. Hanauer *et al*., 2007. Rifaximin for the treatment of active pouchitis: A randomized, double-blind, placebo-controlled pilot study. Inflamm. Bowel. Dis., 13: 1250-1255.

Jadad, A., 1998. Randomized Controlled Trials. BMJ Books, London.

Kailasapathy, K. and J. Chin, 2000. Survival and therapeutic potential of probiotic organisms with reference to *Lactobacillus acidophilus* and *Bifidobacterium* spp. Immunol. Cell Biol., 78: 80-88.

Kruis, W., E. Schutz, P. Fric, B. Fixa, G. Judmaier and M. Stolte, 1997. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. Aliment. Pharmacol. Ther., 11: 853-858.

Kuhbacher, T., S.J. Ott, U. Helwig, T. Mimura and F. Rizzello *et al*., 2006. Bacterial and fungal microbiota in relation to probiotic therapy (VSL#3) in pouchitis. Gut, 55: 833-841.

Kuisma, J., S. Mentula, H. Jarvinen, A. Kahri, M. Saxelin and M. Farkkila, 2003. Effect of *Lactobacillus rhamnosus* GG on ileal pouch inflammation and microbial flora. Aliment. Pharmacol. Ther., 17: 509-515.

Langhendries, J.P., J. Detry and J. Van Hees, 1995. Effect of a fermented infant formula containing viable bifidobacteria on the fecal flora composition and pH of healthy full-term infants. J. Pediatr. Gastroenterol. Nutr., 21: 177-181.

Madden, M.V., A.S. Mc-Intyre and R.J. Nicholls, 1994. *Metronidazole* vs. placebo in chronic unremitting pouchitis. Dig. Dis. Sci., 39: 1193-1196.

Mimura, T., F. Rizzello, U. Helwig, G. Poggioli and S. Schreiber *et al*., 2002. Four-week openlabel trial of metronidazole and ciprofloxacin for the treatment of recurrent or refractory pouchitis. Aliment. Pharmacol. Ther., 16: 909-917.

Mimura, T., F. Rizzello, U. Helwig, G. Poggioli and S. Schreiber *et al*., 2004. Once daily high dose probiotic therapy (VSL 3) for maintaining remission in recurrent or refractory pouchitis. Gut, 53: 108-114.

Nikfar, S., R. Rahimi, F. Rahimi, S. Derakhshani and M. Abdollahi, 2008. Efficacy of probiotics in irritable bowel syndrome: A meta-analysis of randomized, controlled trials. Dis. Colon Rectum, 51: 1775-1780.

Ohge, H., J.K. Furne, J. Springfield, D.A. Rothenberger, R.D. Madoff and M.D. Levitt, 2005. Association between fecal hydrogen sulfide production and pouchitis. Dis. Colon Rectum, 48: 469-475.

Pochapin, M., 2000. The effect of probiotics on *Clostridium difficile diarrhoea*. Am. J. Gastroenterol., 95: 11-13.

Pronio, A., C. Montesani, C. Butteroni, S. Vecchione and G. Mumolo *et al*., 2008. Probiotic administration in patients with ileal pouch-anal anastomosis for ulcerative colitis is associated with expansion of mucosal regulatory cells. Inflamm. Bowel Dis., 14: 662-668.

Rahimi, R., S. Nikfar, A. Rezaie and M. Abdollahi, 2006. A meta-analysis of broad-spectrum antibiotic therapy in patients with active Crohns disease. Clin. Ther., 28: 1983-1988.

Rahimi, R., S. Nikfar, A. Rezaie and M. Abdollahi, 2007a. A meta-analysis of antibiotic therapy for active ulcerative colitis. Dig. Dis. Sci., 52: 2920-2925.

Rahimi, R., S. Nikfar and M. Abdollahi, 2007b. Meta-analysis technique confirms the effectiveness of anti-TNF-á in the management of active ulcerative colitis when administered in combination with corticosteroids. Med. Sci. Monit., 13: 113-118.

Rahimi, R., S. Nikfar and M. Abdollahi, 2007c. Do anti-tumor necrosis factors induce response and remission in patients with acute refractory Crohns disease? A systematic meta-analysis of controlled clinical trials. Biomed. Pharmacother., 61: 75-80.

Rahimi, R., S. Nikfar, F. Rahimi, B. Elahi, S. Derakhshani, M. Vafaie and M. Abdollahi, 2008a. A meta-analysis on the efficacy of probiotics for maintenance of remission and prevention of clinical and endoscopic relapse in Crohns disease. Dig. Dis. Sci., 53: 2524-2531.

Rahimi, R., S. Nikfar and A. Rezaie, 2008b. 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. Arch. Med. Sci., 4: 185-190.

Rezaie, A., S. Nikfar and M. Abdollahi, 2010. The place of antibiotics in management of irritable bowel syndrome: A systematic review and meta-analysis. Arch. Med. Sci., 6: 49-55.

Rolfe, R., 2000. The role of probiotic cultures in the control of gastrointestinal health. J. Nutr., 130: 396-402.

Ruseler-van Embden, J.G., W.R. Schouten and L.M. Van-Lieshout, 1994. Pouchitis: Result of microbial imbalance?. Gut, 35: 658-664.

Sambuelli, A., L. Boerr, S. Negreira, A. Gil and G. Camartino *et al*., 2002. Budesonide enema in pouchitis-A double-blind, double-dummy, controlled trial. Aliment. Pharmacol. Ther., 16: 27-34.

Sandborn, W.J., 1994. Pouchitis following ileal pouch-anal anastomosis: Defnition, pathogenesis and treatment. Gastroenterology, 107: 1856-1860.

Sandborn, W.J., W.J. Tremaine, K.P. Battsa, J.H. Pemberton and S.F. Phillips, 1994. Pouchitis after ileal pouch-anal anastomosis: A pouchitis dis activity index. Mayo. Clin. Proc., 69: 409-415.

Sandborn, W.J., R.S. McLeod and D.P. Jewell, 2000. Pharmacotherapy for induction and maintenance of remission in pouchitis. Cochrane Database Syst. Rev., 2: 1176-1176.

Sen, S., M.M. Mullan, T.J. Parker, J.T. Woolner, S.A. Tarry and J.O. Hunter, 2002. Effect of *Lactobacillus plantarum* 299v on colonic fermentation and symptoms of irritable bowel syndrome. Dig. Dis. Sci., 47: 2615-2620.

Shen, B., J.P. Achkar, B.A. Lashner, A.H. Ormsby and F.H. Remzi *etal*., 2001. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. Inflamm. Bowel Dis., 7: 301-305.

Shen, B., A. Brzezinski, V.W. Fazio, F.H. Remzi and J.P. Achkar *et al*., 2005. Maintenance therapy with a probiotic in antibiotic-dependent pouchitis: Experience in clinical practice. Aliment. Pharmacol. Ther., 22: 721-728.

Stochi, L. and J.H. Pemberton, 2001. Pouch and pouchitis. Gastroenteral. Clin. N. Am., 30: 223-241.

Ulisse, S., P. Gionchetti, S. Dalo, F.P. Russo and I. Pesce *et al*., 2001. Expression of cytokines, inducible nitric oxide synthase and matrix metalloproteinases in pouchitis: Effects of probiotic treatment. Am. J. Gastroenterol., 96: 2691-2699.

Van-Gossum, A., O. Dewit, E. Louis, G. De-Hertogh and F. Baert *et al*., 2007. Multicenter randomized-controlled clinical trial of probiotics (*Lactobacillus johnsonii*, LA1) on early endoscopic recurrence of crohn's disease after ileo-caecal resection. Inflamm. Bowel Dis., 13: 135-142.

Venturi, A., P. Gionchetti, F. Rizzello, R. Johansson and E. Zucconi *et al*., 1999. Impact on the faecal flora composition of a new probiotic preparation. Preliminary data on maintenance treatment of patients with ulcerative colitis (UC) intolerant or allergic to 5-aminosalicylic acid (5-ASA). Aliment. Pharmacol. Ther., 13: 1103-1108.