Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis (Review)

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[Intervention Review]

Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

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ABSTRACT

Background

5-Aminosalicylic acid (5-ASA) is a first-line therapy for inducing and maintaining remission of mild and moderately active ulcerative colitis (UC). When the proximal margin of inflammation is distal to the splenic flexure, 5-ASA therapy can be delivered as a rectal suppository, foam or liquid enema.

Objectives

The primary objective was to assess the efficacy and safety of rectal 5-ASA for maintaining remission of distal UC.

Search methods

We searched MEDLINE (1966 to August 2012), the Cochrane Library (August 2012), abstracts from major gastroenterology meetings (1997-2011) and bibliographies of relevant publications to identify relevant studies.

Selection criteria

Eligible studies were randomized controlled trials comparing rectal 5-ASA to placebo or another active treatment for a minimum duration of six months. Symptom scores needed to be assessed in at least one study outcome. Patients had to be at least 12 years of age with disease extent less than 60 cm from the anal verge or distal to the splenic flexure, as determined by barium enema, colonoscopy or sigmoidoscopy. Patients were expected to be in remission prior to the treatment trial.

Data collection and analysis

Study eligibility was independently assessed by three authors. Data were extracted using standardized forms by two independent reviewers, with inter-rater agreement assessed using Cohen's Kappa and disagreements resolved by consensus. In cases where clarification of study results or methodology was needed, corresponding authors were contacted. The methodological quality of each trial was assessed by the Cochrane risk of bias tool and by a 30-point scale developed and used previously by the authors. Pooled risk ratios

(RR) and corresponding 95% confidence intervals (CI) for continued clinical, endoscopic and histologic remission were estimated for comparisons between rectal 5-ASA and placebo or oral 5-ASA, and for comparisons among 5-ASA doses. Heterogeneity was assessed using the Chi^2 test and visual inspection of forest plots. If no significant heterogeneity was identified ($P > 0.10$ for Chi^2) a fixed-effect model (Mantel-Haenstzel) was used. If heterogeneity was significant, a random-effects model was used.

Main results

Nine studies (484 patients) met the pre-specified inclusion criteria (Kappa 1.00). Six studies were rated as low risk of bias. Three studies were rated as high risk of bias due to blinding (two open label and one single-blind). The total daily dose of rectal 5-ASA ranged from 0.5 g to 4 g, and dose frequency ranged from once to three times daily. 5-ASA was delivered as liquid enema in five studies or as a suppository in four studies. Follow-up ranged from 6 to 24 months. Rectal 5-ASA was significantly superior to placebo for maintenance of symptomatic remission over a period of 12 months.Sixty-two per cent of patients in the rectal 5-ASA group maintained symptomatic remission compared to 30% of patients in the placebo group (4 studies; 301 patients; RR 2.22, 95% CI 1.26 to 3.90; $I^2 = 67\%$; $P < 0.01$). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome was low due to imprecision (i.e. sparse data 144 events) and inconsistency (i.e. unexplained heterogeneity). Rectal 5-ASA was significantly superior to placebo for maintenance of endoscopic remission over a 12 month period. Seventy-five per cent of patients in the rectal 5-ASA group maintained endoscopic remission compared to 15% of patients in the placebo group (1 study; 25 patients; RR 4.88, 95% CI 1.31 to 18.18; $P < 0.05$). There was no statistically significant difference in the proportion of patients who experienced at least one adverse event. Sixteen per cent of patients in the rectal 5-ASA group experienced at least one adverse compared to 12% of placebo patients (2 studies; 160 patients; RR 1.35, 95% CI 0.63 to 2.89; $I^2 = 0\%$; $P = 0.44$). The most commonly reported adverse events were anal irritation and abdominal pain. No statistically significant differences between rectal and oral 5-ASA were identified for either symptomatic or endoscopic remission over a period of six months. Eighty per cent of patients in the rectal 5-ASA group maintained symptomatic remission compared to 65% of patients in the oral 5-ASA group (2 studies; 69 patients; RR 1.24, 95% CI 0.92 to 1.66; $I^2 = 0\%$; $P = 0.15$). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome was low due to imprecision (i.e. sparse data 50 events) and high risk of bias (i.e. both studies in the pooled analysis were open label). Eighty per cent of patients in the rectal 5-ASA group maintained endoscopic remission compared to 70% of patients in the oral 5-ASA group (2 studies; 91 patients; RR 1.14, 95% CI 0.90 to 1.45; $I^2 = 0\%$; $P = 0.26$). In two small trials, one comparing 2 g/day 5-ASA enemas to 4 g/day 5-ASA enemas and the other comparing 0.5 g/day 5-ASA suppositories to 1 g/day 5-ASA suppositories no dose response relationship was observed.

Authors' conclusions

The limited data available suggest that rectal 5-ASA is effective and safe for maintenance of remission of mild to moderately active distal UC. Well designed randomized trials are needed to establish the optimal dosing regimen for rectal 5-ASA, to compare rectal 5-ASA with rectal corticosteroids and to identify subgroups of patients who are more or less responsive to specific rectal 5-ASA regimens. The combination of oral and rectal 5-ASA appears to be more effective than either oral or rectal monotherapy for induction of remission. The efficacy of combination therapy for maintenance of remission has not been assessed and could be evaluated in future trials.

PLAIN LANGUAGE SUMMARY

Rectal 5-aminosalicylic acid (suppository, foam or liquid enema) for maintenance of remission in ulcerative colitis

5-aminosalicylic acid (5-ASA) is a commonly used medication for treatment of mild and moderately active ulcerative colitis (UC) and UC in remission. When UC affects only the lower third of the colon, 5-ASA can be delivered as a rectal suppository, foam or liquid enema. This review includes nine randomized trials with a total of 484 participants. The limited data available suggest that rectal 5-ASA is effective and safe for maintenance of remission in UC. Rectal 5-ASA was found to be superior to placebo (e.g. enema or suppository with no active medicine). There was no difference in the incidence of side effects between rectal 5-ASA and placebo groups. Side effects were generally mild in nature and common side effects included anal irritation and abdominal pain. Studies comparing rectal 5-ASA with oral 5-ASA (pills) found no differences in effectiveness for maintenance therapy. Well designed randomized trials are needed to investigate different doses of rectal 5-ASA for maintenance therapy, Future studies should assess the effectiveness of combination therapy of oral 5-ASA with rectal 5-ASA as this has been found to be effective in active UC and has not been investigated for maintenance therapy. Future studies should also compare rectal 5-ASA with rectal corticosteroids.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Rectal 5-ASA versus placebo for maintenance of remission in ulcerative colitis

Patient or population: patients with quiescent ulcerative colitis
Settings: outpatient
Intervention: rectal 5-ASA 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	Rectal 5-ASA versus placebo				
Symptomatic remission	298 per 1000[1]	662 per 1000 (375 to 1162)	RR 2.22 (1.26 to 3.90)	301 (4 studies)	⊕◯◯◯ 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] Imprecision (sparse data 144 events)
[3] Inconsistency (unexplained heterogeneity $I^2 = 67\%$)

BACKGROUND

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon which results in diarrhea, rectal bleeding and pain and reduced quality of life. The inflammation of UC always involves the rectum, and extends proximally in a continuous fashion for a variable distance. In distal UC, the disease does not extend proximal to the splenic flexure. Patients with UC often experience relapses of their disease followed by periods of remission which can last months or years. The goals of drug therapy are to induce and maintain remission, improve quality of life and minimize side effects. 5-ASA is considered a first-line therapy for mild to moderately active UC. Although its precise mechanism of action remains unclear, 5-ASA is believed to act topically. Oral 5-ASA formulations are designed to release active drug to the site of active inflammation. However 5-ASA can also be administered rectally in the form of a suppository, foam or liquid enema. The use of rectal 5-ASA has a number of potential advantages, including direct delivery of medication to the site of maximum inflammation and reduced systemic toxicity from mucosal absorption.

OBJECTIVES

The primary objective was to assess the efficacy and safety of rectal 5-ASA for maintenance of remission in distal UC.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomized controlled clinical trials were eligible for inclusion.

Types of participants

Subjects were required to be at least 12 years of age with UC disease extent less than 60 cm from the anal verge or distal to the splenic flexure, as determined by barium enema or endoscopy. Subjects were also expected to have been in remission at the time of randomization.

Types of interventions

At least one treatment arm was required to administer rectal 5-ASA as an enema, foam or suppository for a minimum duration of six months. Eligible comparators were placebo and oral 5-ASA formulations.

Types of outcome measures

The principal outcome measure was continued remission by clinical, endoscopic or histologic criteria. Pre-planned secondary analyses included time to relapse and change in disease activity indices (DAI). Subgroup analyses by disease extent and 5-ASA dose were also planned. Because of anticipated heterogeneity in the definition of these outcomes, those of the original authors were accepted.

Search methods for identification of studies

The MEDLINE database (1966 to August 30, 2012) was searched for randomised clinical studies investigating use of rectal 5-ASA for maintaining remission of UC using the following strategy:
1. exp Ulcerative colitis/
2. exp proctocolitis/
3. proctosigmoiditis.mp.
4. rectocolitis.mp.
5. rectosigmoiditis.mp.
6. ulcerative rectocolitis.mp.
7. ulcerative proctocolitis.mp.
8. hemorrhagic ulcerative.mp.
9. exp proctitis/
10. hemorrhagic proctocolitis.mp.
11. or/1-10
12. exp 5-asa/
13. exp 5-aminosalicylate/
14. exp mesalamine/
15. exp Asacol/
16. exp Claversal/
17. exp Pentasa/
18. exp Rowasa/
19. exp Salofalk/
20. exp Mesasal/
21. exp Olsalazine/
22. or/12-21
23. exp Topical administration/
24. exp topical drug administration/
25. exp suppository/
26. rectal administration.mp.
27. rectal instillation.mp.
28. rectal drug administration.mp.
29. anal drug administration.mp.
30. exp foam/
31. exp enema/
32. or/23-31
33. 11 and 22 and 32

The Cochrane Central Register of Controlled Trials (CENTRAL) was searched on August 30, 2012 using the following strategy:
#1 MeSH descriptor Colitis, Ulcerative explode all trees
#2 MeSH descriptor Proctocolitis explode all trees
#3 proctosigmoiditis
#4 rectocolitis

#5 rectosigmoiditis
#6 ulcerative rectocolitis
#7 ulcerative proctocolitis
#8 hemorrhagic ulcerative
#9 MeSH descriptor Proctitis explode all trees
#10 hemorrhagic proctocolitis
#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12 MeSH descriptor Mesalamine explode all trees
#13 olsalazine
#14 (#12 OR #13)
#15 MeSH descriptor Administration, Topical explode all trees
#16 topical drug administration
#17 suppositor*
#18 rectal administration
#19 rectal instillation
#20 rectal drug administration
#21 anal drug administration
#22 MeSH descriptor Enema explode all trees
#23 (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22)
#24 (#11 AND #14 AND #23)

These searches were supplemented by searching the Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/FBD) Review Group Specialized Trials Register and a manual review of bibliographies and abstracts submitted to major gastroenterology meetings (1997 to 2011) published in the following Journals:

- American Journal of Gastroenterology;
- Canadian Journal of Gastroenterology;
- Gastroenterology;
- Gastrointestinal Endoscopy;
- Gut; and
- Scandinavian Journal of Gastroenterology.

Reference lists from retrieved articles were scanned to identify additional citations that may have been overlooked by the database search.

Data collection and analysis

Abstracts from citations retrieved from the literature search were first reviewed by a single author (MT) to exclude those clearly ineligible for inclusion. For the remaining citations, full publications were retrieved and assessed formally for eligibility by three independent authors (MT, JKM, JN). Where key data were not provided, original authors were contacted and asked to provide clarification. Inter-rater agreement was assessed using Cohen's Kappa and disagreements were resolved by consensus.

Eligibility Assessment:

A standardized form was developed to assess the eligibility of trials for inclusion in the review. The following items were rated on a three-point scale ("Yes", "No" and "Not Stated"):

a) All subjects at least 12 years of age;
b) Proven diagnosis of UC in all subjects;
c) All subjects in remission at time of randomization;
d) UC disease extent less than 60 cm from the anal verge or distal to the splenic flexure on barium enema or endoscopy in all subjects;
e) Rectal 5-ASA administered to at least one treatment arm;
f) Randomized treatment allocation; and
g) Symptoms assessed in at least one study outcome.

Data Extraction:

A standardized form was used by two independent authors to extract the following data from each eligible study:

- Number of subjects randomized to rectal 5-ASA and control arms;
- Intervention administered to each study arm (formulation, dose, dose frequency, duration);
- Subject characteristics (e.g. age, gender, disease extent, disease duration, use of concomitant corticosteroids or oral 5-ASA);
- Number of subjects in each arm who are lost to follow-up or drop out due to adverse events;
- Number of subjects in each arm who maintain clinical, endoscopic or histologic remission;
- Median number of days to clinical, endoscopic or histologic relapse;
- Mean disease activity index scores at baseline and at each study assessment; and
- Definitions of remission (clinical, endoscopic and histologic) used in the study.

Methodological Quality Assessment:

The methodological quality of each trial was assessed using the Cochrane risk of bias tool (Higgins 2011) and the Jadad scale (Jadad 1996). In addition, the authors also applied a scale used in their previous published meta-analyses of therapies for UC (Marshall 1995; Marshall 1997; Marshall 2000; Marshall 2010). This scale evaluates 15 individual factors on a 3-point scale (2 = fully described/defined, 1 = partially described and 0 = not described) to yield a total score ranging from 0 to 30:

- Inclusion and exclusion criteria;
- Number of subjects excluded and reasons for exclusion stated;
- Proven diagnosis of UC on histology;
- Exclusion of infectious colitis;

- Patient demographics described and similar among treatment arms;
- Description of drug preparation for all interventions;
- Description of randomisation method;
- Sequential enrolment;
- Assessor blinding to treatment arm;
- Patient blinding to treatment arm;
- Standardized assessment criteria for outcome;
- Frequency and profile of adverse events;
- Description of statistical methods and their appropriateness;
- Accounting of all dropouts; and
- Documentation and monitoring of patient compliance.

The Cochrane risk of bias tool (Higgins 2011) involves an assessment of the following items: the method of allocation generation (i.e. was the allocation sequence adequately generated?), allocation concealment (i.e. was allocation adequately concealed?), blinding (i.e. was knowledge of the allocated intervention adequately prevented during the study?), incomplete outcome data (i.e. were incomplete outcome data adequately addressed?); and selective outcome reporting (i.e. are reports of the study free of suggestion of selective outcome reporting?). A judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias.

We used the GRADE approach for rating the overall quality of evidence for the primary outcomes and selected secondary outcomes of interest. Randomized trials start as high quality evidence, but may be downgraded due to: (1) limitations in design and implementation (risk of bias), (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias). The overall quality of evidence for each outcome was determined after considering each of these elements, and categorized as high quality (i.e. further research is very unlikely to change our confidence in the estimate of effect); moderate quality (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate); low quality (i.e. 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); and very low quality (i.e. we are very uncertain about the estimate) (Guyatt 2008; Schünemann 2011).

Statistical Analysis:

Risk ratios (RR) with 95% confidence intervals (CI) were calculated for each binary endpoint (clinical, endoscopic, and histologic remission) for each trial. An intention to treat principle was followed, with the total number of patients randomized to each study arm used as the denominator for each proportion. A pooled RR and 95% CI was then calculated for each endpoint across all trials reporting that endpoint. A fixed-effect model (Mantel-Haenstzel) was used unless the Chi^2 test and visual examination of forest plots showed significant heterogeneity ($P < 0.10$). In that situation, a random-effects model was used. Pooled risk ratios were calculated for comparisons of rectal 5-ASA versus placebo and rectal 5-ASA versus oral 5-ASA, and for comparisons among rectal 5-ASA doses and formulations.

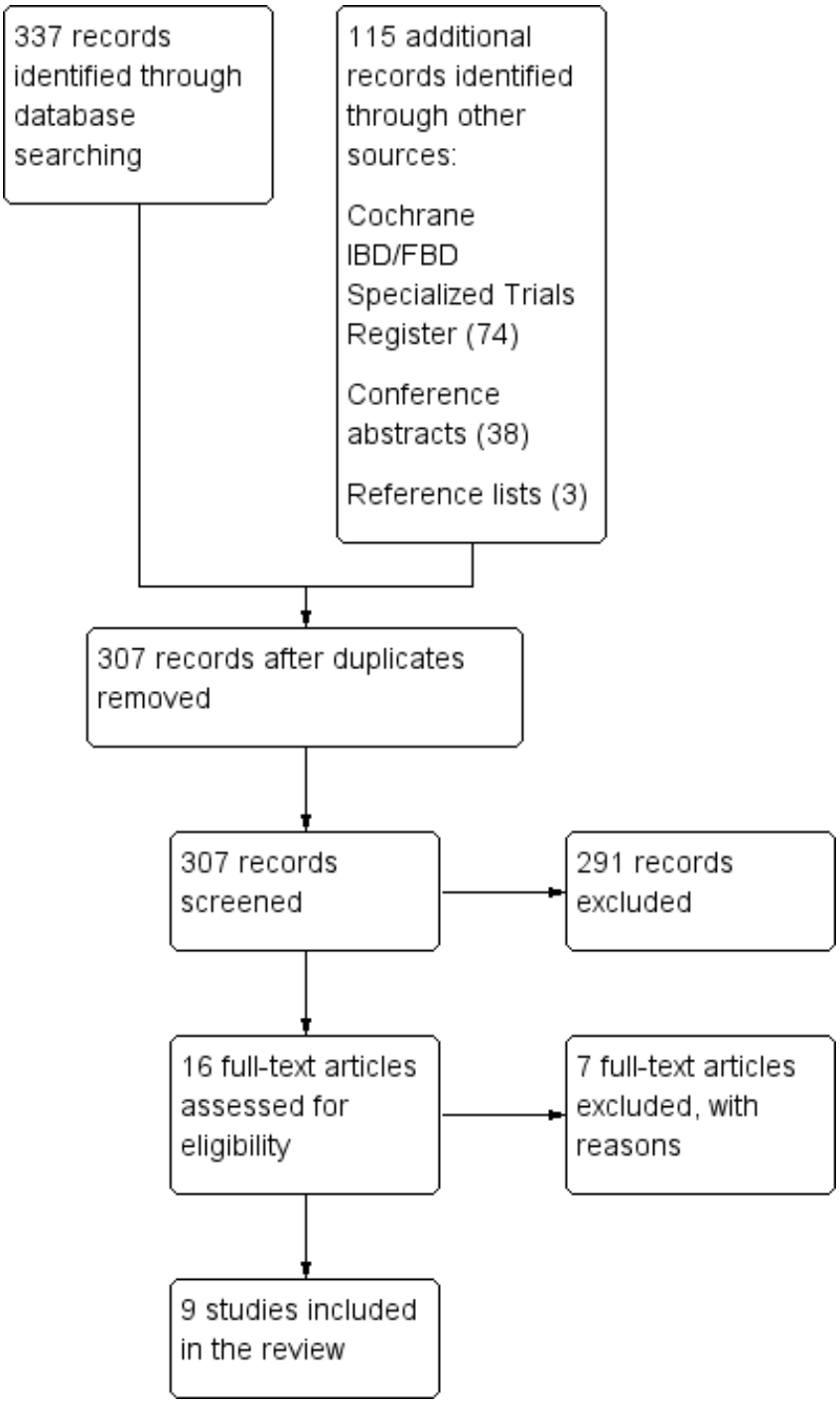
RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

A literature search conducted on August 30, 2012 identified 452 citations. After duplicates were removed a total of 307 citations remained for review of titles and abstracts. After review of titles and abstracts, 16 studies were identified and assessed for eligibility (See Figure 1: Flow chart). Seven studies did not fulfill the inclusion criteria (Kappa 1.00): three were not randomized (D'Arienzo 1987; Bresci 1997; Bresci 2002), three included patients with pancolitis or total colitis (d'Albasio 1997; Piodi 2004; Yokoyama 2007), and one was not a comparative trial (Casellas 1999).

Figure 1. Study flow diagram.



Nine studies involving a total of 484 patients, were selected for inclusion (See Characteristics of included studies). Among these studies, the total daily dose of rectal 5-ASA ranged from 0.5 g to 4 g and dose frequency ranged from once to three times daily. 5-ASA was delivered as liquid enema in five studies (Sutherland 1987; Biddle1988; d'Albasio 1990; Andreoli 1994; Mantazaris 1994) and as a suppository in four studies (D'Arienzo 1990; d'Albasio 1998; Marteau 1998; Hanauer 2000). Follow-up ranged from 6 to 24 months. The characteristics of the included studies are summarized in the Characteristics of included studies tables as well as in additional Table 1 and Table 2.

Andreoli 1994 conducted a two-phase single-blind study in patients with endoscopically documented active mild to moderate left-sided UC. In the first phase, 37 subjects received 5-ASA enemas 4 g daily after stopping all oral 5-ASA therapy. In the second phase, 31 subjects who entered endoscopic and histologic remission were randomized to either 5-ASA enemas 4 g twice weekly (n = 16) or oral sulphasalazine (SASP) 1 g twice daily (n = 15) for six months. Clinical outcomes were assessed monthly, and endoscopy was performed by a blinded endoscopist at six months or upon suspected relapse. The mucosal appearance was graded from zero to three according to McPhee 1987. Endoscopic relapse was defined by an endoscopic score greater than zero. After 6 months, 12 patients on rectal 5-ASA and 9 on oral SASP maintained clinical and endoscopic remission (difference not significant). The mean time to relapse was 3.0 months in the oral SASP group compared to 4.1 months in the rectal 5-ASA group (difference not significant). No significant adverse events were reported. The authors concluded that twice weekly 5-ASA enemas are as effective as oral SASP for maintaining remission induced by rectal 5-ASA.

Biddle1988 randomized 25 subjects with endoscopically documented left-sided UC to 1 g 5-ASA enemas or placebo daily for one year. Subjects were eligible if they had been in symptomatic and endoscopic remission for at least one month using 1 g 5-ASA enemas and having weaned off concomitant oral 5-ASA and corticosteroids. Subjects were assessed clinically and endoscopically every four to six weeks. Disease activity was scored for stool frequency, rectal bleeding, mucosal appearance and physician global assessment with possible scores ranging from 0 to 12. Subjects with either no or mild symptoms, and either normal mucosal appearance or minimally active disease at endoscopy were considered to be in remission. Nine of 12 subjects on 5-ASA and 2 of 13 on placebo group remained in remission for 46 weeks ($P < 0.005$). Two subjects in the 5-ASA group withdrew for personal reasons, and one subject relapsed 8 weeks after discontinuing 5-ASA for allergy (31 weeks after randomization). Of 13 subjects on placebo, 11 relapsed after a mean of 16 weeks. The authors concluded that 1 g 5-ASA enemas are safe and effective in maintaining remission of left-sided UC.

d'Albasio 1990 randomized subjects with symptomatically, endoscopically and histologically quiescent ulcerative proctosigmoiditis, to 5-ASA enemas 4 g daily (n = 29) for the first seven days of each month or oral SASP 2 g daily (n = 31) for two years. All subjects were in clinical, histologic and endoscopic remission for at least two months prior to enrolment. Subjects were assessed clinically every two months. Disease activity was evaluated according to the Truelove 1956 criteria. Colonoscopy was performed by a blinded endoscopist every six months or upon symptom relapse, and graded according to Baron 1964. Subjects with mild symptoms and normal mucosa were considered to be in remission. Six patients on 5-ASA and nine on SASP stopped treatment or dropped out due to poor compliance. The actuarial relapse rates on 5-ASA compared to SASP were 20% and 24% at 12 months, and 37% versus 43% at 24 months (no significant difference). Mean time to relapse and severity of relapse were also similar. The study authors concluded that intermittent 5-ASA enemas are effective for maintaining remission of left-sided UC.

d'Albasio 1998 conducted a multicenter double-blind trial to evaluate the efficacy and tolerability of 5-ASA suppositories (500 mg twice daily or 500 mg once daily) versus placebo to maintain remission of ulcerative proctitis. Eligible subjects had a confirmed diagnosis of ulcerative proctitis that had relapsed within the previous six months but were currently in clinical, endoscopic and histological remission. Oral 5-ASA was stopped at least three days before study entry. Clinical remission was defined as the absence of visible blood and no more than two bowel movements per day. Randomization was carried out in blocks of three and stratified by center. Total duration of treatment was 12 months with clinical and endoscopic assessments at 3, 6, 9 and 12 months. Relapse was defined by symptoms and an endoscopic activity score greater than 1 according to Baron 1964. Histology was assessed by a blinded pathologist according to Truelove 1956. One hundred and eleven patients were randomized to receive 500 mg 5-ASA suppositories twice daily (n = 36) or once daily (n = 40), or placebo (n = 35). Twenty subjects dropped out for poor compliance, withdrew for adverse events or were lost to follow up. Cumulative relapse rates at 12 months were 10% for twice daily 5-ASA, 32% for once daily 5-ASA and 47% for placebo ($P = 0.035$ for comparison of twice daily versus once daily 5-ASA, $P = 0.007$ for comparison of twice daily 5-ASA versus placebo). The authors concluded that 5-ASA suppositories are effective for maintaining remission of ulcerative proctitis.

D'Arienzo 1990 randomized 30 subjects with proctitis or proctosigmoiditis in "complete" steroid-free remission for at least one month to receive either 400 mg 5-ASA suppositories twice daily or placebo for one year in a double-blind trial. All oral 5-ASA was stopped at enrolment. Subjects completed a daily symptom diary and underwent monthly clinical and endoscopic assessments. Endoscopic appearance was graded according to Blackstone 1984

and biopsies were evaluated according to Friedman 1986. Clinical remission was defined as the absence of blood, diarrhea, abdominal pain or tenesmus. Endoscopic and histologic remission were defined by scores of 0 or 1 on their respective scales. Two patients on 5-ASA and one on placebo withdrew. The cumulative remission rate at 12 months was 92% in the 5-ASA group compared to 21% in the placebo group (P < 0.001). The authors concluded that 800 mg/day of 5-ASA administered as suppositories is safe and effective for maintaining remission of distal UC over one year.

Hanauer 2000 conducted a randomized double-blind multi-center trial comparing 5-ASA suppositories at a dose of 0.5 g once daily (n = 31) to placebo (n = 34) to maintain clinical and endoscopic remission of ulcerative proctitis for two years. Eligible subjects had ulcerative colitis limited to the rectum and were on no other oral or rectal medication for UC. Outcomes were assessed at 3, 6, 9, 12, 18 and 24 months using the Disease Activity Index (DAI). Clinical and endoscopic remission was defined as a DAI score of 0. Relapse was defined by endoscopic inflammation with rectal bleeding or increased stool frequency for at least one week. At 12 months, 19 subjects on 5-ASA and 4 on placebo remained in remission. At 24 months, 14 subjects on 5-ASA and 3 on placebo remained in remission (P <0.001). The mean time to relapse was longer on 5-ASA (453 versus 158 days, P <0.001). The authors concluded that 5-ASA suppositories are efficacious and safe for long term maintenance of remission in UC .

Mantazaris 1994 randomized subjects with distal UC in clinical, endoscopic and histologic remission to either 4 g 5-ASA enemas every third night (n = 19) or oral 5-ASA 0.5 g three times per day (n = 19) for two years in an investigator-blind trial. Eligible subjects had not taken steroids for at least two months prior to enrolment. All subjects discontinued oral 5-ASA or SASP at enrolment. Subjects were assessed clinically and endoscopically every two months. Endoscopic disease activity was graded according to Riley 1988 and histology was graded according to D'Arienzo 1990. No subjects were lost to follow-up. Relapse occurred over two years in 5 patients receiving 5-ASA enemas and 13 patients receiving oral 5-ASA. The actuarial relapse rate was 26% in the 5-ASA enema group compared to 68% in the oral 5-ASA group (P <0.001). The authors concluded that intermittent 5-ASA enemas are more effective than oral 5-ASA for maintaining remission of distal UC.

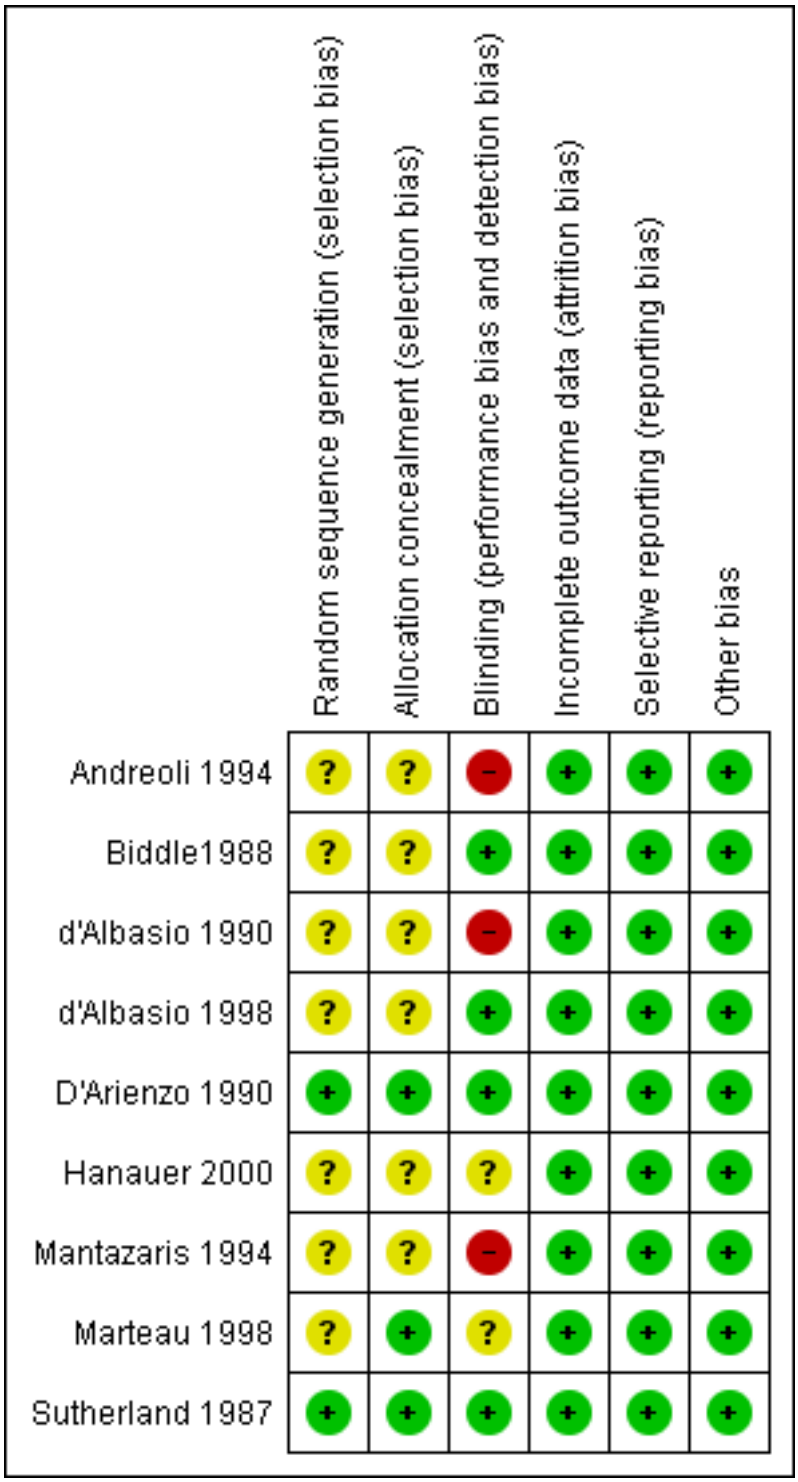
Marteau 1998 conducted a multicenter trial which randomized 95 subjects with ulcerative proctitis in clinical and endoscopic remission to 1 g 5-ASA suppositories three times per week (n = 48) or placebo (n = 47) for 12 months. In the event of a relapse, the suppository dose was increased to daily. If remission was re-attained, daily dosing was continued. If remission was not re-attained, treatment was considered a failure. Eligible subjects had experienced at least two flares in the previous year and had been in clinical remission for less than two weeks (defined by an endoscopy score of zero or one according to Ngô 1992, with no bleeding, mucus, diarrhea, pain or tenesmus). Oral 5-ASA was continued at stable dose throughout the study. Subjects were assessed clinically at 1, 3, 6, 9 and 12 months, and endoscopically at 1, 6 and 12 months. The primary outcome measure was time to relapse, with relapse defined as symptoms with a one-point increase in endoscopy score and rectal bleeding at least twice in one day. Mean survival without relapse was 239 days in the 5-ASA group compared to 166 days in the placebo group (P = 0.067). Overall, 25 patients in the 5-ASA group and 18 in the placebo group remained in remission. The relapse rate was significantly lower on 5-ASA at 90 days (19% versus 38%, P = 0.035), 180 days (29% versus 54%, P = 0.017) and 270 days (38% versus 60%, P = 0.031) but not 365 days (48% versus 62%, P = 0.18). Increasing the dose upon relapse achieved remission in 11 of 18 patients on 5-ASA compared to 2 of 26 on placebo. The authors concluded that 5-ASA suppositories given three times per week are effective for preventing relapse of ulcerative proctitis, and that increasing to daily dosing was effective in a high proportion of subjects who relapsed.

Sutherland 1987 conducted a randomized multi-center double-blind trial comparing 2 g 5-ASA enemas (n = 15) to 4 g 5-ASA enemas (n = 14) over six months in patients with UC extending no more than 50 cm from the anal verge at sigmoidoscopy. The disease activity index (DAI) was required to be less than or equal to four at enrolment. Oral steroids (i.e. less than 30 mg/day prednisolone or equivalent) and SASP were continued for the first month if taken for at least four weeks at stable dose prior to enrolment. These drugs were then discontinued in most subjects. Relapse was defined as a DAI greater than four. Patients were assessed monthly, with sigmoidoscopy repeated at three and six months. After six months, nine patients in each arm had maintained remission. Four subjects in the 2 g group and two subjects in the 4 g dropped out of the study. The authors concluded that 2 g 5-ASA enemas are as effective as 4 g 5-ASA enemas for maintaining remission of distal UC.

Risk of bias in included studies

The risk of bias assessment is summarized in Figure 2. Three studies were rated as high risk of bias due to blinding. D'Arienzo 1990 was an investigator-blinded study. Andreoli 1994 and Mantazaris 1994 were open label studies.

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



The authors applied an instrument reported in their previous systematic reviews of rectal 5-ASA therapy (Marshall 1995; Marshall 1997; Marshall 2000; Marshall 2010) to assess methodological quality. Each study was also assessed using the Jadad scale. The results of these quality analyses are reported in additional Table 3.

Effects of interventions

See: **Summary of findings for the main comparison** Rectal 5-ASA versus placebo for maintenance of remission in ulcerative colitis; **Summary of findings 2** Rectal 5-ASA versus oral 5-ASA for maintenance of remission in ulcerative colitis

Rectal 5-ASA versus Placebo:

Rectal 5-ASA was significantly superior to placebo for maintaining symptomatic remission over a period of 12 months. Sixty-two per cent of patients in the rectal 5-ASA group maintained symptomatic remission compared to 30% of patients in the placebo group (4 studies; 301 patients; RR 2.22, 95% CI 1.26 to 3.90; I^2 = 67%; P < 0.01). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome for the placebo-controlled studies (maintenance of symptomatic remission at study end point) was low due to imprecision (i.e. sparse data 144 events) and inconsistency (i.e. unexplained heterogeneity) (See Summary of findings for the main comparison). Rectal 5-ASA was significantly superior to placebo for maintaining endoscopic remission over a period of 12 months. Seventy-five per cent of patients in the rectal 5-ASA group maintained endoscopic remission compared to 15% of patients in the placebo group (1 study; 25 patients; RR 4.88, 95% CI 1.31 to 18.18; P < 0.05).

There was no statistically significant difference in the proportion of patients who experienced at least one adverse event. Sixteen per cent of patients in the rectal 5-ASA group experienced at least one adverse compared to 12% of placebo patients (2 studies; 160 patients; RR 1.35, 95% CI 0.63 to 2.89; I^2 = 0%; P = 0.44). There was no significant difference in withdrawals due to adverse events. Four per cent of patients in the rectal 5-ASA group withdrew due to adverse events compared to approximately 4% of placebo patients (2 studies; 206 patients; RR 1.04, 95% CI 0.23 to 4.70; P = 0.96).

Adverse events and patient preference are described in detail in additional Table 4. D'Arienzo 1990 reported no adverse events. Commonly reported adverse events include rectal disorder (e.g. hemorrhoids, anal fissure and anal irritation), abdominal pain and headache (Hanauer 2000) and anal or rectal pain (Marteau 1998) and anal canal irritation (Biddle1988). Adverse events leading to withdrawal included anal canal irritation (d'Albasio 1998) abdominal pain and constipation (d'Albasio 1998) and anal or rectal burning (Marteau 1998).

Rectal 5-ASA versus Oral 5-ASA:

There was no statistically significant difference in the proportion of patients who maintained symptomatic remission at six months. Eighty per cent of patients in the rectal 5-ASA group maintained symptomatic remission compared to 65% of patients in the oral 5-ASA group (2 studies; 69 patients; RR 1.24, 95% CI 0.92 to 1.66; I^2 = 0%; P = 0.15). A GRADE analysis indicated that the overall quality of the evidence for the primary outcome for the oral 5-ASA controlled studies (maintenance of symptomatic remission at study end point) was low due to imprecision (i.e. sparse data 50 events) and high risk of bias (i.e. both studies in the pooled analysis were open label) (See Summary of findings 2).

There was no statistically significant difference in the proportion of patients who maintained endoscopic remission. Eighty per cent of patients in the rectal 5-ASA group maintained endoscopic remission compared to 70% of patients in the oral 5-ASA group (2 studies; 91 patients; RR 1.14, 95% CI 0.90 to 1.45; I^2 = 0%; P = 0.26). A GRADE analysis indicated that the overall quality of the evidence for supporting this outcome was low due to imprecision (i.e. sparse data 68 events) and high risk of bias (i.e. the two studies in the pooled analysis were either open label or investigator blinded) (See Summary of findings 2).

Overall safety of rectal 5ASA therapy was favourable. Two studies reported no adverse events (Andreoli 1994; Mantazaris 1994). There was no significant difference in withdrawals due to adverse events. No patients in the rectal 5-ASA group withdrew due to adverse events compared to approximately 6% of oral sulfasalazine patients (1 study; 60 patients; RR 0.21, 95% CI 0.01 to 4.26; P = 0.31).

Several studies reported good patient acceptance of rectal therapy (See additional Table 4). The only study to formally assess preference reported that rectal therapy was favoured (Mantazaris 1994).

Dose ranging studies:

In two trials, one comparing 2 g/day 5-ASA enemas to 4 g/day 5-ASA enemas (Sutherland 1987) and the other comparing 0.5 g/day 5-ASA suppositories to 1 g/day 5-ASA suppositories (d'Albasio 1998), no dose response relationship was observed. Sixty per cent of patients receiving 2 g/day 5-ASA enemas maintained symptomatic remission compared to 64% of patients in 4 g/day 5-ASA enema group (1 study; 29 patients; RR 0.93, 95% CI 0.53 to 1.65; P = 0.81). Fifty-five per cent of patients receiving 0.5 g/day 5-ASA suppositories maintained symptomatic remission compared to 75% of patients in 1 g/day 5-ASA suppositories group (1 study; 76 patients; RR 0.73, 95% CI 0.52 to 1.03; P = 0.07).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Rectal 5-ASA versus oral 5-ASA for maintenance of remission in ulcerative colitis

Patient or population: patients with quiescent ulcerative colitis
Settings: outpatient
Intervention: rectal 5-ASA versus oral 5-ASA

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	Rectal 5-ASA versus oral 5-ASA				
Symptomatic remission	647 per 1000[1]	802 per 1000 (595 to 1074)	RR 1.24 (0.92 to 1.66)	69 (2 studies)	⊕○○○ low[2,3]	
Endoscopic remission	696 per 1000[1]	793 per 1000 (626 to 1009)	RR 1.14 (0.90 to 1.45)	91 (2 studies)	⊕○○○ low[4,5]	

*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] Imprecision (sparse data 50 events)
[3] The two studies in the pooled analysis were open label and were rated as a high risk of bias
[4] Imprecision (sparse data 68 events)
[5] The two studies in the pooled analysis were open label or investigator blinded and were rated as a high risk of bias

DISCUSSION

The results of this systematic review suggest that rectal 5-ASA therapy is effective and safe for maintaining remission of mild to moderately active distal UC. Rectal 5-ASA was significantly superior to placebo for maintaining symptomatic remission in four trials, and endoscopic remission in one trial. However, a GRADE analysis indicated that the overall quality of the evidence for the primary outcome for the placebo-controlled studies (maintenance of symptomatic remission at study end point) was low due to imprecision (i.e. sparse data 144 events) and inconsistency (i.e. unexplained heterogeneity). More research is needed to confirm the efficacy and safety of rectal 5-ASA therapy for maintenance of remission in quiescent UC. Three trials comparing oral with rectal 5-ASA failed to demonstrate a clear advantage for either route of administration. Accordingly, rectal 5-ASA could be considered as an alternative to conventional oral 5-ASA therapy for maintaining remission of UC when the proximal margin of disease is distal to the splenic flexure.

No eligible trials compared rectal 5-ASA to other therapies such as rectal corticosteroids. Lindgren 2002 has compared budesonide to placebo as maintenance therapy for UC, but showed no significant difference in efficacy or adrenal axis activity. Future trials comparing rectal 5-ASA with rectal budesonide (or other topical corticosteroids) are needed.

For this meta-analysis, data were extracted for endpoints of symptomatic and endoscopic remission using the original authors' definitions of endpoints. In fact, we observed considerable heterogeneity among definitions of these endpoints. Standardized definitions of disease activity have been advocated (Travis 2011), to facilitate comparisons of efficacy across trials and to facilitate future quantitative pooling of common outcome measures.

The overall safety of rectal 5ASA appears to be excellent, with no serious adverse effects reported and no significant differences relative to oral therapy. Furthermore, patient acceptance of rectal therapies appears to be good, although this was assessed formally in only one eligible trial. More studies are needed to evaluate patient preference for and compliance with long-term rectally-administered maintenance therapies.

The optimal dosing regimen for rectal 5-ASA maintenance therapy needs to be further investigated. Two trials failed to demonstrate a dose response when comparing different total daily doses of 5-ASA. However, two studies (Andreoli 1994; Marteau 1998) demonstrated the efficacy of intermittent rectal 5-ASA dosing for maintaining remission. Further research is needed to compare dosing regimens that differ by total daily dose, dose frequency and dose formulation (e.g. enema versus foam versus suppository). Furthermore, the duration of studies included in this review ranged from six to twenty four months, but the optimal duration of maintenance therapy after successful induction of remission also remains unclear.

We were unable to compare the efficacy of various rectal 5-ASA regimens across patient subtypes defined by disease severity (e.g. mild versus moderate), prior 5-ASA exposure and response, and proximal disease margin. For induction of remission, rectal 5-ASA has proven to be efficacious and safe for both distal and extensive colitis (Marteau 2005; Marshall 2010). Additional trials are needed to assess response to rectal 5-ASA therapy in these subgroups.

AUTHORS' CONCLUSIONS

Implications for practice

The limited data available suggest that rectal 5-ASA is superior to placebo and may be as effective as oral 5-ASA for maintaining remission of mild to moderately active UC.

Implications for research

Overall, the number of subjects evaluated in clinical trials of rectal 5ASA for maintaining remission of distal UC is small. Well designed randomized trials are needed to establish the optimal dosing regimen for rectal 5-ASA, to compare rectal 5-ASA with rectal corticosteroids and to identify subgroups of patients who are more or less responsive to specific rectal 5-ASA regimens. The combination of oral and rectal 5-ASA appears to be more effective than either oral or rectal monotherapy for induction of remission. The efficacy of combination therapy for maintenance of remission has not been assessed and could be evaluated in future trials.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Andreoli 1994

Methods	Randomized active-controlled trial
Participants	Patients with left-sided ulcerative colitis in clinical and histologic remission (N = 31)
Interventions	5-ASA enema 4 g/100 ml enema twice weekly (n = 16) versus oral SASP 1 g twice daily (n = 15) for 6 months
Outcomes	Clinical and endoscopic relapse
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Unclear risk	Randomization method not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Open label, although endoscopic outcomes assessed blind to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized patients completed the trial
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Biddle1988

Methods	Randomized double-blind placebo-controlled trial
Participants	Patients with left-sided ulcerative colitis in clinical and endoscopic remission (N = 25)
Interventions	5-ASA enema 1 g/60 ml once daily (n = 12) versus placebo (n = 13) for 12 months
Outcomes	Clinical relapse
Notes	

Biddle1988 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Unclear risk	Randomization method not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo identical to study medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs were balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

d'Albasio 1990

Methods	Single-center randomized single-blind active-controlled trial
Participants	Patients with ulcerative proctosigmoiditis in clinical, endoscopic and histologic remission for at least 2 months (N = 60)
Interventions	5-ASA enema 4 g once daily for 7 days each month (n = 29) versus oral SASP 2 g/day (n = 31) for 24 months
Outcomes	Clinical and endoscopic relapse
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Unclear risk	Randomization method not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Investigator blinded

d'Albasio 1990 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

d'Albasio 1998

Methods	Multicenter randomized double-blind placebo-controlled trial	
Participants	Patients with ulcerative proctitis in clinical, endoscopic and histologic remission with a relapse in the last 6 months (N = 111)	
Interventions	5-ASA suppository 0.5 g twice daily (n = 36) versus 5-ASA suppository 0.5 g once daily (n = 40) versus placebo (n = 35) for 12 months	
Outcomes	Clinical and endoscopic relapse	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Unclear risk	Randomization method not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo identical to study medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

D'Arienzo 1990

Methods	Single-center randomized double-blind placebo-controlled trial
Participants	Patients with ulcerative proctitis or proctosigmoiditis in "complete" remission (N = 30)
Interventions	5-ASA suppository 0.4 g twice daily (n = 15) versus placebo (n = 15) for 12 months
Outcomes	Clinical, endoscopic and histologic relapse
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used
Allocation concealment (selection bias)	Low risk	Allocation not predictable
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo identical to study medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Hanauer 2000

Methods	Multicenter randomized double-blind placebo-controlled trial
Participants	Patients with ulcerative proctitis in clinical and endoscopic remission (N = 65)
Interventions	5-ASA suppository 0.5g once daily (n = 31) versus placebo (n = 34) for 24 months
Outcomes	Clinical and endoscopic relapse
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Hanauer 2000 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Unclear risk	Randomization method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo identical to study medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Mantazaris 1994

Methods	Single-center randomized single-blind active-controlled trial
Participants	Patients with ulcerative proctitis or proctosigmoiditis in clinical, endoscopic and histologic remission on oral 5-ASA or SASP (N = 38)
Interventions	5-ASA enema 4 g every 3 days (n = 19) versus oral 5-ASA 0.5 g three times daily (n = 19) for 24 months
Outcomes	Endoscopic and histologic relapse
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Unclear risk	Randomization method not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported

Mantazaris 1994 (*Continued*)

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

Marteau 1998

Methods	Multicenter randomized double-blind placebo-controlled trial
Participants	Patients with ulcerative proctitis in clinical remission with at least two flares in the previous year (N = 95)
Interventions	5-ASA suppository 1 g three times weekly (n = 48) versus placebo (n = 47) for 12 months
Outcomes	Clinical and endoscopic relapse
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Low risk	Sealed envelopes at each center
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated whether placebo is identical to study medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Sutherland 1987

Methods	Multicenter randomized double-blind dose ranging trial
Participants	Patients with distal ulcerative colitis with mild activity or in remission (N = 29)
Interventions	5-ASA enema 2 g/60 ml once daily (n = 15) versus 5-ASA enema 4 g/60 ml once daily (n = 14) for 6 months
Outcomes	Clinical and endoscopic relapse

Sutherland 1987 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table used
Allocation concealment (selection bias)	Low risk	Allocation not predictable
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo identical to study medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

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

Study	Reason for exclusion
Bresci 1997	Design: Not randomized Population: Disease extent greater than 60 cm
Bresci 2002	Design: Not randomized Population: Disease extent greater than 60 cm
Casellas 1999	Study Design: Not a comparative trial
d'Albasio 1997	Population: Some patients with pancolitis
D'Arienzo 1987	Study design: Not a randomized trial
Piodi 2004	Population: Some patients had pancolitis
Yokoyama 2007	Population: Some subjects with total colitis. Period of remission less than 4 weeks

DATA AND ANALYSES

Comparison 1. Rectal 5-ASA versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic remission	4	301	Risk Ratio (M-H, Random, 95% CI)	2.22 [1.26, 3.90]
2 Endoscopic remission	1	25	Risk Ratio (M-H, Random, 95% CI)	4.88 [1.31, 18.18]
3 Adverse events	2	160	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.63, 2.89]
4 Withdrawal due to adverse events	2	206	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.23, 4.70]

Comparison 2. Rectal 5-ASA versus oral 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic remission	2	69	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.92, 1.66]
2 Endoscopic remission	2	91	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.90, 1.45]
3 Withdrawal due to adverse events	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.26]

Comparison 3. Dose ranging rectal 5-ASA 2 g versus 4 g

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic remission	1	29	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.53, 1.65]

Comparison 4. Dose ranging rectal 5-ASA 0.5 g versus 1 g

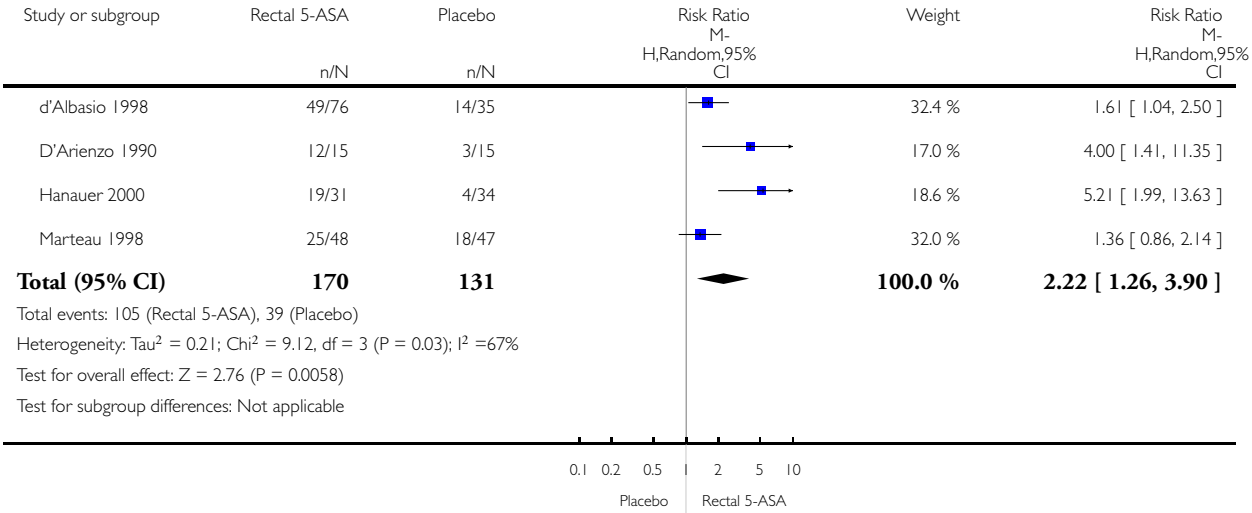
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic remission	1	76	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.52, 1.03]

Analysis 1.1. Comparison 1 Rectal 5-ASA versus placebo, Outcome 1 Symptomatic remission.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 1 Rectal 5-ASA versus placebo

Outcome: 1 Symptomatic remission

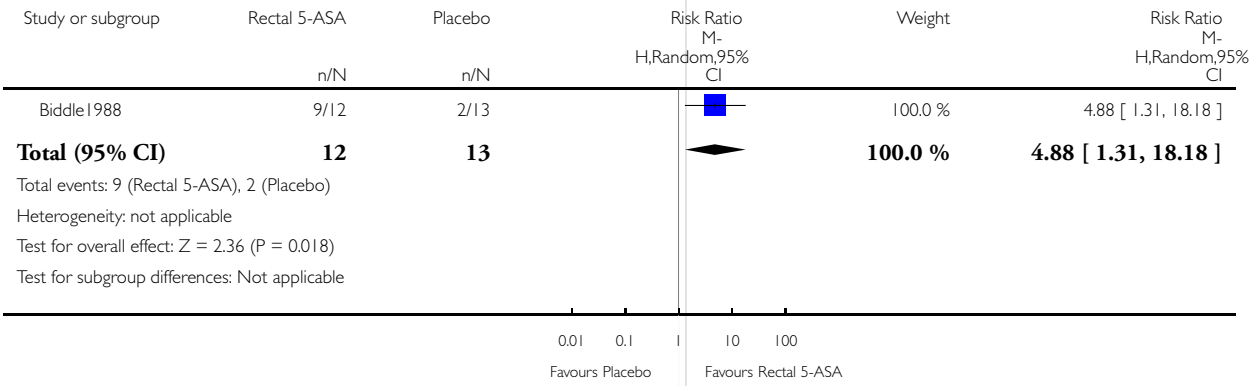


Analysis 1.2. Comparison 1 Rectal 5-ASA versus placebo, Outcome 2 Endoscopic remission.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 1 Rectal 5-ASA versus placebo

Outcome: 2 Endoscopic remission



Analysis 1.3. Comparison 1 Rectal 5-ASA versus placebo, Outcome 3 Adverse events.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 1 Rectal 5-ASA versus placebo

Outcome: 3 Adverse events

Study or subgroup	Rectal 5-ASA n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hanauer 2000	7/31	5/34		48.6 %	1.54 [0.54, 4.34]
Marteau 1998	6/48	5/47		51.4 %	1.18 [0.38, 3.59]
Total (95% CI)	**79**	**81**		**100.0 %**	**1.35 [0.63, 2.89]**
Total events: 13 (Rectal 5-ASA), 10 (Placebo)					
Heterogeneity: Chi^2 = 0.12, df = 1 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 0.77 (P = 0.44)					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 Rectal 5-ASA versus placebo, Outcome 4 Withdrawal due to adverse events.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 1 Rectal 5-ASA versus placebo

Outcome: 4 Withdrawal due to adverse events

Study or subgroup	Rectal 5-ASA n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
d'Albasio 1998	4/76	1/35		40.4 %	1.84 [0.21, 15.88]
Marteau 1998	1/48	2/47		59.6 %	0.49 [0.05, 5.22]
Total (95% CI)	**124**	**82**		**100.0 %**	**1.04 [0.23, 4.70]**

Total events: 5 (Rectal 5-ASA), 3 (Placebo)

Heterogeneity: Chi^2 = 0.66, df = 1 (P = 0.42); I^2 =0.0%

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Rectal 5-ASA versus oral 5-ASA, Outcome 1 Symptomatic remission.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 2 Rectal 5-ASA versus oral 5-ASA

Outcome: 1 Symptomatic remission

Study or subgroup	Rectal 5-ASA n/N	Oral 5-ASA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Andreoli 1994	12/16	9/15		34.4 %	1.25 [0.76, 2.06]
Mantazaris 1994	16/19	13/19		65.6 %	1.23 [0.86, 1.77]
Total (95% CI)	**35**	**34**		**100.0 %**	**1.24 [0.92, 1.66]**

Total events: 28 (Rectal 5-ASA), 22 (Oral 5-ASA)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 1.42 (P = 0.15)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Rectal 5-ASA versus oral 5-ASA, Outcome 2 Endoscopic remission.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 2 Rectal 5-ASA versus oral 5-ASA

Outcome: 2 Endoscopic remission

Study or subgroup	Rectal 5-ASA n/N	Oral 5-ASA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Andreoli 1994	12/16	9/15		22.0 %	1.25 [0.76, 2.06]
d'Albasio 1990	24/29	23/31		78.0 %	1.12 [0.86, 1.46]
Total (95% CI)	**45**	**46**		**100.0 %**	**1.14 [0.90, 1.45]**

Total events: 36 (Rectal 5-ASA), 32 (Oral 5-ASA)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 1.12 (P = 0.26)

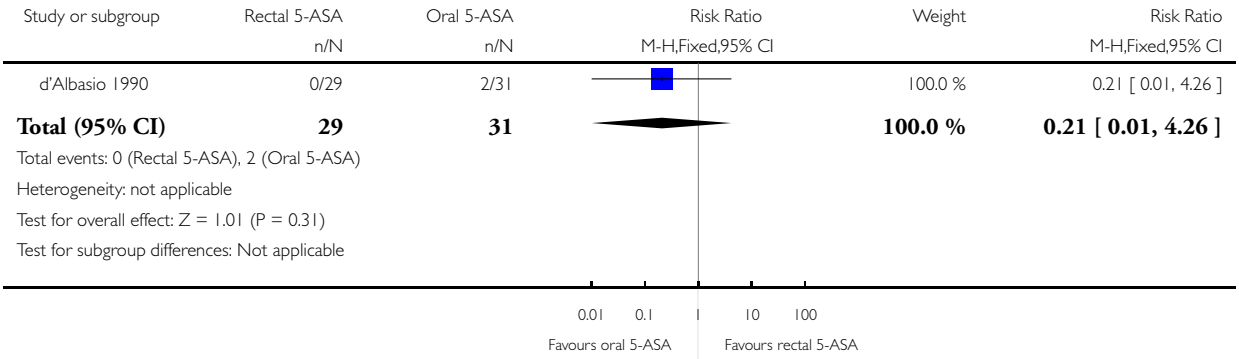
Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Rectal 5-ASA versus oral 5-ASA, Outcome 3 Withdrawal due to adverse events.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 2 Rectal 5-ASA versus oral 5-ASA

Outcome: 3 Withdrawal due to adverse events

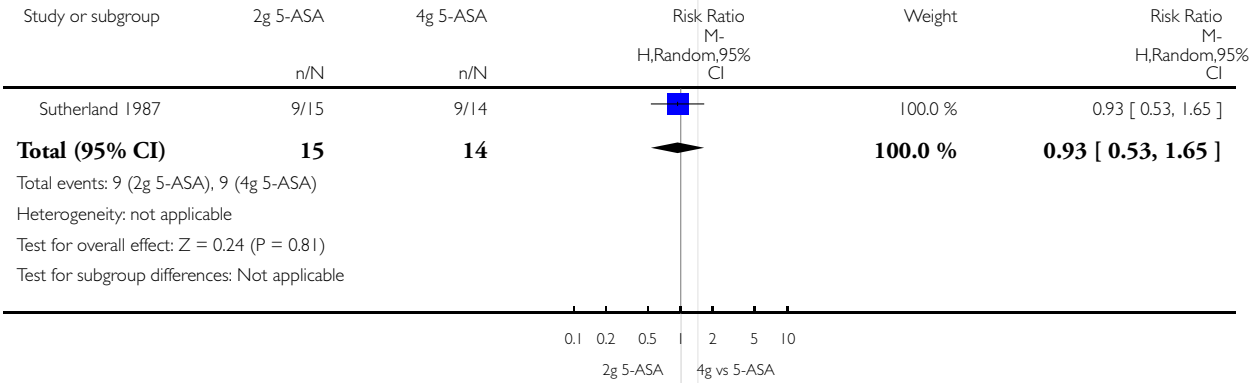


Analysis 3.1. Comparison 3 Dose ranging rectal 5-ASA 2 g versus 4 g, Outcome 1 Symptomatic remission.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 3 Dose ranging rectal 5-ASA 2 g versus 4 g

Outcome: 1 Symptomatic remission

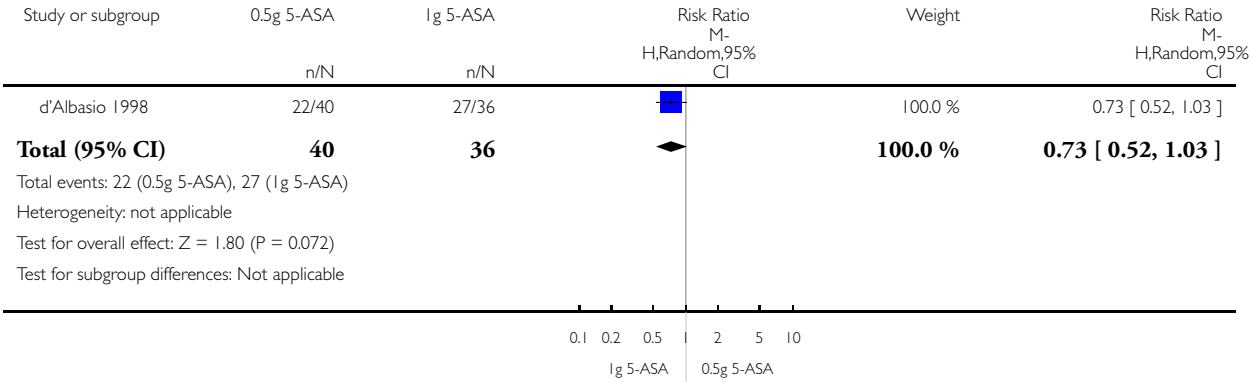


Analysis 4.1. Comparison 4 Dose ranging rectal 5-ASA 0.5 g versus 1 g, Outcome 1 Symptomatic remission.

Review: Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis

Comparison: 4 Dose ranging rectal 5-ASA 0.5 g versus 1 g

Outcome: 1 Symptomatic remission



ADDITIONAL TABLES

Table 1. Summary of Eligible Trials

Author & Year	Study Arm (N per arm)	Duration
Andreoli 1994	5-ASA enema 4 g twice per week (n = 16) versus oral SASP 1 g twice daily (n = 15)	6 months
Biddle 1988	5-ASA enema 1 g once daily (n = 12) versus placebo (n = 13)	12 months
d'Albasio 1990	5-ASA enema 4 g once daily (n = 29) for 7 days per month versus oral SASP 2 g/day (n = 31)	24 months
d'Albasio 1998	5-ASA suppository 0.5 g twice daily (n = 36) versus 5-ASA suppository 0.5 g once daily (n = 40) versus placebo (n = 35)	12 months
D'Arienzo 1990	5-ASA suppository 0.4 g twice daily (n = 15) versus placebo (n = 15)	12 months
Hanauer 2000	5-ASA suppository 0.5 g once daily (n= 31) versus placebo (n = 34)	24 months

Table 1. Summary of Eligible Trials (*Continued*)

Mantazaris 1994	5-ASA enema 4 g every three days (n = 19) versus oral 5-ASA 0.5 g three times daily (n = 19)	24 months
Marteau 1998	5-ASA suppository 1 g three times per week (n = 48) versus placebo (n = 47)	12 months
Sutherland 1987	5-ASA enema 2 g once daily (n = 15) versus 5-ASA 4 g enema once daily (n = 14)	6 months

Table 2. Summary of Endpoint definition

Author & Year	Clinical Relapse	Endoscopic Relapse	Histologic Relapse
Andreoli 1994	Not defined	Endoscopy score at least 1 according to McPhee 1987	Not defined
Biddle 1988	Not defined	Erythema, edema and friability	Not defined
d'Albasio 1990	Symptoms more than mild according to Truelove 1956	Endoscopy score at least 2 according to Baron 1964	Not defined
d'Albasio 1998	Visible blood in stools or more than two bowel movements per day	Endoscopy score at least 2 according to Baron 1964	Histology score at least 2 according to Truelove 1956
D'Arienzo 1990	Visible blood in stools, diarrhea, abdominal pain or tenesmus	Endoscopy score at least 2 according to Blackstone 1984	Histology score at least 2 according to Friedman 1986
Hanauer 2000	Rectal bleeding or increased stool frequency for at least one week	DAI endoscopic score at least 1	Not defined
Mantazaris 1994	Not defined	Endoscopy score at least 1 according to Riley 1988	Histology score at least 2 according to D'Arienzo 1990
Marteau 1998	Rectal bleeding more than twice per day	1-point increase in endoscopy score according to Ngô 1992	Not defined
Sutherland 1987	4-point increase in disease activity index (DAI)	Not defined	Not defined

Table 3. Trial Quality Assessment

Author & Year	Average Jadad Score	Average Quality Assessment Score
Andreoli 1994	2	22.5
Biddle 1988	2	16.5
d'Albasio 1990	2	16.5
d'Albasio 1998	5	27.0
D'Arienzo 1990	5	25.5
Hanauer 2000	3	20.0
Mantazaris 1994	2	19.5
Marteau 1998	3	24.5
Sutherland 1987	4	23.5

Table 4. Summary of Reported Adverse Effects and Preference

Author & Year	Reported Adverse Effects	Preference/ Acceptance
Andreoli 1994	4 g 5-ASA enema twice a week (N = 16): No significant adverse effects 1 g oral SASP twice daily (N = 15): No significant adverse effects	Patients on enema chose to continue long term enema maintenance therapy
Bardazzi 1994	Intermittent 4g 5-ASA enema (N = 29): No adverse effects 2 g/day oral SASP (N =31): Infrequent adverse effects (not specified)	Acceptance of enema therapy reported to be excellent.
Biddle 1988	1g 5-ASA once daily (N = 12): Total with adverse effects 5; anal canal irritation (n = 5) Placebo (N = 13): Total with adverse effects 8; anal canal irritation (n = 8)	Not reported
d'Albasio 1998	500 mg 5-ASA suppository twice daily (N = 36): Total with adverse effects 2; withdrawals due to anal canal irritation and abdominal pain with constipation (n = 2) 500 mg 5-ASA suppository once daily (N = 40): Total with adverse effects 2: withdrawals due to abdominal pain and constipation with swelling (n = 2) Placebo (n = 35): Total with adverse effects 1; withdrawal due to tenesmus and swelling (n = 1)	In patient interviews, repeated administration of suppositories was well accepted

Table 4. Summary of Reported Adverse Effects and Preference (*Continued*)

D'Arienzo 1990	400 mg 5-ASA suppository twice daily (N = 15): No adverse effects Placebo (N = 15): No adverse effects	Not reported
Hanauer 2000	500 mg 5-ASA suppository once daily (N = 31): Total with adverse effects 7; rectal disorder (n = 3), abdominal pain (n = 2), headache (n = 2), vaginitis (n = 1), rash (n = 1), allergic reaction (n = 1), constipation (n = 1), pharyngitis(n = 1) Placebo (N = 34): Total with adverse effects 5; vaginitis (n = 1), edema (n = 1), gastroenteritis (n = 1), rectal hemorrhage (n = 1), urinary tract infection (n = 1), chest pain (n = 1), salpingitis (n = 1), sinusitis (n = 1)	Not reported
Mantazaris 1994	Intermittent 4 g 5-ASA enema (N = 19): No adverse effects 0.5 g oral 5-ASA three times daily (N = 19): No adverse effects	Most patients in the enema group preferred intermittent enemas over continuous oral therapy
Marteau 1998	Intermittent 1 g 5-ASA suppository (N = 48): Total with adverse effects 6; anorectal pain or difficulty introducing suppository (n = 4), asthenia, hypotension and moderate leucopenia (n = 1), hair loss (n = 1), withdrawal due to rectal burning (n = 1) Placebo (N = 47): Total with adverse effects 5; anorectal pain or difficulty introducing suppository (n = 4), withdrawal due to rectal burning (n = 2)	Not reported
Sutherland 1987	2 g 5-ASA enema once daily (N = 15): Few and insignificant adverse effects (not specified) 4 g 5-ASA enema once daily (N = 14): Few and insignificant adverse effects (not specified)	Not reported

HISTORY

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Review first published: Issue 11, 2012

DECLARATIONS OF INTEREST

Dr. Marshall has received honoraria for speaking and/or consulting from Axcan, Aptalis, Ferring, Shire, Warner-Chilcott, Janssen, Abbott and Takeda, and has received research funds from Abbott, Janssen, Centocor, GKS, Amgen and Pfizer.

Dr. Steinhart has received honoraria for speaking and/or consulting from Aptalis, Shire, Janssen and Abbott, and has received research funds from Abbott, Janssen, Centocor, Amgen, Pfizer, GSK and Millenium.

Dr. Thabane has no conflicts of interest.

Dr. Irvine has received honoraria for speaking and/or consulting from Abbott, Shire and Procter & Gamble, and has received research funds from Abbott.

Dr. Newman has no conflicts of interest.

Dr. Anand has no conflicts of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None