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[Intervention Review]

Interventions for treating lymphocytic colitis

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ABSTRACT

Background

Lymphocytic colitis is a cause of chronic diarrhea. It is a subtype of microscopic colitis characterized by chronic, watery, non-bloody diarrhea and normal endoscopic and radiologic findings. The etiology of this disorder is unknown. Therapy is based mainly on case series and uncontrolled trials, or by extrapolation of data for treating collagenous colitis, a related disorder. This review is an update of a previously published Cochrane review.

Objectives

To evaluate the efficacy and safety of treatments for clinically active lymphocytic colitis.

Search methods

The MEDLINE, PUBMED and EMBASE databases were searched from inception to 11 August 2016 to identify relevant papers. Manual searches from the references of included studies and relevant review articles were performed.

Abstracts from major gastroenterological meetings were also searched to identify research submitted in abstract form only. The trial registry web site www.ClinicalTrials.gov was searched to identify registered but unpublished trials. Finally, the Cochrane Central Register of Controlled Trials and the Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group Specialized Trials Register were searched for other studies.

Selection criteria

Randomized controlled trials assessing medical therapy for patients with biopsy-proven lymphocytic colitis were considered for inclusion

Data collection and analysis

Data was independently extracted by at least two authors. Any disagreements were resolved by consensus. Data were analyzed on an intention-to-treat (ITT) basis. The primary outcome was clinical response as defined by the included studies. Secondary outcome measures included histological response as defined by the included studies, quality of life as measured by a validated instrument and the occurrence of adverse events. Risk ratios (RR) and 95% confidence intervals (CI) were calculated for dichotomous outcomes. The methodological quality of included studies was evaluated using the Cochrane risk of bias tool. The overall quality of the evidence supporting the primary outcome and selected secondary outcomes was assessed using the GRADE criteria. Data were combined for analysis if they assessed the same treatments. Dichotomous data were combined using a pooled RR along with corresponding 95% CI. A fixed-effect model was used for the pooled analysis.

Main results

Five RCTs (149 participants) met the inclusion criteria. These studies assessed bismuth subsalicylate versus placebo, budesonide versus placebo, mesalazine versus mesalazine plus cholestyramine and beclometasone dipropionate versus mesalazine. The study which assessed mesalazine versus mesalazine plus cholestyramine and the study which assessed beclometasone dipropionate versus mesalazine were judged to be at high risk of bias due to lack of blinding. The study which compared bismuth subsalicylate versus placebo was judged as low quality due to a very small sample size and limited data. The other 3 studies were judged to be at low risk of bias. Budesonide (9 mg/day for 6 to 8 weeks) was significantly more effective than placebo for induction of clinical and histological response. Clinical response was noted in 88% of budesonide patients compared to 38% of placebo patients (2 studies; 57 participants; RR 2.03, 95% CI 1.25 to 3.33; GRADE = low). Histological response was noted in 78% of budesonide patients compared to 33% of placebo patients (2 studies; 39 patients; RR 2.44, 95% CI 1.13 to 5.28; GRADE = low). Forty-one patients were enrolled in the study assessing mesalazine (2.4 g/day) versus mesalazine plus cholestyramine (4 g/day). Clinical response was noted in 85% of patients in the mesalazine group compared to 86% of patients in the mesalazine plus cholestyramine group (RR 0.99, 95% CI 0.77 to 1.28; GRADE = low). Five patients were enrolled in the trial studying bismuth subsalicylate (nine 262 mg tablets daily for 8 weeks versus placebo). There were no differences in clinical ($P=0.10$) or histological responses ($P=0.71$) in patients treated with bismuth subsalicylate compared with placebo (GRADE = very low). Forty-six patients were enrolled in the trial studying beclometasone dipropionate (5 mg/day or 10 mg/day) versus mesalazine (2.4 g/day). There were no differences in clinical remission at 8 weeks (RR 0.97; 95% CI 0.75 to 1.24; GRADE = low) and 12 months of treatment (RR 1.29; 95% CI 0.40 to 4.18; GRADE = very low). Although patients receiving beclometasone dipropionate (84%) and mesalazine (86%) achieved clinical remission at 8 weeks, it was not maintained at 12 months (26% and 20%, respectively). Adverse events reported in the budesonide studies include nausea, vomiting, neck pain, abdominal pain, hyperhidrosis and headache. Nausea and skin rash were reported as adverse events in the mesalazine study. Adverse events in the beclometasone dipropionate trial include nausea, sleepiness and change of mood. No adverse events were reported in the bismuth subsalicylate study.

Authors' conclusions

Low quality evidence suggests that budesonide may be effective for the treatment of active lymphocytic colitis. This benefit needs to be confirmed by a large placebo-controlled trial. Low quality evidence also suggests that mesalazine with or without cholestyramine and beclometasone dipropionate may be effective for the treatment of lymphocytic colitis, however this needs to be confirmed by large placebo-controlled studies. No conclusions can be made regarding bismuth subsalicylate due to the very small number of patients in the study. Further trials studying interventions for lymphocytic colitis are warranted.

PLAIN LANGUAGE SUMMARY

Treatments for lymphocytic colitis

What is lymphocytic colitis?

Lymphocytic colitis is a type of microscopic colitis, a condition characterized by chronic non-bloody watery diarrhea. People with lymphocytic colitis have a normal appearing bowel when assessed by an endoscope (a camera used to look at the bowel) or an X-ray; but have microscopic (histological) inflammation of the bowel when assessed by a biopsy (a tissue sample taken during endoscopy). The cause of this disorder is unknown. This review is an update of a previously published Cochrane review.

What treatments have been tried for lymphocytic colitis?

Budesonide, mesalazine with or without cholestyramine, beclometasone dipropionate and bismuth subsalicylate (i.e. Pepto-Bismol®) have been tried as treatment for lymphocytic colitis. Budesonide is an immunosuppressive steroid drug that is quickly metabolized by the liver resulting in reduced steroid-related side-effects. It is taken by mouth. Beclometasone dipropionate is also a steroid drug. Steroid drugs are used to treat inflammation. Mesalazine (also known as 5-ASA) is an anti-inflammatory drug which is often taken by mouth. Cholestyramine is a drug that helps the body remove bile acids. Pepto-Bismol®, is an antacid medication used to treat temporary discomforts of the stomach and gastrointestinal tract.

What did the researchers investigate?

The researchers investigated whether these drugs improve the symptoms of lymphocytic colitis (e.g. diarrhea) or microscopic inflammation and whether any side effects result from treatment. The researchers searched the medical literature extensively up to 11 August 2016.

What did the researchers find?

Five studies including 149 participants were identified. These studies assessed budesonide versus placebo (e.g. a sugar pill), mesalazine versus mesalazine plus cholestyramine and beclometasone dipropionate versus mesalazine and Pepto-Bismol® versus placebo. The study which compared mesalazine to mesalazine plus cholestyramine and the study which compared beclometasone dipropionate to mesalazine were judged to be of low quality. The study which compared Pepto-Bismol® bismuth subsalicylate to a placebo was judged as low quality due to a very small sample size (5 participants) and limited data. The other three studies were judged to be high quality.

A pooled analysis of two studies (57 participants) showed that budesonide (9 mg/day for 6 to 8 weeks) was superior to placebo for improvement of diarrhea and improvement of microscopic inflammation of the bowel. Improvement in diarrhea was noted in 88% of budesonide participants compared to 38% of placebo participants. Improvement in microscopic inflammation was reported in 78% of budesonide participants compared to 33% of placebo participants. Forty-one participants were enrolled in the study that compared mesalazine (2.4 g/day) to mesalazine plus cholestyramine (4 g/day). Improvement in diarrhea was noted in 85% of participants in the mesalazine group compared to 86% of participants in the mesalazine plus cholestyramine group. Five patients were enrolled in the trial studying Pepto-Bismol® (nine 262 mg tablets daily for 8 weeks versus placebo). There were no differences in improvement of diarrhea or in improvement of microscopic inflammation of the bowel. Forty-six participants were enrolled in the trial studying beclometasone dipropionate (5 mg/day or 10 mg/day) versus mesalazine (2.4 g/day). Although participants receiving beclometasone dipropionate (84%) and mesalazine (86%) had improved diarrhea at 8 weeks, this improvement was not maintained at 12 months (26% and 20%, respectively). Side effects reported in the budesonide studies include nausea, vomiting, neck pain, abdominal pain, excessive sweating and headache. Side effects reported in the mesalazine plus cholestyramine study included nausea and skin rash. Side effects in the beclometasone dipropionate trial included nausea, sleepiness and change of mood. No side effects were reported in the Pepto-Bismol® study.

Low quality evidence suggests that budesonide may be an effective therapy for the treatment of lymphocytic colitis. Low quality evidence also suggests that mesalazine with or without cholestyramine and beclometasone dipropionate may be effective for treatment of lymphocytic colitis. No conclusions can be made regarding bismuth subsalicylate due to the very small number of participants in the study. In the future, researchers should consider further large placebo-controlled trials of budesonide to confirm the suggested benefit and safety of this therapy. Bismuth subsalicylate, which has less potential for toxicity than budesonide, also warrants further study. The effectiveness and safety of mesalazine with or without cholestyramine, and beclometasone dipropionate need to be investigated in a large placebo-controlled studies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Bismuth subsalicylate versus placebo for treating lymphocytic colitis

Bismuth subsalicylate versus placebo for treating lymphocytic colitis

Patient or population: patients with active lymphocytic colitis

Settings: outpatient

Intervention: bismuth subsalicylate versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	control	bismuth vs placebo				
Clinical response	0 per 1000 ¹	0 per 1000	RR 5.25 (0.94 to 1.90)	5 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	
Histological response	500 per 1000 ¹	665 per 1000 (135 to 3300)	RR 1.33 (0.27 to 6.6)	5 (1 study)	⊕⊕⊕⊕ very low ^{2,3}	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to unclear risk of bias for allocation concealment.

³ Downgraded two levels due to very sparse data (3 events).

Summary of findings 2. Budesonide versus mesalazine for treating lymphocytic colitis

Budesonide versus mesalazine for treating lymphocytic colitis

Patient or population: patients with active lymphocytic colitis

Settings: outpatient
Intervention: budesonide versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	control	budesonide versus placebo				
Clinical response	440 per 1000 ¹	893 per 1000 (550 to 1000)	RR 2.03 (1.25 to 3.33)	57 (2 studies)	⊕⊕○○ low ^{2,3}	
Histological response	313 per 1000 ¹	763 per 1000 (353 to 1000)	RR 2.44 (1.13 to 5.28)	39 (2 studies)	⊕⊕○○ low ⁴	
Adverse events	143 per 1000 ¹	96 per 1000 (17 to 513)	RR 0.67 (0.12 to 3.59)	42 (1 study)	⊕⊕○○ low ⁵	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to unclear risk of bias for blinding or participants and personnel

³ Downgraded one level due to sparse data (39 events).

⁴ Downgraded two levels due to very sparse data (23 events).

⁵ Downgraded two levels due to very sparse data (5 events).

Summary of findings 3. Mesalazine versus mesalazine + cholestyramine for treating lymphocytic colitis

Mesalazine versus mesalazine + cholestyramine for treating lymphocytic colitis

Patient or population: patients with maintenance of remission in lymphocytic colitis

Settings: outpatient

Intervention: Mesalazine versus mesalazine + cholestyramine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	mesalazine	mesalazine plus cholestyramine				
Clinical response	857 per 1000	849 per 1000 (660 to 1000)	RR 0.99 (0.77 to 1.28)	41 (1 study)	⊕⊕⊕⊕ low ^{2,3}	
Histological response	857 per 1000	849 of 1000 (660 to 1000)	RR 0.99 (0.77 to 1.28)	41 (1 study)	⊕⊕⊕⊕ low ^{2,3}	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to high risk of bias (no blinding) and unclear allocation concealment

³ Downgraded one level due to sparse data (35 events)

Summary of findings 4. Beclometasone dipropionate versus mesalazine for treating lymphocytic colitis

Beclometasone dipropionate versus mesalazine for treating lymphocytic colitis

Patient or population: Patients with active or quiescent lymphocytic colitis

Settings: outpatient

Intervention: Beclometasone dipropionate versus mesalazine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Mesalazine	beclometasone				

Clinical response at 8 weeks	867 per 1000 ¹	841 per 1000 (650 to 1075)	RR 0.97 (0.75 to 1.24)	46 (1 study)	⊕⊕○○ low ^{2,3}
Maintenance of clinical response at 12 weeks	200 of 1000 ¹	258 per 1000 (80 to 836)	RR 1.29 (0.40 to 4.18)	46 (1 study)	⊕○○○ very low ^{2,4}

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Control group risk estimates come from control arm of meta-analysis, based on included trials.

² Downgraded one level due to high risk of bias (no blinding) .

³ Downgraded one level due to sparse data (39 events)

⁴ Downgraded two levels due to very sparse data (11 events)

BACKGROUND

Lymphocytic colitis is a cause of chronic watery diarrhea. It is related to collagenous colitis, and together these two disorders are more broadly categorized as "microscopic colitis", with normal radiologic and endoscopic findings, but typical histological features on biopsies. Population-based studies in Europe have reported an annual incidence of collagenous colitis ranging from 0.6 to 5.2 per 100,000 persons and a prevalence of 10 to 15.7 per 100,000 population, while lymphocytic colitis has a reported annual incidence ranging from 3.1 to 4.4 per 100,000 persons and a prevalence of 14.2 per 100,000 population (Agnarsdottir 2002; Bohr 1995; Fernandez 1999; Olesen 2004a; Raclot 1994). A population based study in the United States reported an annual incidence of collagenous and lymphocytic colitis of 5.1 and 9.8 per 100,000 persons and a prevalence of 36 and 64 per 100,000 population respectively (Pardi 2004a).

Lymphocytic colitis is distinguished from collagenous colitis by the presence of an increased number of intraepithelial lymphocytes (>20 per 100 epithelial cells) and the absence of a markedly thickened subepithelial collagen band. The etiology and pathogenesis of lymphocytic colitis are uncertain, although links to autoimmune disorders and the use of nonsteroidal anti-inflammatory drugs have been suggested (Loftus 2003; Pardi 2004b; Schiller 2004). Treatment has been mainly based on anecdotal evidence, and includes dietary modification, antidiarrheals, bulking agents, bile acid binding agents, spasmolytics, antibiotics, bismuth subsalicylate, sulfasalazine/other 5-ASA products, traditional corticosteroids, budesonide, azathioprine/6-mercaptopurine, cyclosporine, probiotics and surgery (See Table 1). Various therapies have been evaluated in randomized controlled studies in patients with collagenous colitis (Chande 2008a), but it is not known if the results of these studies can be extrapolated to treating patients with lymphocytic colitis. Treatments for lymphocytic colitis that have been investigated in randomized controlled trials include budesonide (Miehlike 2009; NCT00184171; Pardi 2009), mesalazine with or without cholestyramine (Calabrese 2007), bismuth subsalicylate (Fine 1999; NCT00184171) and beclometasone dipropionate (Latella 2010). This systematic review is an update of a previously published Cochrane review (Chande 2007; Chande 2008b).

OBJECTIVES

To evaluate the effectiveness of therapies for clinically active lymphocytic colitis studied in randomized trials.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials were considered for inclusion. Studies published as abstracts were only included if the authors could be contacted to obtain further information.

Types of participants

Patients with biopsy-proven clinically active lymphocytic colitis without other significant radiologic or endoscopic findings were considered for inclusion.

Types of interventions

All types of therapy were eligible for inclusion.

Types of outcome measures

The primary outcome measure was clinical response as defined by the included studies (e.g. decreased stool frequency or stool weight or both). Secondary outcome measures included histological response as defined by the included studies, quality of life as measured by a validated instrument and the occurrence of adverse events.

Search methods for identification of studies

Electronic searches

EMBASE, MEDLINE, the Cochrane Library (CENTRAL) and the Cochrane IBD Group Specialized Register were searched from inception to 11 August 2016. The search strategies are listed in Appendix 1. Conference abstracts from Digestive Disease Week and the United European Gastroenterology Week were also searched to identify abstract publications.

Searching other resources

We searched reference lists from potentially relevant papers to identify additional studies that may have been missed using the computer-assisted search strategy. The trial database clinicaltrials.gov was also searched to identify studies that may have not been reported.

Data collection and analysis

Study Selection:

At least two authors (NY, TMN or TB) Each author independently reviewed potentially relevant studies to determine eligibility based on the criteria specified above. Studies published in abstract form were only included if the authors could be contacted to clarify details about the protocol and results. Any disagreement was resolved by consensus.

Data Collection:

A data extraction form was developed and used to extract information on results of included studies. A minimum of two authors (NY, TMN or TB) independently extracted the data, any disagreement among authors was resolved by consensus.

Statistical Analysis:

Data was analyzed using Review Manager (RevMan 5.3.5). If cross-over studies are identified in future updates, only data from the first arm will be included. All data were analyzed on an intention-to-treat basis. Data were extracted and converted into two by two tables (treatment versus comparator and clinical response versus no response; treatment versus comparator and histological response versus no response). For therapies assessed in one trial only, P values were derived using the Chi² test. If in the future, therapies are assessed in more than one trial, summary test statistics will be derived by calculating the risk ratio (RR) and corresponding 95% confidence interval (95% CI). The authors of each paper set the definitions of clinical and histological response and the data were combined for analysis only if these definitions were sufficiently similar (determined by consensus). The presence of heterogeneity among studies was assessed using the Chi² test (a P value of 0.10 will be regarded as statistically significant). If

statistically significant heterogeneity is identified the RR and 95% CI will be calculated using a random-effects model.

Quality Assessment:

At least two authors (NY, TMN or TB) independently assessed the methodological quality of included studies using the Cochrane risk of bias tool ([Higgins 2011](#)). Factors assessed included:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants, outcome assessors and investigators;
4. Incomplete outcome reporting (i.e. there was an acceptable method of dealing with attrition);
5. Selective outcome reporting (i.e. all outcomes described in the methods were included in the analysis);
6. Other potential sources of bias.

A judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias. Disagreements were resolved by consensus. Study authors were contacted when insufficient information was provided to determine risk of bias.

We used the GRADE criteria to assess the overall quality of the evidence supporting the primary outcome and selected secondary outcomes ([Schünemann 2011](#)). The overall quality of evidence can be graded as:

1. High: Further research is very unlikely to change our confidence in the estimate of effect;
2. Moderate: Further research is likely to have an impact on our confidence in the estimate of effect and may change the estimate;

3. Low: Further research is very likely to have an important impact on our confidence on the estimate of effect and is likely to change the estimate; or

4. Very low: Any estimate of effect is very uncertain.

The overall quality of evidence can be downgraded by one (serious concern) or two levels (very serious concern) for the following reasons: risk of bias, inconsistency (e.g. unexplained heterogeneity), indirectness (e.g. indirect population, intervention, control or outcomes), publication bias, and imprecision (e.g. sparse data, few events). Imprecision was determined principally by a small number of studies for a comparison (two or fewer studies) and fewer than 100 events for that comparison. We used the GRADEproGDT software to produce Summary of Findings Tables.

RESULTS

Description of studies

A literature search conducted on August 11, 2016 identified 333 records. Two additional studies were identified through searching of conference and other sources. After duplicates were removed, a total of 248 trials remained for review of titles and abstracts. Twenty-seven studies were selected for full text review (see [Figure 1](#)). Twenty studies were excluded (See: [Characteristics of excluded studies](#)). Seven reports of 5 studies (n = 149 patients) met the pre-defined inclusion criteria and were included in the review ([Fine 1999](#); [Calabrese 2007](#); [Miehlke 2009](#); [Pardi 2009](#); [Latella 2010](#)). A search of clinical trials.gov identified two ongoing randomized trials ([NCT00184171](#); [NCT01209208](#)). The [NCT00184171](#) study plans to assess the treatment of lymphocytic colitis with budesonide (9 mg/day), bismuth or fiber. The [NCT01209208](#) plans to assess treatment of lymphocytic colitis with budesonide (9 mg/day), mesalazine (3 g/day) or placebo. The results of these ongoing studies will be included in future updates of this review when the study results become available.

Figure 1. Study flow diagram.

Fine 1999, which was published in abstract form only, was a randomized, double-blind, placebo-controlled trial that compared bismuth subsalicylate to placebo in 14 patients (11 females; 3 males; age range 35 to 78 years) with microscopic colitis. Of these, five patients had lymphocytic colitis and nine had collagenous colitis. Patients were treated with bismuth subsalicylate ($n = 3$; nine 262 mg chewable tablets daily in 3 divided doses) or an identical placebo ($n = 2$) for 8 weeks. Each patient underwent 48-hour stool collection prior to treatment and on the last two days of treatment stool weight and consistency were evaluated using standardized criteria. All patients underwent flexible sigmoidoscopy with standardized biopsy prior to entry and after treatment. Patients were not to take antibiotics or anti-inflammatory agents for a minimum of 6 weeks, and antidiarrheals for minimum of 2 weeks prior to entry. Clinically active lymphocytic colitis was defined as at least eight weeks of non-bloody watery diarrhea with normal radiologic and endoscopic findings. Lymphocytic colitis was confirmed by histopathology consisting of excess mononuclear inflammatory cells in the lamina propria and surface epithelium without significant neutrophilic or eosinophilic inflammation, numerous crypt abscesses, or granuloma; the absence of a thickened subepithelial collagen band; and no other evidence of Crohn's disease. The histological score ranged from 0 to 10 and was based on the following five parameters: surface epithelium (microulceration, cell flattening and mucin depletion - scored 0 to 2); crypts; lamina propria cellularity; numbers of intraepithelial lymphocytes within the surface epithelium and the number of intra epithelial lymphocytes within the crypt epithelium. A clinical response was defined as the improvement of diarrhea to the passage of two or less formed or semi formed stools per day. A histological response was defined as a reduction in the histopathology score by greater than 50%. Adverse events were also documented.

Calabrese 2007 was a randomized, open-label trial comparing mesalazine to mesalazine plus cholestyramine for the treatment of patients with active microscopic colitis. The study included 23 patients with collagenous colitis and 41 with lymphocytic colitis. Patients were randomized via a computer generated list to oral mesalazine 800 mg three times daily ($n = 20$) or oral mesalazine 800 mg three times daily plus cholestyramine 4 g once daily ($n = 21$) for 6 months of treatment. The diagnosis of lymphocytic colitis was based on clinical and histological criteria. Clinically active lymphocytic colitis was defined as chronic or recurrent non-bloody diarrhea. Histological criteria included increased chronic inflammatory infiltrate (plasma cells, lymphocytes, eosinophils) in the lamina propria; increased number of intraepithelial lymphocytes, damage to surface epithelium, with flattening of epithelial cells or epithelial loss or both and detachment and minimal crypt architecture distortion. In addition, the number of intraepithelial lymphocytes had to be greater than 20 per 100 epithelial cells in the absence of a thickened subepithelial collagen layer to diagnose lymphocytic colitis. Patients with a clear correlation between symptoms and consumption of drugs (e.g. nonsteroidal anti-inflammatory drugs (NSAIDs), ticlopidine, or proton pump inhibitors) were excluded. All patients underwent a colonoscopy pre-treatment and 20 patients also underwent a colonoscopy at the end of 6 months. Outcomes included complete and partial clinical response and histological response. Complete response was defined as complete resolution of diarrhea. Partial clinical response was defined as improvement but not resolution of diarrhea. Histological response was defined as normalization of

histologic pattern at the end of six months. Adverse events were also reported.

Miehlke 2009 was a randomized, double-blind, placebo-controlled trial that compared oral budesonide to placebo in patients with lymphocytic colitis. Forty-two patients (28 females; 14 males; median age 61) with lymphocytic colitis were randomized in a 1:1 ratio via a centralized randomization list in blocks of four to receive oral budesonide (9 mg/day, $n = 21$) or placebo ($n = 20$) for 6 weeks of treatment. Non-responders at week six were treated with open-label budesonide (9 mg/day) for an additional 6 weeks. Clinically active lymphocytic colitis was defined as more than three watery or loose stools per day on average, for at least 4 weeks. The diagnosis of lymphocytic colitis was based on histology and confirmed by the central pathologist. The number of intraepithelial lymphocytes had to be greater than 20/100 epithelial cells, with inflammation of the lamina propria. The primary outcome measure was clinical remission at 6 weeks which was defined as no more than 3 non-watery stools per day on average, and a reduction in more than stool compared with screening. Complete colonoscopy including histology was assessed at entry and after 6 weeks, and was used to determine rates of histological remission and histological response. Histological remission was defined as a reduction in the number of intraepithelial lymphocytes to less than 20/100 epithelial cells, plus a reduction in lamina propria inflammation. Histological response was defined as a greater than 50% reduction in the number of intraepithelial lymphocytes compared to baseline or a reduction in lamina propria inflammation or both. Other outcome measures included clinical remission from lymphocytic colitis after 3 weeks, quality of life, which was assessed at entry and after 6 weeks with the validated SF-36 instrument (a 36 item questionnaire measuring both physical and mental components of quality of life), and the occurrence of adverse events.

Pardi 2009 was a double-blind, randomized controlled trial comparing controlled ileal-release budesonide to placebo for the treatment of patients with diarrhea and microscopically confirmed lymphocytic colitis (the criteria were not described). Patients with possible drug-induced lymphocytic colitis were excluded, unless symptoms persisted despite discontinuation of the offending medication. The study included 15 patients who were randomized to receive either 9 mg/day of budesonide (3 x 3 mg; $n = 11$) or three placebo capsules ($n = 4$). Symptoms were self-recorded daily then averaged for each week of the study. The primary outcome was global assessment of improvement in diarrhea as assessed by the patient. This was defined as at least a 50% improvement in the frequency of bowel movements in at least three of the last four weeks of the study, compared to baseline. Clinical histologic features were graded on a four-point scale which accounted for features such as intraepithelial lymphocyte infiltration and lamina propria cellularity. Colon biopsies were taken before study entry, and follow-up sigmoidoscopy and biopsy was requested from each subject at the end of the study. No definitions were provided for either complete or partial clinical remission, or histologic remission. As such, all results were described in terms of either improvement or worsening of the patient's condition. In our analysis, we defined clinical response as an improvement in global assessment score and histologic response as an improvement in the histologic score. Secondary outcomes included improvement in number of bowel movements per day, consistency of stool, abdominal discomfort, histology and adverse events.

Latella 2010, which was published in abstract form only, was a randomized, open-label trial comparing beclometasone dipropionate to mesalazine for the treatment of patients with lymphocytic colitis. The study included 46 patients with lymphocytic colitis. The diagnosis of lymphocytic colitis was based on clinical and histological criteria. Clinically active lymphocytic colitis was defined as greater than 3 watery or loose stools per day on average per week and a history of diarrhea lasting for more than four weeks. Histologic criteria included a complete colonoscopy with colonic biopsies within four weeks of entry, and a histologically confirmed diagnosis of active lymphocytic colitis.

Patients were randomized to receive beclometasone dipropionate 5 mg/day (n = 18), beclometasone dipropionate 10 mg/day (n = 13) or mesalazine 2.4 g/day (n = 15) for 8 weeks. Outcomes included clinical remission at 8 weeks, defined as less than or equal to 3 soft or solid stools per day during the last week of treatment, and relapse at 6 and 12 months after treatment, defined as greater than three stools per day on four or more consecutive days.

Risk of bias in included studies

The overall results of the risk of bias analysis are reported in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Calabrese 2007	+	?	-	+	+	+
Fine 1999	+	?	+	+	+	+
Latella 2010	+	+	-	+	+	+
Miehlke 2009	+	+	+	+	+	+
Pardi 2009	+	+	?	+	+	+

Allocation

Fine 1999 reported that randomization was achieved by pulling pieces of paper out of a sealed box. Based on this information we decided to rate random sequence generation as low risk. The other four studies reported the use of computer-generated

randomization and these studies were also rated as low risk of bias (Calabrese 2007; Latella 2010; Miehlke 2009; Pardi 2009).

Two studies did not describe methods used for allocation concealment and were rated as unclear for this item (Calabrese 2007; Fine 1999). Two studies employed a centralized

randomization scheme and were rated as low risk of bias for allocation concealment (Miehlke 2009; Latella 2010). The Pardi 2009 used opaque sealed envelopes to conceal allocation and therefore this was rated as low risk of bias for this item.

Blinding

Two studies were open-label and were rated as high risk of bias for blinding (Calabrese 2007; Latella 2010). Both the caregivers and data analysts were blinded for the Latella 2010 study. Two studies were described as double-blind and utilized an identical placebo and thus were rated as low risk of bias for blinding (Fine 1999; Miehlke 2009). The Pardi 2009 study was described as double-blind. However, an identical placebo was not available from the sponsor at the time of the study. All research personnel including the pathologist were blinded to treatment assignment. Patients did not know treatment assignment unless they discovered what budesonide was supposed to look like. The authors did not formally assess whether patients knew which treatment they received. The Pardi 2009 study was rated as unclear risk of bias for blinding.

Incomplete outcome data

Three studies reported that there were no drop outs (Calabrese 2007; Pardi 2009; Latella 2010). These studies were rated as low risk of bias for incomplete outcome data. One patient dropped out of the Fine 1999 study, which was rated as low risk of bias for incomplete outcome data. Dropouts were balanced across treatment groups in the Miehlke 2009 study and this study was rated as low risk of bias for incomplete outcome data.

Selective reporting

All of the included studies were rated as low risk of bias for selective outcome reporting as all expected outcomes were reported.

Other potential sources of bias

All of the included studies were rated as low risk of bias for other potential sources of bias. These studies appeared to be free of other potential sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison Bismuth subsalicylate versus placebo for treating lymphocytic colitis](#); [Summary of findings 2 Budesonide versus mesalazine for treating lymphocytic colitis](#); [Summary of findings 3 Mesalazine versus mesalazine + cholestyramine for treating lymphocytic colitis](#); [Summary of findings 4 Beclometasone dipropionate versus mesalazine for treating lymphocytic colitis](#)

Bismuth subsalicylate versus placebo

Clinical response

In the Fine 1999 study, all 3 patients in the bismuth subsalicylate group achieved a clinical response after 8 weeks of treatment, while those 2 patients assigned to placebo did not (RR 5.25, 95% CI 0.41 to 67.73). A GRADE analysis rated the overall quality of the evidence supporting this outcome as very low due to unclear risk of bias (allocation concealment) and very serious imprecision (3 events; See [Summary of findings for the main comparison](#)).

Histological response

In Fine 1999, 2 of 3 patients in the bismuth subsalicylate group achieved a histological response after 8 weeks of treatment, compared to 1 of the 2 patients treated with placebo (RR 1.33, 95% CI 0.27 to 6.61). A GRADE analysis rated the overall quality of the evidence supporting this outcome as very low due to unclear risk of bias (allocation concealment) and very serious imprecision (3 events; See [Summary of findings for the main comparison](#)).

Quality of life

Fine 1999 did not report on quality of life as an outcome measure.

Adverse events

Fine 1999 reported no adverse events in either the bismuth subsalicylate or placebo groups.

Budesonide versus placebo

Clinical response

In Miehlke 2009, 18 of 21 patients in the budesonide group achieved a clinical response after 6 weeks of treatment, compared to 10 of 21 patients in the placebo group (RR 1.80, 95% CI 1.11 to 2.91). The number needed to treat to achieve a clinical response with budesonide was 3 patients.

In Pardi 2009, 10 of 11 patients in the budesonide group achieved a clinical response after 8 weeks of treatment, compared to 1 of 4 patients in the placebo group (RR 3.64, 95% CI 0.66 to 20.06).

The pooled analysis for clinical response showed a statistically significant benefit for budesonide over placebo. Clinical response was noted in 88% of budesonide patients compared to 38% of placebo patients (2 studies; 56 participants; RR 2.03, 95% CI 1.25 to 3.33; $I^2 = 0\%$). The number needed to treat to achieve a clinical response with budesonide was two. A GRADE analysis rated the overall quality of the evidence supporting this outcome as low due to unclear risk of bias for blinding and sparse data (39 events; See [Summary of findings 2](#)).

Histological response

In Miehlke 2009, 11 of 15 patients in the budesonide group who underwent a follow-up colonoscopy achieved a histological response after 6 weeks of treatment, compared to 4 of 13 patients in the placebo group who underwent a follow-up colonoscopy (RR 2.81, 95% CI 1.00 to 5.69). The number needed to treat to achieve a histological response with budesonide was 3 patients.

In Pardi 2009, 7 of 8 patients in the budesonide group who underwent follow-up sigmoidoscopy achieved a histological response after 8 weeks of treatment, compared to 1 of 3 patients in the placebo group (RR 2.63 95% CI 0.52 to 13.29).

The pooled analysis for histological response showed a statistically significant benefit for budesonide over placebo. Histological response was noted in 78% of budesonide patients compared to 33% of placebo patients (2 studies; 39 participants; RR 2.44, 95% CI 1.13 to 5.28; $I^2 = 0\%$). The number needed to treat to achieve a histological response with budesonide was three. A GRADE analysis rated the overall quality of the evidence supporting this outcome as low due to very sparse data (23 events; See [Summary of findings 2](#)).

Quality of life

SF-36 scores at baseline were reduced compared to normal values for both the physical and mental domains. In the budesonide group, the mean physical sum score increased from 42.0 at baseline to 49.7 after 6 weeks of treatment, while the mean mental sum score was unchanged, with a value of 46.5 at baseline and 46.9 after 6 weeks (Miehlke 2009). In the placebo group, the mean physical sum score increased from 44.1 at baseline to 48.0 after 6 weeks of treatment, while the mean mental sum score was unchanged, with a value of 49.0 at baseline and 49.1 after 6 weeks (Miehlke 2009).

Adverse events

In Miehlke 2009, 6 adverse events occurred in 2 patients (10%) in the budesonide group, compared to 9 adverse events in 3 patients (15%) in the placebo group (RR 0.63, 95% CI 0.12 to 3.41). A GRADE analysis rated the overall quality of the evidence supporting this outcome as low due to very sparse data (5 events; See [Summary of findings 2](#)). All adverse events were graded as mild or moderate in intensity. The most common adverse event were headaches. One patient in the budesonide group withdrew due to adverse events (nausea and headache) and one patient in the placebo group withdrew due to adverse events. Serious adverse events were reported in two placebo patients (nausea, abdominal pain, and hyperhidrosis in one patient; and headache, neck pain, and abdominal discomfort in the other patient).

Pardi 2009 reported no adverse events in either budesonide or placebo treatment groups.

Mesalazine versus mesalazine + cholestyramine

Clinical response

In Calabrese 2007, 17 of 20 patients in the mesalazine alone group achieved a clinical response after 6 months of treatment, compared to 18 of 21 patients in the mesalazine + cholestyramine group (RR 0.99; 95% CI 0.77 to 1.28). A GRADE analysis rated the overall quality of the evidence supporting this outcome as low due to high risk of bias (blinding), unclear allocation concealment and sparse data (35 events; See [Summary of findings 3](#)).

Histological response

In Calabrese 2007, all patients with lymphocytic colitis who had a clinical response showed a normalization of histological features, specifically normalization of intraepithelial lymphocytes. Seventeen of 20 patients in the mesalazine group had a histological response compared to 18 of 21 patients in the combined mesalazine + cholestyramine group (RR 0.99; 95% CI 0.77 to 1.28). A GRADE analysis rated the overall quality of the evidence supporting this outcome as low due to high risk of bias (blinding), unclear allocation concealment and sparse data (35 events; See [Summary of findings 3](#)).

Quality of life

In Calabrese 2007, quality of life was not reported as an outcome measure.

Adverse events

In Calabrese 2007, 2 of 21 patients (10%) in the mesalazine + cholestyramine group reported nausea as an adverse event. This was considered a mild event and did not lead to study withdrawal. No events were reported in the mesalazine alone group.

Beclometasone dipropionate versus mesalazine

Clinical response

In Latella 2010, 15 of 18 patients in the 5 mg/day beclometasone dipropionate group achieved a clinical remission after 8 weeks of treatment, compared to 11 of 13 in the 10 mg/day beclometasone dipropionate group, and 13 of 15 in the mesalazine group. There was no statistically significant difference in the proportion of patients who achieved clinical remission. Eighty-four per cent (26/31) of patients in the beclometasone dipropionate group achieved remission compared to 86% (13/15) of mesalazine patients (RR 0.97, 95% CI 0.75 to 1.29). A GRADE analysis rated the overall quality of the evidence supporting this outcome as low due to high risk of bias (blinding) and sparse data (39 events; See [Summary of findings 4](#)).

At 12 months, 5 of 18 patients (28%; 95% CI 12% to 51%) in the beclometasone dipropionate group maintained clinical remission compared to 3 of 13 patients (23%; 95% CI 8% to 50%) in the 10 mg/day beclometasone dipropionate group and 3 of 15 patients (20%; 95% CI 7% - 45%) in the mesalazine group. There was no statistically significant difference in the proportion of patients who maintained clinical remission. Twenty-six per cent (8/31) of patients in the beclometasone dipropionate group maintained remission at 12 months compared to 20% (3/15) of mesalazine patients (RR 1.29, 95% CI 0.40 to 4.18). A GRADE analysis rated the overall quality of the evidence supporting this outcome as very low due to high risk of bias (blinding) and very sparse data (11 events; See [Summary of findings 4](#)).

Histological response

Latella 2010 did not report on histological response as an outcome measure.

Quality of life

Latella 2010 did not report on quality of life as an outcome measure.

Adverse events

In the Latella 2010 study, 3 of 46 patients discontinued treatment prematurely because of adverse events; one from each of the three groups. Adverse events reported in the beclometasone dipropionate group were nausea, sleepiness and change of mood in the 5 mg/day and 10 mg/day groups, respectively. In the mesalazine group, one patient discontinued treatment due to a skin rash.

DISCUSSION

Lymphocytic colitis is a cause of chronic diarrhea. It is related to collagenous colitis, and together these two disorders fall under the more general term 'microscopic colitis'. In the past, most research has focused on the therapy of collagenous colitis, and as a result, clinicians treating patients with lymphocytic colitis have relied on the results of uncontrolled trials, case series, and the extrapolation

of data for treating collagenous colitis. However, there are currently five RCTs that exist for the treatment of lymphocytic colitis.

The results of [Miehlke 2009](#) and [Pardi 2009](#) provide low quality evidence suggesting that budesonide may be effective at inducing both clinical and histological responses in patients with active lymphocytic colitis. Budesonide also appears to be well-tolerated in these patients. However, both trials were small in size ([Miehlke 2009](#) with 42 patients, [Pardi 2009](#) with 15 patients) and the results should be interpreted with caution. In comparison, three studies examined the use of budesonide as therapy for active collagenous colitis, demonstrating both a clinical and histological benefit after six to eight weeks of treatment with 9 mg daily or in a tapering schedule ([Baert 2002](#); [Bonderup 2003](#); [Miehlke 2002](#)). Additionally, two studies demonstrated that budesonide is effective at maintaining clinical and histological responses in collagenous colitis over a period of six months ([Bonderup 2007](#); [Miehlke 2007b](#)). It is conceivable that budesonide would be similarly effective in patients with lymphocytic colitis, but this needs to be proven in larger randomized placebo-controlled trials.

[Calabrese 2007](#) included 41 patients with lymphocytic colitis in a trial of mesalazine versus mesalazine plus cholestyramine. Clinical response was achieved in 85% of patients who received mesalazine compared to 86% of patients who received mesalazine plus cholestyramine ($P = 0.95$). The addition of cholestyramine to the treatment regimen did not provide any additional benefit for patients with lymphocytic colitis. Both treatments appeared to be well-tolerated. The results of this study provide low quality evidence suggesting that mesalazine (800 mg three times daily) with or without cholestyramine may be effective for treatment of lymphocytic colitis. Additionally, 23 patients with collagenous colitis enrolled in the same trial responded similarly to these treatments. However, these results should be interpreted with caution due to the small number of patients enrolled, the lack of blinding and no placebo control. Some of the measured effect in both groups may have been due to spontaneous improvement of the disease. The potential benefits and harms of mesalazine with or without cholestyramine needs to be confirmed by a large placebo-controlled study.

[Latella 2010](#) assessed the 12-month clinical outcomes of 46 patients with lymphocytic colitis who were randomized to beclometasone dipropionate at doses of 5 mg/day or 10 mg/day or mesalazine at a dose of 2.4 g/day. Clinical remission was achieved in 84% of patients in the beclometasone dipropionate group and 86% of the mesalazine group at 8 weeks ($P = 0.80$). This study provides low quality evidence suggesting that beclometasone dipropionate and mesalazine may be effective in achieving clinical remission. However, at 12 months only 26% of patients in the beclometasone dipropionate group and 20% in the mesalazine group maintained clinical remission ($P = 0.67$). This study provides very low quality evidence suggesting that these interventions may not be effective in maintaining remission. Moreover, this trial should be interpreted with caution as there was a small number of patients enrolled, and there was a lack of blinding and no placebo control. Both treatments appear to be well tolerated. The efficacy and safety of beclometasone dipropionate and mesalazine in achieving and maintaining remission needs to be assessed in a large placebo-controlled trial.

[Fine 1999](#), which studied bismuth subsalicylate therapy for lymphocytic colitis included only five patients with this diagnosis.

Although all three patients receiving active drug experienced clinical improvement compared to none of the placebo patients there were no statistically significant differences in clinical or histological response. While these findings are of interest and provide very low quality evidence suggesting that this medication may be effective for treating lymphocytic colitis, no conclusions can be made from such a small number of patients. Additionally, nine patients with collagenous colitis enrolled in this study demonstrated a clinical and histological benefit with bismuth subsalicylate over placebo.

Although lymphocytic colitis and collagenous colitis are similar disorders, it has not been proven that therapies effective for one disorder will also be effective for the other. Epidemiologically, these two disorders are quite similar. Although most early reports of patients with microscopic colitis described collagenous colitis rather than lymphocytic colitis ([Zins 1995](#)), recent population-based studies suggest similar frequencies for these disorders ([Fernandez 1999](#); [Olesen 2004a](#)). Both disorders are more common in women than in men, although the relative frequency of collagenous colitis in women is greater than that for lymphocytic colitis ([Chande 2005](#); [Fernandez 1999](#); [Olesen 2004a](#)). The mean age at diagnosis is in the sixth or seventh decade ([Agnarsdottir 2002](#); [Fernandez 2003](#); [Goff 1997](#); [Olesen 2004a](#)). An association with autoimmune diseases ([Bohr 1996](#); [Fernandez 2003](#); [Kitchen 2002](#)), and the use of NSAIDs is also common in both lymphocytic colitis and collagenous colitis ([Bohr 1996](#); [Chande 2005](#); [Goff 1997](#); [Kitchen 2002](#); [Pardi 2002](#); [Riddell 1992](#); [Wang 1999](#)).

Despite sharing certain epidemiologic features, lymphocytic colitis and collagenous colitis have important pathologic differences. The presence of a thickened subepithelial collagen band is the key diagnostic feature found in collagenous colitis. A marked increase in the number of intraepithelial lymphocytes is required to diagnose lymphocytic colitis. Treatments aimed at decreasing the thickness of the collagen band may not necessarily influence the number of intraepithelial lymphocytes. However, most medications used to treat collagenous colitis have anti-inflammatory activities and consequently might be effective at reducing the number of mucosal inflammatory cells in patients with lymphocytic colitis. In fact, some studies of collagenous colitis treatment with follow-up histology have shown a decrease in the number of inflammatory cells, findings which could potentially be translated to patients with lymphocytic colitis ([Baert 2002](#); [Bonderup 2003](#); [Fine 1999](#); [Miehlke 2002](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Low quality evidence suggests that budesonide may be an effective therapy for the treatment of lymphocytic colitis. Low quality evidence also suggests that mesalazine with or without cholestyramine and beclometasone dipropionate may be effective for treatment of lymphocytic colitis. No conclusions can be made regarding bismuth subsalicylate.

Implications for research

Further large placebo-controlled trials of budesonide are necessary to confirm the suggested benefit and safety of this therapy. Bismuth subsalicylate, which has less potential for toxicity than budesonide, also warrants further study. The efficacy and safety

of mesalazine with or without cholestyramine, and beclometasone dipropionate need to be investigated in a large placebo-controlled study. Other treatments that have been suggested to be beneficial in uncontrolled studies and case series should also be considered for randomized placebo controlled trials.

There are no established definitions for clinical or histological remission in lymphocytic colitis. As a result, the authors of each individual study must determine what they believe to be appropriate endpoints of therapy. Although these endpoints may be similar between studies, important differences may render it inappropriate to compare outcomes between trials. In addition, the clinical relevance of these arbitrary definitions is uncertain. If standardized definitions of clinical and histological remission can be established, the outcomes of these trials would be more applicable to clinical practice.

Most randomized trials in lymphocytic colitis and collagenous colitis deal with short-term outcomes (generally 6 to 8 weeks, with a maximum of 12 months). Both lymphocytic colitis and collagenous colitis are chronic diseases, and longer-term outcomes are important. Once standardized definitions of clinical and histological remission are established, trials with long-term follow-up are warranted to study the effectiveness of both establishing and maintaining remission, as well as to determine the potential for adverse effects with prolonged treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Calabrese 2007

Methods	Randomized, unblinded, open-label study. N=41 with lymphocytic colitis (and 23 with collagenous colitis). Duration of the study was 6 months. Patients underwent a colonoscopy pre-treatment. Twenty patients also underwent a colonoscopy at the end of 6 months. Randomization was performed with a computer generated list
Participants	Clinical: Chronic or recurrent non-bloody diarrhea Histological: Increased chronic inflammatory infiltrate (plasma cells, lymphocytes, eosinophils) in the lamina propria; increased number of intraepithelial lymphocytes, damage to surface epithelium, with flattening of epithelial cells or epithelial loss or both and detachment and minimal crypt architecture distortion. More than 20 intraepithelial lymphocytes per 100 epithelial cells in the absence of a thickened subepithelial collagen layer (< 10 um) was also required to diagnose lymphocytic colitis. Patients with a clear correlation between symptoms and assumption of drugs (e.g. NSAIDs, ticlopidine, PPI) were excluded
Interventions	Mesalazine 800 mg po tid (n=20) vs. mesalazine 800 mg po tid + cholestyramine 4 g po od (n=21) for 6 months
Outcomes	Clinical: Complete response was complete resolution of diarrhea. Partial response was improvement but not resolution of diarrhea Histological: Normalization of histologic pattern at the end of 6 months
Notes	Biopsies were performed in a blinded fashion by a single pathologist

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed with a computer generated list

Calabrese 2007 (Continued)

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open-labeled trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Fine 1999

Methods	Randomized, double-blind, placebo-controlled. Duration of study was 8 weeks N=5. Each patient underwent 48-hour stool collection before treatment and on the last 2 days of treatment. Stool weight and consistency were assessed based on standardized criteria. All patients underwent flexible sigmoidoscopy with standardized biopsy protocol pre- and post-treatment. Randomization was by pulling pieces of paper out of a sealed box.	
Participants	Clinical: 8 weeks of non-bloody watery diarrhea (without steatorrhea) and normal endoscopic appearance of the colonic mucosa. Histological (including involvement of the distal colon): excess mononuclear inflammatory cells in the lamina propria and surface epithelium without significant neutrophilia or eosinophilic inflammation, numerous crypt abscesses, or granuloma; and no other evidence of Crohn's disease. For the histological outcome analysis, a histopathology score from 0 to 10 was based on the following parameters: surface epithelium assessed for micro-ulceration, cell flattening, and mucin depletion (scored: 0 - normal, 1 - moderate, 2 - severe); crypts (scored: 0 - normal, 1 - distorted architecture or cryptitis with neutrophils, 2 - containing crypt abscesses); lamina propria cellularity (scored: 0 - normal, 1 - focally increased with neutrophils, mononuclear inflammatory cells, or both, 2 - diffusely increased with neutrophils, mononuclear inflammatory cells, or both); number of intraepithelial lymphocytes within surface epithelium (scored 0 - normal, 1 - moderately increased, 2 - significantly increased); number of intraepithelial lymphocytes within crypt epithelium (scored 0 - normal, 1 - moderately increased, 2 - significantly increased).	
Interventions	Bismuth subsalicylate (9 262 mg chewable tablets daily in 3 divided doses) versus placebo for 8 weeks	
Outcomes	Clinical: improvement of diarrhea to passage of 2 or less formed or semi formed stools/day. Histological: improvement of histopathology score by at least 50%	
Notes	Patients were not to take antibiotics or anti-inflammatory agents for minimum 6 weeks, and not to take antidiarrheals for minimum 2 weeks prior to the beginning of the study	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed by pulling pieces of paper out of a sealed box
Allocation concealment (selection bias)	Unclear risk	Not described

Interventions for treating lymphocytic colitis (Review)

Fine 1999 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind, identical coloured and flavoured placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient dropped out of the placebo group
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other potential sources of bias

Latella 2010

Methods	Randomized, unblinded, open-label study. N=46 with lymphocytic colitis. Duration of study was 8 weeks, with a 6 and 12 month follow-up. Patients were treated with either beclometasone dipropionate or mesalazine	
Participants	Patients with clinical and histologically confirmed lymphocytic colitis Clinical criteria: >3 watery/loose stools per day on average per week, history of diarrhea >4 weeks Histological criteria: complete colonoscopy with colonic biopsies within the last 4 weeks before randomization and a histologically confirmed diagnosis of active lymphocytic colitis	
Interventions	Beclometasone dipropionate 5 mg/day (n=18) vs beclometasone dipropionate 10 mg/day (n=13) vs mesalazine 2.4 g/day (n=15) for 8 weeks	
Outcomes	The primary outcome was clinical remission at 8 weeks. Clinical remission was pre-defined as no more than 3 soft or solid stools per day during the last week of treatment. Clinical relapse at 6 and 12 months, was pre-defined as greater than 3 stools per day on more than 4 consecutive days	
Notes	Additional information provided by the lead author	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization sequence
Allocation concealment (selection bias)	Low risk	Centralized randomization scheme
Blinding (performance bias and detection bias) All outcomes	High risk	Open label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients dropped out
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported

Interventions for treating lymphocytic colitis (Review)

Latella 2010 (Continued)

Other bias	Low risk	The study appears to be free of other potential sources of bias
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Miehlke 2009

Methods	Randomized, double-blind, placebo-controlled. Duration of study was 6 weeks. Open label budesonide was offered to non responders for a further 6 weeks. Patients underwent a colonoscopy including histology at baseline and 6 weeks. Randomization was performed with a computer generated list
Participants	Patients with lymphocytic colitis and chronic diarrhea. Clinical: more than 3 watery/loose stools per day on average for at least 4 weeks Histological: The intraepithelial lymphocytes had to be greater than 20/100 epithelial cells, with inflammation of the lamina propria
Interventions	Budesonide 9 mg/day (n = 21) or placebo (n = 21) for 6 weeks
Outcomes	The primary outcome was clinical remission at week 6. Clinical remission was pre-defined as no more than 3 non-watery stools per day. Secondary outcomes included histological remission or response and quality of life (SF-36). Histological remission was defined as a reduction in the number of IEL <20 IEL /100 epithelial cells plus a reduction in lamina propria inflammation. Histological response was defined as >20 IEL/100 epithelial cells but reduction of more than 50% compared to baseline or reduction in lamina propria inflammation or both. Clinical remission at 3 weeks

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization sequence
Allocation concealment (selection bias)	Low risk	Centralized sequence concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo and budesonide were administered in identical capsules. Histological samples were examined by a blinded pathologist
Incomplete outcome data (attrition bias) All outcomes	Low risk	Patient withdrawals and missing outcome data were reported and evenly distributed across treatment groups
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other potential sources of bias

Pardi 2009

Methods	Randomized, double-blind, placebo controlled study (N = 15) A stool specimen and blood sample was taken from each participant at the start of the study Patients took either budesonide (n = 11) or placebo (n = 4) for 8 weeks
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Interventions for treating lymphocytic colitis (Review)

Pardi 2009 (Continued)

At the end of treatment, patients had stool collection and sigmoidoscopy

Participants	Patients (>18 years) with diarrhea - defined as greater than 4 bowel movements per day and greater than "mild" - and currently on no treatment or despite active treatment. Lymphocytic colitis was confirmed histologically within one year of enrolment
Interventions	Budesonide (9 mg/day) compared to placebo
Outcomes	The primary outcome measure was satisfactory control of diarrhea during at least three of the last four weeks. The secondary outcome measures were 1) histologic improvement in post treatment colon biopsies compared to baseline biopsies and 2) side effects and time (in days) to recurrence of diarrhea after discontinuation of study drug
Notes	Additional information provided by the lead author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Identical placebo was not available from the sponsor at the time of the study. All research personnel including the pathologist were blinded to treatment assignment. Patients did not know treatment assignment unless they discovered what budesonide was supposed to look like. The authors did not formally assess whether patients knew which treatment they received
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no drop outs and no missing data
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other potential sources of bias

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bauma 2015	Not a randomized control trial
Gentile 2015	Not a randomized control trial
Jo 2014	Not a randomized control trial
Loftus 2003	Not a randomized control trial
Madisch 2007	Not a randomized controlled trial
Miehlke 2013	Not a randomized control trial

Interventions for treating lymphocytic colitis (Review)

Study	Reason for exclusion
Nyhlin 2006	Not a randomized control trial
Pardi 2002	Not a randomized control trial
Pardi 2014	Not a randomized control trial
Parkes 2007	Not a randomized control trial
Rohatgi 2008	Abstract only, no sufficient details
Rohatgi 2015	No outcome specific to lymphocytic colitis
Stewart 2011	Not a randomized control trial
Stroehlein 2004	Not a randomized control trial
Tagkalidis 2002	Not a randomized control trial
Taheri 2011	This study assessed probiotics compared to placebo The abstract did not report on clinical symptoms or histology Authors reported mean defecation results without standard deviations We tried contacting the authors to get the actual values, but we were unsuccessful in obtaining further data
Temmerman 2009	Not a randomized control trial
Triadafilopoulos 2014	Not a randomized control trial
Tysk 2005	Not a randomized control trial
Tysk 2009	Not a randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT00184171

Trial name or title	Treatment of microscopic colitis (collagenous colitis and lymphocytic colitis) with budesonide, bismuth or fiber
Methods	Randomized, open-label, active control, parallel group efficacy study
Participants	Patients aged > 17 years Inclusion criteria: microscopic colitis verified with biopsies from the colon Symptoms to such an extent that treatment is indicated Informed consent
Interventions	Patients assigned to budesonide (9 mg/day) or bismuth and fiber for 8 weeks
Outcomes	Primary outcome: stool frequency and consistency

NCT00184171 (Continued)

Secondary outcome: histological findings in biopsies from colon

Starting date	Start date: November 2001 Estimated study completion date: April 2014
Contact information	Study chair: Per G Farup, PhD, Norwegian University of Science and Technology
Notes	ClinicalTrials.gov identifier: NCT00184171

NCT01209208

Trial name or title	Double-blind, double-dummy, randomised, placebo-controlled, multi-centre phase III study on the efficacy and tolerability of a 8-week treatment with budesonide vs. mesalazine vs. placebo in patients with lymphocytic colitis
Methods	Randomized, double-blind, double-dummy, parallel group efficacy study
Participants	Patients aged 18 to 90 years Inclusion Criteria: symptoms and signs of indication of lymphocytic colitis Signed informed consent
Interventions	Budesonide (9 mg/day), mesalazine (3 g/day) or placebo for 8 weeks
Outcomes	Primary outcome: rate of clinical remission at 8 weeks Secondary outcome: proportion of patients with histological improvement at 8 weeks
Starting date	Start date: May 2010 Estimated study completion date: April 2015
Contact information	Principal Investigator: Professor Stephan Miehke, Magen-Darm-Zentrum, IKE - Internistische Kooperation Eppendorf, Hamburg, Germany
Notes	ClinicalTrials.gov identifier: NCT01209208

DATA AND ANALYSES

Comparison 1. Bismuth subsalicylate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical response	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Histological response	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Bismuth subsalicylate versus placebo, Outcome 1 Clinical response.

Study or subgroup	Bismuth n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fine 1999	3/3	0/2		5.25[0.41,67.73]
Favours placebo 0.005 0.1 1 10 200 Favours bismuth				

Analysis 1.2. Comparison 1 Bismuth subsalicylate versus placebo, Outcome 2 Histological response.

Study or subgroup	Bismuth n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fine 1999	2/3	1/2		1.33[0.27,6.61]
Favours placebo 0.01 0.1 1 10 100 Favours bismuth				

Comparison 2. Budesonide versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical response	2	57	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.25, 3.33]
2 Histological response	2	39	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [1.13, 5.28]
3 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Budesonide versus placebo, Outcome 1 Clinical response.

Study or subgroup	Budesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Miehlke 2009	18/21	10/21		87.21%	1.8[1.11,2.91]
Pardi 2009	10/11	1/4		12.79%	3.64[0.66,20.06]
Total (95% CI)	32	25		100%	2.03[1.25,3.33]
Total events: 28 (Budesonide), 11 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0.69, df=1(P=0.41); I ² =0%					
Test for overall effect: Z=2.84(P=0)					
Favours placebo 0.01 0.1 1 10 100 Favours budesonide					

Analysis 2.2. Comparison 2 Budesonide versus placebo, Outcome 2 Histological response.

Study or subgroup	Budesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Miehlke 2009	11/15	4/13		74.66%	2.38[1.5,6.9]
Pardi 2009	7/8	1/3		25.34%	2.63[0.52,13.29]
Favours placebo 0.01 0.1 1 10 100 Favours budesonide

Analysis 2.3. Comparison 2 Budesonide versus placebo, Outcome 3 Adverse events.

Comparison 3. Mesalazine versus mesalazine + cholestyramine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical response	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Histological response	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.77, 1.28]

Analysis 3.1. Comparison 3 Mesalazine versus mesalazine + cholestyramine, Outcome 1 Clinical response.

Analysis 3.2. Comparison 3 Mesalazine versus mesalazine + cholestyramine, Outcome 2 Histological response.

Comparison 4. Beclometasone dipropionate versus mesalazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical response at 8 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Maintenance of clinical response at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Beclometasone dipropionate versus mesalazine, Outcome 1 Clinical response at 8 weeks.

Study or subgroup	BD n/N	Mesalazine n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Latella 2010	26/31	13/15		0.97[0.75,1.24]

Analysis 4.2. Comparison 4 Beclometasone dipropionate versus mesalazine, Outcome 2 Maintenance of clinical response at 12 months.

Study or subgroup	BD n/N	Mesalazine n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Latella 2010	8/31	3/15		1.29[0.4,4.18]

ADDITIONAL TABLES

Table 1. Non-randomized studies of therapies for lymphocytic colitis

Therapy	References
Antiallergic therapy	Weidenhiller 2005
Antibiotics	Baert 1999; Hilmer 2006; Mullhaupt 1998; Olesen 2004b; Puri 1994; Swensson 1999
Antidiarrheal agents	Baert 1999; Fekih 2006; Fernandez 2003; Hilmer 2006; Hollerweger 2003; Mullhaupt 1998; Olesen 2004b; Pardi 2002; Wang 1999
Azathioprine/6-mercaptopurine	Ben Soussan 2001; Pardi 2001; Pardi 2002; Vennamaneni 2001
Bile acid binding agents	Baert 1999; Baert 2004; Einarsson 1992; Fernandez 2001; Fernandez 2003; Mahmoud 2005; Olesen 2004b; Pardi 2002; Ung 2002
Bismuth subsalicylate	Bohr 1999; Fine 1998; Pardi 2002

Table 1. Non-randomized studies of therapies for lymphocytic colitis *(Continued)*

Budesonide	Barta 2005; Chopra 2006; Fomegne 2005; Hollerweger 2003; Olesen 2004b; Van Gossum 1998; Wiedermann 2007
Bulking agents	Olesen 2004b
Corticosteroids (traditional)	Baert 1999; Bonner 2000; Olesen 2004b; Fernandez 2003; Kitchen 2002; Pardi 2002; Persoz 2001; Sandmeier 2004; Swensson 1999; Wang 1999
Cyclosporine	Eijsbouts 1995
Dietary modification/ or elemental diet (check)	Fekih 2006; Baert 1999; Jensen 2005; Teahon 1994; Weidenhiller 2005
Probiotics	Rohatgi 2015; Taheri 2011
Spasmolytics	Mullhaupt 1998
Sulfasalazine/other 5-ASA	Abdo 2001; Baert 1999; Bonner 2000; De Waele 1994; Fekih 2006; Fernandez 2003; Hollerweger 2003; Kitchen 2002; Mennecier 1999; Mullhaupt 1998; Netzer 1997; Olesen 2004b; Pardi 2002; Perk 1999; Wang 1999
Surgery	Varghese 2002; Yusuf 1999

APPENDICES

Appendix 1. Search Strategies

MEDLINE Search Strategy:

1. random\$.tw.
2. factorial\$.tw.
3. (crossover\$ or cross over\$ or cross-over\$).tw.
4. placebo\$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl\$ adj blind\$).tw.
9. (double\$ adj blind\$).tw.
10. (tripl\$ adj blind\$).tw.
11. assign\$.tw.
12. allocat\$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/

16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. lymphocytic colitis.mp. or exp lymphocytic colitis/
22. microscopic colitis.mp or exp microscopic colitis/
23. collagenous colitis.mp or exp collagenous colitis/
24. 21 or 22 or 23
25. 20 and 24

EMBASE Search Strategy:

1. random\$.tw.
2. factorial\$.tw.
3. (crossover\$ or cross over\$ or cross-over\$).tw.
4. placebo\$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl\$ adj blind\$).tw.
9. (double\$ adj blind\$).tw.
10. (tripl\$ adj blind\$).tw.
11. assign\$.tw.
12. allocat\$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. lymphocytic colitis.mp. or exp lymphocytic colitis/
22. microscopic colitis.mp or exp microscopic colitis/
23. collagenous colitis.mp or exp collagenous colitis/
24. 21 or 22 or 23

25, 20 and 24

Cochrane Library Search Strategy:

1. microscopic colitis OR lymphocytic colitis OR collagenous colitis

Cochrane IBD Specialized Register

1. microscopic colitis (ab/ti)

2. lymphocytic colitis (ab/ti)

3. collagenous colitis (ab/ti)

WHAT'S NEW

Date	Event	Description
14 November 2017	Amended	Correction of minor error in Figure 1

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 1, 2007

Date	Event	Description
11 August 2016	New citation required and conclusions have changed	Updated review with changes to conclusions and new authors
11 August 2016	New search has been performed	New literature search performed on 11 August 2016. Two new studies were added.
11 February 2008	New citation required and conclusions have changed	Substantive amendment. See "other versions" for previously published versions of this review.

DECLARATIONS OF INTEREST

Nilesh Chande: Dr Chande has received fees for consultancy from AbbVie, Janssen, Takeda, and Ferring, and fees for lectures from AbbVie, Actavis and Janssen. All of these financial activities are outside the submitted work.

Noor Al Yatama: None known

Tania Bhanji: None known

Tran M Nguyen: None known

John WD McDonald: None known

John K MacDonald: None known

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents [therapeutic use]; Antidiarrheals [*therapeutic use]; Beclomethasone [therapeutic use]; Bismuth [therapeutic use]; Budesonide [therapeutic use]; Cholestyramine Resin [therapeutic use]; Colitis, Lymphocytic [*drug therapy];

Mesalamine [therapeutic use]; Organometallic Compounds [*therapeutic use]; Randomized Controlled Trials as Topic; Salicylates [therapeutic use]

MeSH check words

Humans