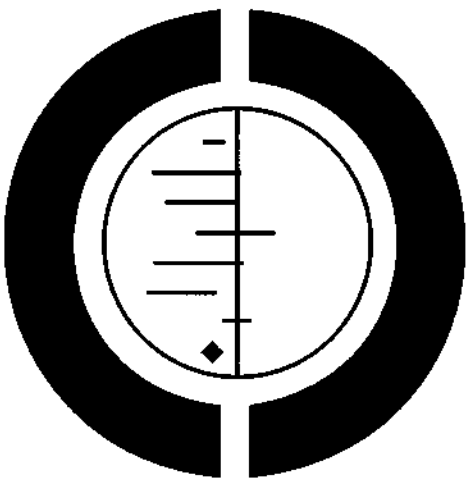
Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis (Review)

Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ



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[Intervention Review]

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

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ABSTRACT

Background

5-Aminosalicylates (5-ASA) are considered a first-line therapy for inducing and maintaining remission of mild to moderately active ulcerative colitis (UC). When inflammation in UC is limited to the distal colon, 5-ASA can also be administered rectally as a suppository, enema or foam.

Objectives

A systematic review was undertaken to evaluate the efficacy of rectal 5-ASA for treating active distal UC.

Search strategy

Electronic searches of the MEDLINE database (1966-2008), the Cochrane Central Register of Controlled Trials and the Cochrane IBD/FBD Group Specialized Trials Register were supplemented by manual reviews of reference listings and conference proceedings.

Selection criteria

Randomized trials comparing rectal 5-ASA to placebo or another active therapy were eligible for inclusion. Eligible trials enrolled patients with a distal disease margin less than 60 cm from the anal verge or distal to the splenic flexure. Trials that enrolled subjects less than 12 years of age were excluded.

Data collection and analysis

Eligibility was assessed by three authors. Data were extracted by two authors using standardized forms. Pooled odds ratios (POR) for inducing improvement and remission by symptomatic, endoscopic and histologic criteria were calculated using an intention to treat principle. Fixed effects models were used unless heterogeneity was encountered within groups ($P < 0.10$), where random effects models were used. All statistical analyses were performed using RevMan 5. Where sufficient data were available, subgroup analyses were performed for disease extent, total daily 5-ASA dose, 5-ASA formulation (enema,suppository, foam) and the type of control intervention (placebo or another active therapy).

Main results

Thirty-eight studies fulfilled the inclusion criteria. Rectal 5-ASA was superior to placebo for inducing symptomatic, endoscopic and histological improvement and remission, with POR for symptomatic improvement 8.87 (8 trials, 95% CI: 5.30 to 14.83; P < 0.00001), endoscopic improvement 11.18 (5 trials, 95% CI 5.99 to 20.88; P < 0.00001), histologic improvement 7.69 (6 trials, 95% CI 3.26 to 18.12; P < 0.00001), symptomatic remission 8.30 (8 trials, 95% CI 4.28 to 16.12; P < 0.00001), endoscopic remission 5.31 (7 trials, 95% CI 3.15 to 8.92; P < 0.00001), and histologic remission 6.28 (5 trials, 95% CI 2.74 to 14.40; P < 0.0001). Rectal 5-ASA was superior to rectal corticosteroids for inducing symptomatic improvement and remission with POR 1.56 (6 trials, 95% CI 1.15 to 2.11; P = 0.004) and 1.65 (6 trials, 95% CI 1.11 to 2.45; P = 0.01), respectively. Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement (POR 2.25; 95% CI 0.53 to 19.54; P = 0.27). Neither total daily dose nor 5-ASA formulation affected treatment response.

Authors' conclusions

Rectal 5-ASA should be considered a first-line therapy for patients with mild to moderately active distal UC. The optimal total daily dose and dose frequency of 5-ASA remain to be determined. Future research should define differences in efficacy among patient subgroups defined by proximal disease margin and disease activity. There is a strong need for consensus standardization of outcome measurements for clinical trials in ulcerative colitis.

PLAIN LANGUAGE SUMMARY

5-ASA suppositories, enemas or foam for induction of remission in ulcerative colitis

Ulcerative colitis (UC) is a chronic condition wherein the innermost lining of the large bowel becomes inflamed. If UC affects only the last part of the bowel (distal UC), medications can be given rectally. 5-Aminosalicylic acid (5-ASA) is used commonly to treat mild to moderately active UC. A review of the literature was undertaken to determine how effective rectal 5-ASA (e.g. enemas, suppositories or foam) is for treating distal UC. Thirty-eight studies met the criteria for inclusion in the review. Pooled results from these studies show that rectal 5-ASA is superior to placebo (fake suppositories, enemas or foam) for improving symptoms, improving the appearance of the bowel lining at colonoscopy, and improving the appearance of biopsies of the bowel examined microscopically. Rectal 5-ASA is also superior to rectal steroids for improving symptoms. Side effects were generally mild in nature and included abdominal pain or distention, nausea and anal discomfort or irritation. From these results, it was concluded that rectal 5-ASA should be a first-line treatment for patients with mild to moderately active distal UC.

BACKGROUND

Ulcerative colitis (UC) is a chronic inflammatory disorder of the large intestine that causes diarrhoea, rectal bleeding and abdominal pain. The inflammation of UC always involves the rectum, and extends proximally in a continuous fashion for a variable distance. In most patients, the disease does not extend proximal to the splenic flexure at presentation. 5-Aminosalicylic acid (5-ASA) is considered to be a first-line therapy for mild to moderately active UC. 5-ASA can be administered orally, or delivered rectally in the form of a suppository, foam or liquid enema.

The use of rectal therapy to treat UC has several potential advantages. Because medication can be delivered directly to the site of maximum inflammation, mucosal drug exposure can be increased. Local therapy can also reduce mucosal absorption and systemic toxicity. However, gains in efficacy and safety must be weighed against patient preference, which often favours oral delivery.

In order to further define the role of rectal 5-ASA in the management of UC, a systematic review and meta-analysis were undertaken to compare the efficacy of rectal 5-ASA to other oral or rectal therapies and to placebo, for the treatment of mild to moderately active distal UC.

OBJECTIVES

To evaluate the efficacy of rectal 5-ASA in the treatment of active distal UC.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing the efficacy of rectal 5-ASA to that of placebo or another active drug in the treatment of distal UC were eligible for inclusion in the review.

Types of participants

Studies were accepted if they enrolled subjects who were at least 12 years of age with a distal disease margin less than 60 cm from the anal verge or distal to the splenic flexure, as determined by either barium enema or colonoscopy. A minimum age threshold was applied to limit potential differences in distribution of rectal formulations that may result from age related differences in colonic volume.

Types of interventions

Trials were eligible for inclusion if rectal 5-ASA (formulated as a liquid enema, foam or suppository) was used in at least one treatment arm.

Types of outcome measures

The primary outcome measure was symptomatic improvement. Secondary measures included symptomatic remission, histologic improvement or remission, endoscopic improvement or remission, and change in Disease Activity Index (DAI). The influences of 5-ASA dose and disease extent on efficacy were explored in subgroup analyses. It was anticipated, a priori, that there would be substantial differences among trials regarding the definitions of response and remission by clinical, endoscopic and histologic criteria. Accordingly, the original authors' definitions for each of these outcomes were accepted. Where studies reported only a composite outcome that combined symptom response with either endoscopic or histologic response, this outcome was considered to be a measure of symptomatic response or remission.

Search methods for identification of studies

A computer aided search was conducted in the MEDLINE database (1966 to 2008) to identify randomised clinical trials evaluating rectal 5-ASA for treatment of active UC in patients over age 12. Search strategies used the Boolean operator "and" to combine the following groups of medical subject headings (MeSH):

- MeSH for ulcerative colitis (combined using "or"): ulcerative colitis, proctocolitis, proctosigmoiditis, rectocolitis, recto-sigmoiditis, ulcerative rectocolitis, ulcerative proctocolitis, hemorrhagic ulcerative, hemorrhagic proctocolitis and proctitis.
- MeSH for 5-aminosalicylic acid (combined using "or"): 5-ASA, 5-aminosalicylate, mesalamine, Mesalazine, Asacol, Claversal, Pentasa, Rowasa, Salofalk, Mesasal and olsalazine.
- MeSH for form of intervention (combined using "or"): topical administration, topical drug administration, suppository, rectal administration, rectal instillation, rectal drug administration, anal drug administration, foam and enema.

The MEDLINE database search was supplemented by a search of the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane IBD Review Group Specialized Trials Register and a manual review of bibliographies and abstracts submitted to major gastroenterology meetings (1997 to 2008) published in the following journals: Gastroenterology; Gut; American Journal of Gastroenterology; Canadian Journal of Gastroenterology; Gastrointestinal Endoscopy; European Journal of Gastroenterology and Hepatology; and Scandinavian Journal of Gastroenterology. Reference lists from all articles retrieved were also scanned to identify additional citations that were overlooked in the initial search.

Data collection and analysis

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

Eligibility Assessment:

A standardized form was used to assess eligibility for inclusion in the review. Each of the following criteria were rated on a three-point scale as "yes", "no" or "not stated":

- Age of all participants at least 12 years;
- Proven diagnosis of UC in all subjects;
- Disease extent less than 60cm from anal verge or distal to the splenic flexure on barium enema or colonoscopy;
- Rectal 5-ASA assessed as intervention in at least one treatment arm;

- Treatment allocation randomised or quasi-randomised; and
- Symptom score included as at least one study outcome.

Data Extraction:
A standardized data extraction form was used by two independent authors. Data extracted from each eligibility study included the following:

- Numbers of subjects randomised to the 5-ASA treatment and control arms;
- Intervention used in each arm (dose, formulation, dose frequency, duration);
- Patients characteristics (age, gender, disease extent, disease duration, and use of concomitant oral corticosteroids and 5-ASA);
- Numbers of subjects in each arm who completed treatment, dropped out, or dropped out due to adverse effects;
- Numbers of subjects in each arm who improved or entered remission by symptomatic, histologic and endoscopic criteria;
- Median numbers of days to symptomatic response and symptomatic remission;
- Mean changes in DAI; and
- Definitions of improvement and remission (symptomatic, endoscopic and histologic) used in the study.

Quality assessment of trials:
The methodologic quality of each trial was assessed using the Jadad Scale (Jadad 1996), which evaluates the adequacy of blinding, randomisation and reporting of withdrawals and dropouts. In addition to the Jadad scale, the authors also applied a face-validated scale used in their previous published meta-analyses of therapies for UC (Marshall 1995; Marshall 1997). For each of the following methodologic criteria this instrument assigns a score 0 (not described), 1 (partially described) or 2 (fully described) and possible scores range 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 as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) was also utilized. Briefly, an assessment was made of 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.

Data Analysis:
Odds ratios with 95% confidence intervals (CI) were calculated for each endpoint (improvement and remission by symptomatic, endoscopic and histologic criteria) for each trial. An intention to treat principle was used, with the total number of patients randomised to each study arm as the denominator for each proportion. A pooled odds ratio (POR) for each endpoint was then calculated for all trials reporting that endpoint using a fixed effects model (Mantel-Haenstzel). PORs were calculated for comparisons of rectal 5-ASA versus placebo, rectal corticosteroids and oral 5-ASA, and for comparisons among rectal 5-ASA doses and formulations. Homogeneity was assessed using the chi-square test and by visual inspection of Forest plots. If heterogeneity was encountered within groups ($P < 0.10$), a random effects model was used. All statistical analyses were performed using RevMan 5. Where sufficient data were available, these analyses were repeated within subgroups of patients defined by disease extent, total daily 5-ASA dose, 5-ASA formulation (enema, suppository, foam) and the type of control intervention (placebo or another active therapy).

RESULTS

Description of studies

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

A total of 65 studies were retrieved and assessed for eligibility. Of these, 27 did not meet the inclusion criteria; 10 were not randomised (Barber 1985; Biddle 1990; Bresci 1997 D'Arienzo 1987; Fedotin 1985; Guarino 1987; Kandel 1987; McPhee 1987; Robinson 1990; Serebro 1977); six included patients with disease proximal to the splenic flexure, (Paolozi 2002; Van Bodegraven 1996; Willoughby 1986; Marteau 2005; Yokoyama H 2007; Vecchi 2001); two included patients with Crohn's disease (Klotz 1980; Lucidarme 1997), six had serious methodological flaws (Campieri 1987; Campieri 1989; Fruhmorgen 1980; Pullan 1993; Van Hees 1980; van Hogezand 1988); one used N-Acetyl 5-ASA

as the treatment drug (Willoughby 1980); one included patients with age less than 12 years (Campieri 1981); and one reported single centre results from a multicenter trial included in the review (Sutherland 1987b). In the 38 studies that satisfied the inclusion criteria (kappa 0.97) the total daily dose of 5-ASA ranged from 1g to 4g and the duration of follow up ranged from two to eight weeks. Ten studies (Campieri 1990a; Campieri 1991a; Campieri 1990b; Campieri 1991b; Hanauer 1998; Moller 1978; Palmer 1981; Pokrotnieks 2000; Sutherland 1987a; Williams 1987) compared rectal 5-ASA to placebo, 11 rectal 5-ASA to rectal corticosteroids (Biancone 2007; Anonymous 1987; Farup 1995; Friedman 1986; Gionchetti 2005; Lee 1996; Lemann 1995; Mulder 1988; Mulder 1996; Bianchi-Porro 1995; Senagore 1992) and 4 rectal 5-ASA to oral 5-ASA (Gionchetti 1998; Kam 1996; Safdi 1997; Prantera 2005). Eleven studies (Andus 2008; Ardizzone 1999; Basilico 1987; Campieri 1988; Campieri 1993; Cortot 2008; Eliakim 2007; Gionchetti 1999; Gionchetti 1997; Malchow 2002; Powell-Tuck 1986) compared different rectal 5-ASA formulations and/or doses. The remaining two studies (Miner 2006; Campieri 1984) compared rectal 5-ASA to alicarfosen or 4-ASA. 5-ASA was delivered as liquid or gel enema in 28 studies, as a foam enema in 7 studies, and as a suppository in 7 studies. See Additional Table 1 and Table 2 for further details.

Table 1. Summary of Eligible Trials

Author / Year	Study Arm(N per arm)	Follow up Duration
Andus 2008	1g 5-ASA suppository OD (N=201) vs 0.5 g 5-ASA suppository TID (N=207)	6 weeks
Ardizzone 1999	2g 5-ASA foam BID (N=97: n=26 proctitis; n=52 proctosigmoiditis; n=20 left sided colitis) vs 2g 5-ASA enema BID (N=98: n=23 proctitis; n=57 proctosigmoiditis; n=17 left sided colitis)	3 weeks
Basilico 1987	1.5g 5-ASA enema BID (N=13: n=5 proctitis; n=8 proctosigmoiditis)vs 1.5g sulphasalazine enema BID (N=14: n=10 Proctitis; n=4 proctosigmoiditis)	28 days
Biancone L. 2007	3mg beclomethasone dipropionate enema OD (N=26) vs 3mg beclomethasone dipropionate foam OD (N=24) vs 3g 5-ASA enema OD (N=22) vs 3g 5-ASA foam OD (N=20)	8 weeks
Campieri 1984	2g 4ASA enema OD (N= 31: n=6 proctitis; n=11 proctosigmoiditis; n=14 left sided colitis) vs 2g 5-ASA enema 0D (N=32: n=8 proctitis; n=13 proctosigmoiditis; n=11 left sided colitis))	15 days

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

Campieri 1988	2g 5-ASA enema OD(N=20) vs 1g 5-ASA suppository BID (N=19)	30 days
Campieri 1990	1g 5-ASA suppository OD (N=32: n=23 proctitis; n=9 distal proctosigmoiditis)vs1.5g 5-ASA suppository OD (N=31: n=19 proctitis; n=12 distal proctosigmoiditis)vs placebo (N=31: n=23 proctitis; n=8 distal proctosigmoiditis)	4 weeks
Campieri 1991	2g 5-ASA enema OD (N=18: n=3 proctitis; n=10 proctosigmoiditis n=5 left sided colitis) vs 10g sucralfate enema OD (N=18: n=2 proctitis; n=10 proctosigmoiditis n=6 left sided colitis) vs placebo (N=14: n=3 proctitis; n=9 proctosigmoiditis n=2 left sided colitis)	30 days
Campieri 1993	2g 5-ASA foam OD (N=63: n=55 proctosigmoiditis, n=8 left sided colitis) vs 2g 5-ASA enema OD (N=54: n=48 proctosigmoiditis, n=6 left sided colitis) vs 4g 5-ASA foam OD (N=60: n= 36 rectum sigmoid, n=24 left colon) vs 4g 5-ASA enema OD (N=56: n=28 proctosigmoiditis, n=28 left sided colitis)	3 weeks
Campieri M 1990	0.5g 5-ASA suppository TID (N=32) vs placebo suppository (N=30)	1 month
Campieri M 1991	1g 5-ASA enema (N=27: n=7 proctitis; n=8 proctosigmoiditis n=12 left sided colitis) vs 2g 5-ASA enema (N=30: n=10 proctitis; n=9 proctosigmoiditis n=11 left sided colitis) vs 4g 5-ASA enema (N=29: n=8 proctitis; n=12 proctosigmoiditis n=9 left sided colitis) vs placebo (N=27: n=8 Proctitis; n=10 proctosigmoiditis n=9 left sided colitis))	30 days
Corrot 2008	1g 5-ASA foam enema(N=191: n=81 proctitis; n=97 proctosigmoiditis n=11 left sided colitis n=2 unclear not included in the analysis) vs 1g 5-ASA liquid enema (N=184: n=82 proctitis; n=91 proctosigmoiditis n=6 left sided colitis, n=5 unclear not included in the analysis) vs 4g 5-ASA enema (N=29: n=8 proctitis; n=12 proctosigmoiditis n=9 left sided colitis) vs placebo (N=27: n=8 proctitis; n=10 proctosigmoiditis n=9 left sided colitis))	4 weeks
Danish 5-ASA Grp1987	1g 5-ASA enema OD (N=62) vs 25mg prednisolone enema OD (N=61)	14 days

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

Eliakim 2007	1g 5-ASA foam OD (N=163: n=91 proctitis; n=72 proctosigmoiditis)vs 1g 5-ASA foam OD (N=167: n=85 Proctitis; n=82 proctosigmoiditis)	6 weeks
Farup 1995	0.5g 5-ASA suppository BID (N=41: n=24 proctitis; n=17 proctosigmoiditis)vs 178mg hydrocortisone BID (N=38: n=26 proctitis; n=12 proctosigmoiditis)	4 weeks
Friedman 1986	4g 5-ASA enema OD (N=9) vs 100mg hydrocortisone enema OD (N=9)	3 weeks
Gionchetti 1997	1g 5-ASA suppository OD (N=25) vs 0.5g 5-ASA suppository BID (N=25)	4 weeks
Gionchetti 1998	0.8g 5-ASA tablets TID (N=29) vs 0.4g 5-ASA suppository TID (N=29)	4 weeks
Gionchetti 1999	2g 5-ASA enema OD (N=50: n=38 proctosigmoiditis n=12 left sided colitis) vs 2g 5-ASA foam OD (N=53: n=36 proctosigmoiditis n=17 left sided colitis)	4 weeks
Gionchetti 2005	1g 5-ASA enema OD (N=106: n=60 proctitis; n=31 proctosigmoiditis n=15 left sided colitis) vs 3mg BDP enema OD (N=111: n=56 proctitis; n=31 proctosigmoiditis n=24 left sided colitis)	6 weeks
Hanuaer 1998	1g 5-ASA enema OD (N=73) vs 2g 5-ASA enema OD (N=71) vs 4g 5-ASA enema OD (N=73) vs placebo(N=70)	8 weeks
Kam 1996	4g 5-ASA enema OD (N=19) vs 1g Oral sulphasalazine QID (N=19)	6 weeks
Lee 1996	2g 5-ASA foam OD (N=167: n=14 proctitis; n=97 proctosigmoiditis n=37 left sided colitis: n=1 unknown) vs 20mg prednisolone foam OD(N=167:n=15 proctitis; n=101 proctosigmoiditis; n=27 left sided colitis; n=3 unknown)	4 weeks
Lemann 1995	1g 5-ASA enema OD (N=49) vs 2mg budesonide enema OD (N=48)	4 weeks
Malchow 2002	2g 5-ASA foam OD (N=133) vs 4g 5-ASA enema OD (N=167)	4 weeks

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

Miner 2006	4g 5-ASA enema OD (N=54) vs 120mg alicaforsen enema OD (N=55) vs 2mg alicaforsen enema OD (N=50)	6 weeks
Moller 1978	3g sulphasalazine enema (N=16) vs placebo(N=14)	2 weeks
Mulder 1988	3g 5-ASA enema OD (N=15) vs 30mg prednisolone phosphate sodium OD (N=14)	28 days
Mulder 1996	2g 5-ASA enema OD (N=21) vs 3mg BDP enema OD (N=20) vs 3mg BDP + 2g 5-ASA enema OD(N=19)	4 weeks
Palmer 1981	3g sulphasalazine enema OD (N=17) vs placebo (N=23)	2 weeks
Pokrotnieks 2000	2g 5-ASA foam OD (N=54: n=13 proctitis; n=31 proctosigmoiditis n=10 left sided colitis) vs placebo (N=57: n=20 proctitis; n=29 proctosigmoiditis n=8 left sided colitis)	6 weeks
Porro-Bianchi 1995	1g 5-ASA enema OD (N=27: n=9 proctitis; n=11 proctosigmoiditis n=7 left sided colitis) vs 100mg hydrocortisone enema OD (N=25: n=7 proctitis; n=11 proctosigmoiditis n=7 left sided colitis)	3 weeks
Powell-Tuck 1986	1g 5-ASA enema OD (N=12) vs 2g 5-ASA enema OD (N=13)	28 days
Prantera 2005	1.2g 5-ASA oral MMX TID + placebo enema OD (N=40: n=27 proctosigmoidiris n=13 left sided colitis) vs 4g 5-ASA enema OD + placebo tablet TID (N=39: n=32 proctosigmoiditis n=7 left sided colitis)	8 weeks
Safdi 1997	4g 5-ASA enema OD (N=18) vs 0.4g 5-ASA tablets TID (N=22) vs 4g 5-ASA enema OD + 0.4g 5-ASA tablets TID (N=20)	6 weeks
Senagore 1992	4g 5-ASA enema OD (N=19) vs 100mg hydrocortisone enema OD (N=12) vs 120mg short chain fatty acid enema BID (N=14)	6 weeks
Sutherland 1987	4g 5-ASA enema OD (N=76: n=28 proctitis; n=29 proctosigmoiditis n=9 distal ulcerative colitis) vs placebo (N=77: n=24 proctitis; n=41 proctosigmoiditis; n=12 distal ulcerative colitis)	6 weeks

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

Williams 1987	0.5g 5-ASA suppository TID (N=14) vs placebo (N=13)	6 weeks

Table 2. Summary of Endpoint Definition

Author year	Clinical Remission	Endo. Remission	Histol. Remission	Clinical Improvement	Endo Improvement	Histol. Improvement
Andus 2008	CAI </=4 on Sutherland Scale	EI<4 on Sutherland Scale	DAI mucosal </= 1 according to FDA recommendation			
Ardizzone 1999	CAI </=4 on Rachmilewitz scale	EI<6 on Rachmilewitz scale				
Basilisco 1987	Subjective well being described as well. Absent blood or mucopus in the faeces	nonhaemorthagic sigmoidoscopic appearance				
Biancone L 2007	DAI < 3 on Rachmilewitz scale	DAI<3 on Rachmilewitz scale		Reduction of DAI score of at least one point	Reduction of DAI score of at least one point	
Campieri 1984				According to Truelove and Witts	According to Truelove and Richards	Evident trend in globet cell restoration, reduction of inflammatory cell content and reduction of vascular congestion according to Truelove and Witts
Campieri 1988	Complete disappearance of symptoms (motions, blood mucus) according to Truelove and Richards	Repaired Rectal mucosa according to Truelove and Richards	Signs of inflammation absent according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards

Table 2. Summary of Endpoint Definition *(Continued)*

Campieri 1990	Symptoms free with no more than 2 bowel movements/ day and without visible blood in stools	According to Baron Criteria	According to Truelove and Richards	Decrease in the severity of symptoms but not meeting remission criteria	change in improvement of at least one grade activity according to Baron criteria	change in improvement of at least one grade activity according to Truelove and Richards
Campieri 1991	Disappearance of symptoms of active disease (bleeding or mucus) according to TrueLove and Richards	Repaired Rectal mucosa according to Truelove and Richards	Signs of inflammation absent according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards
Campieri 1993	Return to normal stool frequency, no visible blood in stools, No abdominal symptoms on	Grade=0 (normal mucosa or distortion of vascular pattern) on modified Baron criteria	According to TrueLove and Richards	Decrease in the severity of symptoms not meeting remission criteria	Decrease in mucosal inflammation by one grade relative to initial assessment	Decrease in mucosal inflammation by one grade relative to initial assessment
Campieri M 1990	Complete disappearance of symptoms according to Truelove and Richards	Repaired rectal mucosa according to Truelove and Richards	No signs of inflammation according to Truelove and Richards	Reduction of at least one grade activity from baseline according to Truelove and Richards	Reduction of at least one grade activity from baseline according to Truelove and Richards	Reduction of at least one grade activity from baseline according to Truelove and Richards
Campieri M 1991	No symptoms of acute disease according to Truelove and Richards	Repaired rectal mucosa according to Truelove and Richards	No signs of inflammation according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards	Reduction of at least one grade activity according to Truelove and Richards
Cortot 2008	CAI(1-4) </= 2 on Rachmilewitz scale	EI<4 on Rachmilewitz scale				
Danish 5-ASA Grp1987	According to Binder scale	According to Binder scale		According to Binder scale	According to Binder scale	
Eliakim 2007	CAI </= 4 on Rachmilewitz scale	EI<4 on Rachmilewitz scale	HI=1 according to Riley	>/= 1 decrease from baseline		

Table 2. Summary of Endpoint Definition *(Continued)*

Farup 1995	Complete response DAI</= 2 according to predefined criteria		According to slightly modified Friedman scale	DAI>2 but had decreased from baseline		
Friedman 1986	According to predefined criteria	According to predefined criteria	According to predefined criteria	Decrease of one point on the scale from baseline		
Gionchetti 1997	DAI =0 on the clinical portion of DAI according to predefined scale	DAI =0 on the endoscopic portion of DAI according to predefined scale	HI=1 according to Truelove and Richards	PGAand DAI</= 2	DAI</= 2	
Gionchetti 1998	DAI =0 on the clinical portion of DAI according to Sutherland scale	DAI =0 on the endoscopic portion of DAI according to Sutherland scale	HI=1 according to Truelove and Richards	PGAand DAI</= 2	DAI</= 2	
Gionchetti 1999	DAI =0 on the clinical portion of DAI according to Baron criteria	DAI =0 on the endoscopic portion of DAI to Baron scale	Score = 0/1 according to Truelove and Richards	Decrease by at least one grade on clinical component of DAI	Decrease by one grade on DAI	Decrease by 1 or 2 points
Gionchetti 2005	DAI =0 according to Sutherland			Reduction of at least 3 points in the DAI score from baseline		
Hanauer 1998	Complete remission defined as PGA score =1 according to predefined scale	Composite score <4 at 8 weeks or at discontinuation according to predefined scale	Score =0/1, with at least 1 point reduction from baseline according to predefined scale	PGA score =2, defined as marked improvement in symptoms	Minimal reduction of the composite score by 5 points	Improved by at least one category
Kam 1996	DAI=0, Rectal bleeding score = 0, Evacuation frequency score =0, physician overall assessment of disease severity score=0 accord-	Mucosal appearance =0 according to Sutherland				

Table 2. Summary of Endpoint Definition *(Continued)*

	ing to Suithrland score					
Lee 1996	</= 3 stools per day with no blood	Grade=1 at week 4 or at withdrawal according to predefined scale	Active inflammation score =0 at 4 weeks or withdrawal in patients where the score was greater than 0 at entry according to Rudell		Median score of grade 2	
Lemann 1995	Presence of blood score=0 , and presence of mucus score =0/1 on predefined scale	Score=0 on predefined scale	Score=1 on Floren scale		Reduced score	Reduced score
Malchow 2002	CDAI</= 2 on Rachmilewitz scale	EI</ = 2 on Rachmilewitz		Shift in CAI after 4 weeks		
Miner 2006	DAI</= 2, stool frequency </=1, rectal bleeding =0, endoscopy=0, PAD</=1 on summation of Schroeder and Hanauer scale			Decrease in DAI by 3 points		
Moller 1978	Excellent =full remission rectoscopically, subjective normalization according to predefined scale	Excellent =full remission rectoscopically, subjective normalization according to predefined scale		Good= normalization of defecation frequency and or less blood and mucus in the stool	Good=marked improvement rectoscopically	
Mulder 1988				Decrease in clinical activity >2 according to Van der Heide	Decrease in endoscopic activity >3 according to Van der Heide	Decrease in total score of 8 or more according to Van der Heide

Table 2. Summary of Endpoint Definition *(Continued)*

Mulder 1996				Decrease in clinical score of 2 or more according to Van der Heide and Mulder	Decrease in endoscopic score of 3 or more according to Van der Heide and Mulder	Decrease in histological score of 2 or more according to Van der Heide and Mulder
Palmer 1981				A positive change of 1 grade : Score of 1 or 2 according to Wright and Truelove	A positive change of 1 grade: score of 1 or 2 according to Wright and Truelove	A positive change of 1 grade according to Wright and Truelove
Pokrotneiks 2000	CDAI</4 associated with a decrease of at least 2 points from baseline according to Rachmilewitz	EI</=3 on Rachmilewitz				Reduction of at least 1 score from baseline according to Floren
Porro-Bianchi 1995	Disappearance of symptoms Score =0 on Truelove and Witts	EIndoscopic Score =0 on Truelove and Witts	Histologic Score =0 on Truelove and Witts	At least one grade lower compared to baseline. Grading according to Truelove and Witts and Tuelove and Richards	At least one grade lower compared to baseline. Grading according to Truelove and Witts and Tuelove and Richards	At least one grade lower compared to baseline. Grading according to Truelove and Witts and Truelove and Richards
Powell-Tuck 1986	Score =0 on all clinical variables according to Powell Tuck 1982 scale	Endoscopic grade =0 non friable mucosa according to Powell- Tuck 1982	Histology grade=0			
Prantera 2005	CAI</= 2 on Rachmilewitz scale	EI </= 2 on Rachmilewitz	Histology remission according to score of Floren	Improvement of at least 1 point on CAI scale		
Safdi 1997				Absence of blood in stools for a minimum of 4 days and thereafter until the Patient terminated the study		

Table 2. Summary of Endpoint Definition *(Continued)*

Senagore 1992		Recovery but not defined
Sutherland 1987	According to predefined scale	
Williams 1987	DAI= 0 on predefined scale	

Andus 2008 undertook a 6-week single blind randomised multicenter trial that compared the efficacy and tolerability of 5-ASA suppositories 1.0 g daily (n = 201) compared to 0.5 g three times daily (n = 207) in 408 adult patients with ulcerative proctitis extending no more than 15 cm from the anal verge and with disease activity index (DAI) scores between 3 and 11 (Sutherland 1987b). Patients who had received oral or rectal 5-ASA within 4 weeks, immunosuppressants within 3 months, or corticosteroids within one month of the baseline assessment were excluded. The primary endpoint was clinical remission (defined as DAI < 4) at the final/withdrawal visit. Secondary endpoints included clinical activity index (CAI), endoscopic and histologic remission and improvement (Sutherland 1987b) and PGA (Hanauer 1993). The rates of remission were similar on 1.0 g daily vs. 0.5 g three times daily: (clinical in 84.0% versus 84.7%, endoscopic in 80.1% versus 85.4% and histologic in 3.0% versus 3.9%). The authors concluded that both treatments were of similar efficacy and well tolerated.

Anonymous 1987 reported a randomised double-blind multi-centre trial comparing 5-ASA enemas (1 g/day) to prednisolone enemas (25 mg/day) administered for 4 weeks in 123 patients with mild to moderately active distal UC. Clinical and endoscopic disease activity was graded according to Binder 1970, with treatment responses categorized as remission, improvement, no change or deterioration. The overall response to therapy was defined as the sum of the clinical and endoscopic effects, wherein a negative effect on one outcome could cancel a positive effect on another. Subjects who were asymptomatic at 2 weeks discontinued the study medication, while the remainder continued on treatment for another 2 weeks. Among 61 subjects randomised to 5-ASA and 62 to prednisolone, 4 were withdrawn for protocol violation, 2 for poor compliance and 3 for adverse events. Adverse events were reported in 13 patients on 5-ASA (3 leading to study withdrawal) compared to 6 on prednisolone, a difference that was not statistically significant. All adverse events were described as minor and reversible. Twenty seven subjects discontinued study medication at 2 weeks because of remission (15 on 5-ASA versus 12 on prednisolone) and 12 subjects discontinued therapy because of worsening disease, leaving 75 who were treated for an additional 2 weeks. Overall, 77% on 5-ASA versus 72% on prednisolone improved after 2 weeks (no significant difference), but 51% versus 31% entered remission (P < 0.05). Among the 27 subjects withdrawn at 2 weeks because of remission, rates of relapse over the subsequent 2 weeks were similar in both arms. Among those who continued treatment for an additional 2 weeks, incremental rates of remission and improvement were similar in the two arms. The authors concluded that topical 5-ASA is an acceptable alternative to topical corticosteroid therapy in mild to moderately active distal UC.

Ardizzone 1999 conducted a multi-centre randomised, cross-over trial comparing 5-ASA foam 2 g twice daily to 5-ASA enema 2 g twice daily for 3 weeks (Phase I). If remission was not achieved by 3 weeks, patients were crossed over to the other treatment for a further 3 weeks (Phase II). Patients were included if they were 18 to 70 years of age and had endoscopically confirmed proctitis, proctosigmoiditis or left-sided UC. Mucosal biopsies and stool cultures were required only for new diagnoses. Subjects were excluded if they had used glucocorticosteroids within one month or immunosuppressive drugs within 3 months. Oral 5-ASA was permitted only if the current flare had occurred while on oral 5-ASA and the dose was not changed. Outcome measures included clinical symptoms (symptom diary cards), clinical examination, sigmoidoscopy and quality of life. Disease activity was evaluated according to the Clinical Activity Index (CAI) and Endoscopic Index (EI) of Rachmilewitz 1989. Clinical remission was defined as CAI < 4 and endoscopic remission as an EI score < 6. An intention-to-treat analysis was used. Of 195 patients randomised to 5-ASA enema (n = 98) or 5-ASA foam (n = 97) for Phase I, 58 completed Phase II. Twenty five patients withdrew prematurely (9 in the enema group and 16 in the foam group. A further 10 patients (2 in the enema group, 8 in the foam group) were lost to follow-up. There was an imbalance between the groups with

respect to concomitant oral 5-ASA use (41% enema , 29% foam) but baseline characteristics were otherwise similar. Clinical remission in Phase I was achieved by 77% treated with enema versus 62% treated with foam. Endoscopic remission in Phase I was achieved by 70% on enemas versus 57% on foam. Both clinical and endoscopic remission in Phase I was achieved by 67% and 54%, respectively. In Phase II, clinical and endoscopic remission was achieved in 66% of subjects who crossed over to the enema and 70% of those who crossed over to the foam. No difference in remission rates achieved statistical significance. Although this study did not use a non-inferiority design, the authors concluded that 5-ASA foam and 5-ASA enema were of similar efficacy.

Basilico 1987 randomised 30 patients with mild to moderate distal UC to 5-ASA enemas 1.5 g twice daily (n = 13) or sulphasalazine enemas 1.5 g twice daily (n = 14) for 4 weeks. Patients had ulcerative proctitis or proctosigmoiditis confirmed by sigmoidoscopy and bistology. Oral 5-ASA maintenance therapy was allowed to continue at fixed dose, but corticosteroids and immunosuppressive agents were prohibited. Clinical, histologic and endoscopic outcomes were graded on 3-point scales by blinded evaluators. Patients were said to be in remission when subjective well-being was "well", no blood or mucopus was present in the faeces, and the sigmoidoscopic appearance was not hemorrhagic. Three patients (2 on 5-ASA and 1 on sulphasalazine) did not adhere to the protocol and were excluded from analysis. Patient demographics were similar between the two groups with the exception of disease location (10 and 4 patients, respectively, on sulphasalazine had proctitis and proctosigmoiditis versus 5 and 8, respectively, on 5-ASA). Among subjects who completed the trial, remission was achieved in 9 of 13 patients in the 5-ASA group versus 3 of 14 on sulphasalazine. No adverse events occurred. The authors concluded that the 5-ASA enema was superior to the sulphasalazine enema for inducing remission when given at similar doses, and suggested that this was because sulphasalazine yields a lower effective dose of 5-ASA.

Bianchi-Porro 1995 randomised 52 patients with moderately active UC distal to the splenic flexure, to receive 1g 5-ASA (n = 27) or 100 mg hydrocortisone enemas (n = 25) for 3 weeks in a double-dummy design. Sulphasalazine and 5-ASA were continued at stable doses. Subjects were excluded if they had used steroids within 4 weeks. Clinical, endoscopic and histological activity was assessed using the criteria of Truelove and Witts (Truelove 1955) and Truelove and Richards (Truelove 1956). Remission was defined as disappearance of symptoms and endoscopic and histological signs of disease activity index (grade = 0). Improvement was defined as reduction one or more grade from baseline. The groups were similar at baseline. No adverse events were reported. Clinical, endoscopic and histologic improvement was seen in 89%, 74% and 56% of the 5-ASA group compared to 70%, 56% and 60% of the hydrocortisone group. The authors noted the unusually high rate of clinical improvement in the 5-ASA group and concluded that rectal 5-ASA is an acceptable and safe alternative to topical steroids for treatment of mild to moderately active distal UC.

Biancone 2007 conducted an 8-week randomised multicenter, double blind trial comparing 3 mg beclomethasone dipropionate (BDP) foam (n = 26) or enema (n = 24) to 2 g 5-ASA foam (n = 20) or enema (n = 22) in patients with mild to moderate UC. Eligible subjects had a baseline DAI between 3 and 9 and endoscopic score or 1 or 2 (Rachmilewitz 1989), and had not been in remission for at least 3 months. Histology was graded according toTruelove and Richards (Truelove 1956). Corticosteroids (topical, oral, parenteral), immunosuppressants, and topical sulphasalazine or 5-ASA were not allowed. However, oral sulphasalazine and 5-ASA were continued in patients who had relapsed on maintenance treatment. The primary end point was remission at 4 weeks defined as DAI < 3. Secondary endpoints included remission at 8 weeks and response (defined as a reduction in DAI of at least 1 point). Rates of remission did not differ significantly between BDP and 5-ASA (24% versus 28% at 4 weeks and 36% versus 52% at 8 weeks). DAI dropped significantly from baseline at 4 and 8 weeks on both BDP and 5-ASA. Response rates were also similar in both groups at both time points. Adverse events were reported in 33% of patients on BDP versus 25% on 5-ASA. Treatment was discontinued in 6.0% on BDP versus 7.5% on 5-ASA. The authors concluded that rectal BDP and rectal 5-ASA had comparable tolerability and efficacy in the treatment of mild to moderate UC.

Campieri 1984 conducted a randomised, double-blind clinical trial comparing 4-ASA enemas (2 g/day; n = 31) to 5-ASA enemas (2 g/day; n = 32) in 63 patients with mild to moderately active distal UC. Disease activity was evaluated before and after a 15-day treatment period, using clinical, sigmoidoscopic and histologic criteria. Clinical and histological grading was based on Truelove and Witts (Truelove 1955) and sigmoidoscopy grading was based on Truelove and Richards (Truelove 1956). Disease could not extend beyond the splenic flexure on either endoscopy or barium enema. Randomization was stratified by use and non-usage of Salazopyrin 2 g/day maintenance therapy- which was continued. Baseline characteristics were similar between the groups. No dropouts or adverse events were observed. Clinical improvement was experienced by 77% of 4-ASA patients compared to 81% of 5-ASA patients. Sigmoidoscopic improvement occurred in 77% and 78%, and histological improvement occurred in 41% and 46% of 4-ASA and 5-ASA patients, respectively. Although a non-inferiority design was not used, the authors concluded that both rectal 4-ASA and rectal 5-ASA are effective for distal UC.

Campieri 1988 randomised 39 subjects with mild to moderately active distal UC to 2 g 5-ASA enemas once daily or 1 g 5-ASA suppositories twice daily for 1 month. Disease extent was confirmed between 10 cm and 20 cm from the anal verge at sigmoidoscopy. Sulphasalazine was continued in patients on maintenance therapy. Clinical, sigmoidoscopic and histologic responses were defined by one-point reductions in the corresponding Truelove and Richards score (Truelove 1956). Clinical remission required subjects to be

symptom free. Sigmoidoscopic remission was defined as repaired rectal mucosa and histologic remission was defined as the absence of inflammation. Practicality and tolerability were also scored by subjects. Among 20 patients randomised to enemas and 19 randomised to suppositories, baseline characteristics were similar with the exception of gender (25% female on enemas versus 63% on suppositories). No drop-outs or adverse events were reported. At 4 weeks, outcomes on enemas versus suppositories were 90% versus 85% for clinical improvement, 80% versus 75% for clinical remission, 85% versus 85% for endoscopic improvement, and 65% versus 70% for endoscopic remission, 80% versus 80% for histologic improvement, and 45% versus 60% for histologic remission. None of these comparisons was significant. Both enemas and suppositories were well tolerated but most patients preferred suppositories. The authors concluded that 5-ASA enemas and 5-ASA supposirories are of similar efficacy for treatment of ulcerative proctitis.

Campieri 1990a reported a multi-centre double-blind study comparing 5-ASA suppositories at total daily doses of 1 g (n = 32) and 1.5 g (n = 31) to placebo (n = 31) for 4 weeks in subjects with mild to moderately active ulcerative proctosigmoiditis. Disease margin extended no more than 20cm from the anal verge. Oral 5-ASA and sulphasalazine were continued at stable dose but steroids were not permitted within 7 days of enrolment. Clinical remission was defined as the absence of symptoms with no more than two bowel movements per day and no blood. Clinical improvement was defined as any other decrease in symptom scores. Endoscopic and histologic remissions were defined as one point reductions in the Baron 1964 and Truelove and Richards scales (Truelove 1956), respectively. Analysis followed an intention-to-treat principle. Baseline characteristics were similar except for gender (58% female on 1.5 g 5-ASA versus 25% on 1 g 5-ASA and 32% on placebo). Eleven patients did not complete the trial (2 on 5-ASA 1.5 g/day and 9 on placebo), mostly for non-compliance or worsening of symptoms. At week 4, clinical remission was observed in 39% on placebo versus 69% on 5-ASA 1 g/day and 74% on 5-ASA 1.5g/day ($P < 0.01$ for 5-ASA versus placebo but no significant difference between 5-ASA doses). Similarly, endoscopic remission was observed in 23% on placebo versus 55% on 1 g 5-ASA and 59% on 1.5 g 5-ASA. Histologic remission was attained in 6% on placebo versus 10% on 1 g 5-ASA and 16% on 1.5 g 5-ASA. Few adverse events were documented. The authors concluded that 5-ASA suppositories are effective for mild to moderately active ulcerative proctosigmoiditis, but that no dose effect could be confirmed.

Campieri 1991a reported a double-blind placebo-controlled study comparing sucralfate 10 g (n = 18) versus 5-ASA 2 g (n = 18) and placebo (n = 14) as 100 ml liquid enemas in patients with mild to moderately active UC with proximal disease margin confirmed by endoscopy to extend no further than the splenic flexure. Sulphasalazine was continued if at a stable dose for at least one month prior to enrolment, but steroids were not permitted. Clinical, endoscopic and histological activity was assessed using Truelove and Richards' criteria (Truelove 1956), with improvement defined as a one-point reduction in each score. Baseline characteristics of the three treatment groups were similar. Clinical improvement was reported in 22% on sucralfate, 94% on 5-ASA and 14% on placebo. Endoscopic improvement was seen in 22%, 88% and 14%, respectively. Histology improved in 17%, 83% and 7%, respectively. All outcomes with 5-ASA were significantly better than those with sucralfate and placebo, but sucralfate showed no benefit over placebo. The authors concluded that 5-ASA enemas, but not sucralfate enemas, are effective for distal UC.

Campieri 1993 reported a randomised investigator-blind trial comparing 5-ASA foam to 5-ASA enema for three weeks in patients with a mild to moderate relapse of distal UC extending more than 15 cm from the anal verge. Subjects were excluded if the flare had lasted longer than two weeks, if they were already receiving rectal 5-ASA, or if they had received steroids for more than seven days. The dose of study medication was adjusted to disease activity; subjects with mild disease (n = 117) received 2 g/day while those with moderate disease (n = 116) received 4 g/day. Oral sulphasalazine and 5-ASA were continued at stable doses. Clinical disease activity was assessed by the investigaror as remission, improved, unchanged and worsened. Endoscopic appearance and grading was assessed using modified Baron 1964 criteria, and histology was rated according to Truelove and Richards (Truelove 1956). Baseline characteristics were similar in both arms in both disease activity strata. In the mild disease stratum, clinical remission was seen in 54% of foam patients compared to 31% of enema patients at 10 days, and in 83% versus 74% respectively at 3 weeks. This difference was statistically significant at 10 days but not at 3 weeks. At 3 weeks, endoscopic remission was achieved by 65% and 56%, and histological remission was achieved by 40% and 41% of foam and enema patients respectively. A total of 6 subjects dropped out or were lost to follow-up. In the moderate disease activity stratum, clinical remission on foam versus enema was seen in 63% versus 52% at 3 weeks. Endoscopic remission was achieved by 38% and 34%, and histological remission was achieved by 28% and 20%, of foam and enema patients, respectively. A total of 11 patients dropped out of the study. The authors concluded that no significant difference was seen overall between foam and enemas, but that numeric trends favoured foam and that foam induced response more rapidly in patients with mild disease.

Campieri 1990b reported a randomised double-blind placebo-controlled study of 5-ASA suppositories 1.5 g/day for one month in 62 patients with mild to moderately active UC extending less than 20 cm from the anal verge at sigmoidoscopy. Oral sulphasalazine was continued at a stable dose, but corticosteroids were not permitted. Clinical, endoscopic and histological activity was assessed after 15 days and 1 month according to Truelove and Richards (Truelove 1956), with improvement defined as a one-

point reduction in each score. Clinical remission was defined as a complete disappearance of symptoms, endoscopic remission as repaired mucosa and histologic remission as the absence of active inflammation on biopsy. Baseline characteristics in both arms were similar. At 30 days, clinical remission was achieved by 56% of 5-ASA patients compared to 7% of placebo patients. Endoscopic remission was achieved by 41% versus 7%, and histological remission by 28% versus 3%. No adverse effects or drop outs were reported. For all endpoints, 5-ASA suppositories were significantly superior to placebo ($P < 0.01$). The authors confirmed that 5-ASA suppositories should be the first-line treatment for patients with mild to moderately active ulcerative proctitis.

Campieri 1991b reported a randomised double-blind dose-response trial comparing 5-ASA enemas (1 g, 2 g and 4 g) to placebo for 4 weeks in 113 patients with mild to moderately active UC distal to the splenic flexure at endoscopy. Patients were stratified by use of sulphasalazine. Clinical, endoscopic and histologic activity was assessed according to Truelove and Richards (Truelove 1956), with improvement in each category defined as a one point reduction from baseline. Clinical remission was defined as complete resolution of acute symptoms. Endoscopic remission was described as repaired mucosa with a visible vascular pattern, and histologic remission as the absence of active inflammation. Twenty seven patients were randomised to the 1 g 5-ASA group, 30 to 2 g 5-ASA, 29 to 4 g 5-ASA and 27 to placebo. Baseline characteristics of the treatment groups were similar, no drop outs occurred and 1 patient in each group reported a minor adverse event. Clinical remission was noted at 30 days in 85% of subjects on 1 g 5-ASA, 83% on 2 g 5-ASA, 86% on 4 g 5-ASA and 41% on placebo. Endoscopic improvement or remission was achieved in 74%, 73%, 79% and 30% respectively. Histologic improvement or remission was achieved in 63%, 70%, 76% and 15%. There were no statistically significant differences among the 5-ASA treatment arms, but all outcomes for 5-ASA patients were superior to placebo. The authors concluded that topical 5-ASA is effective for treatment of distal UC, but that its efficacy is not dose-dependent. Accordingly, the lowest dose was advocated as first-line therapy.

Cortot 2008 reported a randomised controlled investigator blind non-inferiority trial comparing 5-ASA foam enemas (1 g/ 80 ml/day) to liquid enemas (1 g/100 ml/day) for 4 weeks in 395 patients with mild to moderate left sided active UC distal to the splenic flexure by colonoscopy or endoscopy. Patients were stratified according to disease extent; first stratum included patients with proctitis and proctosigmoiditis and second stratum included patients with disease extension from 60 cm to to splenic flexure. Patients on a stable oral dose of 5-ASA maintenance treatment for at least one month or stable dose of azathioprine or methotrexate for at least six months prior to study were included. Clinical and endoscopic activity was assessed according to Rachmilewitz 1989 with clinical remission defined by a CAI score of ≤ 2 and endoscopic remission by EI score of < 4. One hundred and ninety one patients were randomised to receive foam enema and 184 to liquid enema.Baseline characteristics of the treatment groups were similar but there were more men than women in the foam group. Fifty-two patients in the foam group and 59 patients in the liquid enema group reported minor adverse effects(AE) with gastrointestinal disorders as the most frequently reported AE. At 4 weeks clinical remission was noted in 66.7% of patients in the foam group compared to 70.5% in the liquid enema group. Endoscopic remission was achieved in 64.2% patients in the foam group and 72.7% in the liquid enema. In secondary analysis, clinical remission was achieved at 2 weeks in 48.1%% of patients receiving foam enema to 50.6% in the liquid enema group. The authors concluded that 5-ASA mesalamine foam provides a therapeutic alternative to liquid enema in mild to moderately active left sided UC. Non-inferiority of the foam enema was achieved at 2 and 4 weeks in the ITT population and at 2 weeks in the PP analysis.

Eliakim 2007 conducted a randomised multicenter trial comparing low volume 5-ASA foam (1 g/30 ml) to high volume 5-ASA foam (1 g/60 ml) in 330 patients with distal UC. Eligible patients had baseline CAI > 4 and endoscopy index (EI) > 4 (Rachmilewitz 1989). Histology was graded according to Riley 1991. Patients who had received steroids within one month or immunosuppressants within three months prior to entry, and those who had relapsed on oral sulphasalazine, oral 5-ASA > 2 g/day or rectal 5-ASA > 1 g/day were excluded. All oral and rectal treatments for UC were stopped at baseline. The primary objective was clinical remission at the final visit, defined as CAI < 4. Secondary endpoints included clinical improvement based on CAI, DAI and EI. Clinical remission rates at 6 weeks were 77% on low-volume foam (n = 163) and 77% on high-volume foam (n = 167). The percentages of patients experiencing adverse events were similar in both groups: 31% versus 29% for mild events and 10% versus 11% for moderate events on low- versus high-volume foam. The authors concluded that low-volume 5-ASA foam is as effective as high-volume foam in the treatment of UC, but that the low-volume foam might offer the advantage of improved compliance.

Farup 1995 reported a 4-week randomised trial comparing 5-ASA suppositories (500 mg bid) to hydrocortisone foam (178 mg bid) in 79 patients with mild to moderately active distal UC. Randomization was stratified by disease extent (proctitis versus proctosigmoiditis). For entry, the proximal disease margin had to extend no further than the splenic flexure, with a disease activity index (DAI) score greater than 6. Oral 5-ASA and sulphasalazine were continued at stable doses. The DAI was defined as the sum of the CAI and EAI. The CAI scored stool frequency, stool consistency, presence of blood, abdominal pain, rectal urgency and a physician rating of disease activity. The EAI scored mucosal granularity, vascular pattern, friability and damage (exudate, erosions and ulcers). Histology was graded using modified Friedman 1986 criteria. Remission was defined as a DAI less than 2. Improvement was defined as a DAI greater than 2 but lower than the

baseline score. Non-responders had no change or worsening of the DAI score. Subjects who were in remission or non-responders at 2 weeks were withdrawn from the study, while the remainder completed a 4-week treatment course. Baseline demographics of the 5-ASA group (n = 41) and the hydrocortisone group (n = 38) were similar. Six patients in each group reported adverse events but all completed the trial. Twenty seven subjects were withdrawn after 2 weeks (17 for remission and 10 for non-response), while 52 completed 4 weeks of treatment. Compliance was adequate (> 80%). The 5-ASA suppository was better tolerated than the hydrocortisone foam. Remission rates at 2 and 4 weeks were 27% and 16% for 5-ASA suppositories compared to 42% and 34% for hydrocortisone foam (differences not significant). Response rates were higher among patients with proctitis than among those with proctosigmoiditis. There was a non-significant trend toward better histologic improvement with 5-ASA suppositories at 2 and 4 weeks (70% and 78% versus 50% and 61%). Subjects on 5-ASA suppositories had a greater mean increase in DAI than those on hydrocortisone foam, which was attributed to better efficacy in the subgroup with proctitis. The authors concluded that, although both 5-ASA suppositories and hydrocortisone foam are effective for distal UC, 5-ASA suppositories should be the first choice in patients with proctitis due to better efficacy, favourable safety and good tolerability.

Friedman 1986 reported a small randomised double-blind trial comparing 5-ASA enemas (4 g/day) to hydrocortisone enemas in 18 patients with UC who had not responded to 3 weeks of hydrocortisone enemas. The proximal disease margin was between 5 cm and 60 cm from the anal verge at endoscopy. Systemic steroids or immunosuppressants were allowed if administered at stable dose for one month before study entry. Endoscopy was graded as normal, erythema, friability, spontaneous bleeding or exudates and ulceration. The CAI assessed stool frequency and the proportion of stools with watery consistency or blood. A change of 1 point in the CAI was determined to be clinically significant. Histology was graded as normal, chronic inflammatory infiltration of the lamina propria with no acute inflammation and or no mild architectural distortion, mild cryptitis with acute inflammatory cell infiltrate and crypt abscesses or extensive crypt injury with abscesses and ulceration. There were no significant differences in baseline characteristics. Compliance was greater than 90%, according to symptom diaries and empty medication containers. After 3 weeks 78% of subjects on 5-ASA versus 22% on hydrocortisone experienced clinical improvement. Both endoscopic and histologic scores improved in 67% on 5-ASA versus 22% on hydrocortisone. No adverse events were reported. Patients randomised to hydrocortisone were offered a further 3 weeks of open-label 5-ASA enemas, and 4 of 6 patients experienced clinical improvement. The authors concluded that 5-ASA enemas are effective in patients with distal UC not responding to hydrocortisone enemas (with or without sulphasalazine).

Gionchetti 1997 reported a randomised trial comparing once daily 1 g 5-ASA suppositories to twice daily 500 mg 5-ASA suppositories for 4 weeks in 50 patients with active UC extending no more than 20 cm from the anal verge as confirmed by endoscopy and histology. Participants were required to have a baseline DAI score > 3 and were excluded if they had previously failed topical 5-ASA or had taken any rectal therapy within 14 days. Immunosuppressive therapy was discontinued for 3 months and steroids for 2 weeks before study entry. Oral sulphasalazine or 5-ASA at a stable dose for 4 weeks was continued. The trial was only investigator-blind, due to differences in dose frequency and suppository size between the two groups. Clinical and endoscopic outcomes were assessed using the DAI and physician's global assessment (PGA) with clinical remission defined as a DAI of 0. The clinical component of the DAI assessed stool frequency and rectal bleeding. The endoscopic component was graded as normal, mild (erythema, decreased vascular pattern, mild friability), moderate (marked erythema, absent vascular pattern, friability, erosions) or severe (spontaneous bleeding, ulceration). Histology was assessed using Truelove and Richards' criteria (Truelove 1956) with remission defined as a score of 1. Twenty five patients received 5-ASA 1 g once daily and 25 patients received 5-ASA 500 mg twice daily. The two groups had similar demographic characteristics at study entry and all subjects completed the 4 week trial. After 2 weeks, those in the 1 g group demonstrated a greater reduction in physician global assessment (PGA) and DAI scores, and were more likely to be in remission. These differences did not persist at 4 weeks. The proportion of patients in each group who reached clinical, endoscopic or histological remission was not statistically different (84%, 80% and 52% in the 1 g group compared to 76%, 72% and 48% in the 500 mg group, respectively). No significant adverse events were reported in either group but the 1 g suppository was better tolerated. The authors concluded that 1 g suppositories once daily induced faster improvement and remission than 500 mg suppositories twice daily.

Gionchetti 1998 compared oral 5-ASA (800 mg TID) to 5-ASA suppositories (400 mg TID) for 4 weeks in 58 patients with UC extending less than 15cm from the anal verge at endoscopy and DAI > 3 in an investigator-blind randomised trial. Patients who had previously failed 5-ASA or who were taking 5-ASA or oral sulphasalazine at baseline were excluded. Immunosuppressive agents had to be discontinued for 3 months and corticosteroids for 2 weeks before entry. Clinical and endoscopic activity was assessed using Sutherland 1987a criteria at Weeks 0, 2 and 4 with remission defined as a DAI sub-scale score of 0. Histology was assessed using Truelove and Richards' criteria (Truelove 1956) with remission defined as a score of 1. The treatment groups had similar demographic characteristics and all subjects completed the trial. At 4 weeks the mean DAI was significantly lower on 5-ASA suppositories (1.48 versus 3.48, P < 0.001). Rates of clinical, endoscopic and histologic remission were 89.6%, 72.4% and 62% on suppositories versus 41.4%, 34.5% and 17.2% on oral 5-ASA (P

< 0.01). No suppository patients compared to 6 oral 5-ASA patients reported adverse events (headache, abdominal pain, nausea). There were no serious adverse events. The authors concluded that 5-ASA suppositories should be considered first-line treatment for patients with active distal UC.

Gionchetti 1999 reported a randomised, investigator blind, multicenter trial comparing 5-ASA gel enema 2 g/day (n = 50) to 5-ASA foam enema 2 g/day (n = 53) in with mild to moderately active distal UC with DAI at least 3. Patients who had flared while receiving rectal steroids or 5-ASA or who had taken oral steroids or immunosuppressives within 3 months were excluded. Those on oral 5-ASA could continue at a stable dose throughout the study. Primary endpoints were clinical, endoscopic and histologic improvement and remission. Endoscopy was assessed using the Baron 1964 score. Clinical or endoscopic improvement was defined by a 1 point improvement in the appropriate DAI subscale and remission as a sub-scale score of 0. Histologic response was assessed using the criteria of Truelove and Richards (Truelove 1956) with remission defined as a score of 1 and improvement as a decrease of a 1 point from baseline. Only a per protocol analysis was reported. Treatment groups had similar baseline characteristics. A total of 7 patients were excluded from the clinical and endoscopic analysis (1 in the gel group for protocol violation, 6 in the foam group: 1 noncompliance, 3 protocol violation, 2 lost to follow up), leaving 96 subjects. An additional 11 patients were excluded from analysis of histologic outcomes (8 on gel and 3 on foam) because of histologic remission at study entry. Five patients in the foam group withdrew due to lack of improvement or poor compliance, but were included in the ITT analysis. At 4 weeks, clinical, endoscopic and histologic improvement was achieved by 18%, 37% and 45% in the gel group compared to 19%, 34% and 50% in the foam group. At 4 weeks clinical, endoscopic and histologic remission was achieved by 76%, 51% and 30% in the gel group, versus 69%, 52% and 30% in the foam group. There was no significant difference between the treatment groups. Mean DAI scores fell significantly in both groups, but there was no difference between the groups. There was no difference in safety between the two groups, but the gel enema was better tolerated. The authors concluded that 5-ASA gel enema is at least as effective as 5-ASA foam and may be better tolerated

Gionchetti 2005 randomised patients with active distal UC (DAI 3 to 10) to receive 5-ASA 1 g enemas (n = 106) or beclomethasone dipropionate (BDP) 3 mg enemas (n = 111) for 6 weeks. The study was investigator-blind. The primary outcome was the Sutherland 1987a DAI, with improvement defined as a decrease of 3 points and remission as a score of 0. Sulphasalazine and oral 5-ASA were continued if their dose had been stable for 6 weeks. Patients on steroids or immunosuppressive agents were excluded. Demographic characteristics of the two groups were similar. There were a total of 34 withdrawals (18 BDP and 16 5-ASA) and 32 adverse events (15 in BDP and 17 in 5-ASA), with only one serious event in the BDP group that was judged not to be related to the study drug. DAI significantly decreased in both groups. Rates of clinical improvement and remission were 37% and 30% for BDP patients compared to 49% and 25% for 5-ASA patients (differences not statistically significant). The authors concluded that both BDP and 5-ASA enemas improve disease activity and are well tolerated.

Hanauer 1998 randomised 287 patients with mild to moderately active UC extending less than 30 cm from the anal verge to 5-ASA enemas (1 g, 2 g or 4 g daily) or placebo enemas for 8 weeks. Patients were excluded if they had taken steroids or 5-ASA within 7 days or immunosuppressives within 90 days of entry. Outcomes were assessed at 0, 1, 4 and 8 weeks. Patients rated their symptoms on a visual analog scale. A blinded physician provided a global assessment (PGA), with improvement defined as a score of 1 or 2. Endoscopic response was assessed in the most severe segment between 5 and 15cm from the anal verge using a 15-point scale comprising erythema, friability, granularity/ulceration, mucopus and vascularity. Endoscopic improvement was defined as a 5-point reduction in the score and remission as a score < 4. Histology was graded as normal (score 0), inactive (score 1), low-grade activity (score 2) or high-grade activity (score 3). Histologic improvement was defined as a 1-point decrease and remission as a score of 0 or 1 with a 1-point decrease. Clinical remission required a PGA of 1 with endoscopic score < 4 and histologic score 0 or 1 with a 1-point decrease from baseline. Analysis was by intention to treat. All groups were similar with respect to baseline characteristics. Adverse events were equal amongst all groups, but there were significantly more dropouts in the placebo group due to "treatment failure." Clinical improvement was achieved by 27%, 67%, 65% and 75% on placebo (n = 70), 1 g 5-ASA (n = 73), 2 g 5-ASA (n = 71) and 4 g 5-ASA (n = 73) groups respectively. Clinical remission was attained by 14%, 47%, 49% and 44%, respectively. Sigmoidoscopic remission was attained by 24%, 59%, 65% and 66%, and histologic remission was achieved by 16%, 42%, 49% and 55%, respectively. All outcomes were significantly better for 5-ASA compared to placebo, but there was no 5-ASA dose response. The authors concluded that 5-ASA enemas were superior to placebo for inducing clinical, endoscopic and histological improvement and remission in mild to moderately active distal UC.

Kam 1996 conducted a randomised, double-blind double-dummy study comparing 4 g 5-ASA enema to oral sulphasalazine 1 g qid administered for 6 weeks in 37 patients with active UC extending 5 to 50 cm from the anal verge and DAI 4 to 9. Patients were excluded if they had had prior bowel resections, diverticulitis, or 5-ASA failure. Oral steroids could be continued if patients had been treated for at least 4 weeks and the dose remained less than 15 mg prednisolone throughout the trial. Immunosuppressives were also continued if they had been used for at least 90 days before study entry and remained at stable doses. The Sutherland DAI Sutherland 1987a, a 7-point clinical global improvement

(CGI) scale and a 7-point patient global improvement (PGI) scale were used to assess response. Complete remission was defined as a DAI of 0, rectal bleeding score 0, evacuation frequency score 0, mucosal appearance score 0 and PGI score 0. Demographic characteristics were similar on 5-ASA (n = 19) and sulphasalazine (n = 18); 84% on 5-ASA and 72% on sulphasalazine completed the trial. There was 1 patient lost to follow up and 1 patient in protocol violation in the 5-ASA group. In the sulphasalazine group 3 patients had adverse events (all minor) leading to withdrawal and 2 were lost to follow up. In total, 8 patients on 5-ASA compared to 15 on sulphasalazine experienced minor adverse events (P = 0.02), and 3 patients on sulphasalazine group withdrew from due to adverse events. At 6 weeks, both groups had a significant decrease in the mean DAI score (P < 0.001), although the groups did not differ. CGI scores also improved in both groups but did not differ between groups. The 5-ASA group had significantly better PGI scores than the sulphasalazine group. Complete remission was achieved by 21% on 5-ASA compared to 22% on sulphasalazine. The authors concluded that rectal 5-ASA was as effective as oral sulphasalazine for treating active distal UC with rapid onset and good safety.

Lee 1996 compared 2 g 5-ASA foam to 20 mg prednisolone foam for 4 weeks in 295 patients with mild to moderately active UC distal to the splenic flexure in a randomised, investigator blind trial at 39 centres in the United Kingdom. Oral steroids, rectal steroids or rectal 5-ASA were not permitted within one month of the trial, but oral sulphasalazine was permitted at a stable dose. Symptom diaries were completed at 2 and 4 weeks, and endoscopy was performed at 4 weeks. Clinical remission was defined as 3 or fewer stools per day with no blood. The endoscopic appearance was graded as normal (including minor abnormalities in the vascular pattern), abnormal with loss of vascularity and granularity but no friability, or abnormal with visible bleeding and/or ulceration. Histologic grading was graded according to Rudell 1980 and remission was defined as a score of 0 if the entry score was greater than 0. Patients on 5-ASA (n = 149) and prednisolone (n = 146) were well matched with respect to sociodemographic characteristics. Clinical remission was achieved by 52% of 5-ASA patients compared to 31% of prednisolone patients (P < 0.001). 5-ASA and prednisolone did not differ for endoscopic (40% versus 31%) or histologic remission (27% versus 21%). Adverse events were uncommon in both groups. The authors concluded that 5-ASA foam enemas were associated with higher clinical remission rates than prednisolone foam enemas, and hypothesized that longer follow up might have demonstrated differences in endoscopic and histological remission.

Lemann 1995 conducted a 4 week randomised, investigator blinded comparison of budesonide enemas (2.3 mg) with 5-ASA enemas (1 g) in 97 patients with UC distal to the splenic flexure at endoscopy. Oral 5-ASA was continued if at stable dose for 2 weeks before study entry. Patients who had received steroids (oral or rectal) within one month or who had previously failed 5-ASA were excluded. Endoscopic appearance was classified as: normal (score 0); granularity, edema and loss of vascularity (score 1); hyperemia, friability and petechiae (score 2) or ulceration (score 3). Endoscopic remission was defined as a score of 0, and improvement as any reduction from baseline. Histology was assessed according to Floren 1987 on a 5-point scale, with remission defined as a score of 1 and improvement as any reduction from baseline. Clinical parameters (stool frequency and rectal bleeding) were assessed as secondary outcomes. Remission was defined as no blood and little or no mucus per rectum. The budesonide group (n = 48) and 5-ASA group (n = 49) were well matched with respect to demographic characteristics. Nine patients in each group were excluded from the per protocol analysis for protocol violation (7 on budesonide, 6 on 5-ASA) or loss to follow-up (2 on budesonide, 3 on 5-ASA). There was 1 serious adverse event in each group, judged not to be related to the study drug. There was no statistically significant difference between budesonide and 5-ASA in rates of endoscopic improvement (76% versus 81%), endoscopic remission (13% versus 13%), histologic improvement (63% versus 67%) or histologic remission (12% versus 20%). Although there was no difference in clinical improvement, clinical remission was achieved by 38% of budesonide patients compared to 60% of 5-ASA patients (P = 0.03). The authors reported that 2 mg budesonide enemas were a good alternative to rectal 5-ASA in patients with active distal UC.

Malchow 2002 compared 2 g 5-ASA Mesalazine foam to 4 g 5-ASA liquid enema in patients with UC distal to the splenic flexure but at least 12 cm from the anal verge with clinical activity index (CAI) > 4 in a randomised, investigator blind trial. Patients were excluded if they were presenting with their first flare or had received immunosuppressants or antibiotics for UC. Oral 5-ASA was continued if at stable dose for at least 4 weeks. Clinical and endoscopic assessment were according to Rachmilewitz 1989. The primary endpoint was clinical remission at 2 or 4 weeks, defined as a CAI < 2. Other outcomes included clinical improvement (defined as a shift in CAI after 4 weeks) and endoscopic remission defined as EI < 2), histologic change and quality of life (IBDQ). Of 400 patients screened, 266 were suitable and randomised, 133 in each group (2 patients randomised to liquid enema were not treated due to safety concerns). Treatment groups did not differ, except that oral 5-ASA was used by more subjects in the foam group (48.6% versus 43.2%). Tolerability was similar. Adverse events were more common in the foam group. Of those judged not to be minor (3 on foam, 1 on liquid), none was fatal or related to study medication. After 4 weeks, 65% on foam compared to 70% on liquid enema achieved clinical remission and 86% compared to 93% achieved clinical improvement. Endoscopic remission was attained by 38% in both groups. Histologic remission was seen in 46% on foam compared to 50% on liquid enemas. Quality of life scores were slightly higher in the foam group, but no significance test was reported. The authors concluded that 2 g 5-ASA foam enema is an effective, safe and tolerable treatment for active distal

UC, and is equivalent to 4 g 5-ASA liquid enema.

Miner 2006 compared enemas containing 120 mg (n = 55) or 240 mg (n = 50) of the antisense oligonucleotide alicaforsen to 5-ASA 4g (n = 54) enemas in 159 patients with mild to moderately active UC extending no more than 50 cm from the anal verge in a randomised, double-blind trial for 6 weeks. Clinical and endoscopic severity was the summation of DAI index scores according Hanauer 1993 and Schroeder 1987. Eligible patients had a DAI of 4 to 10. Oral 5-ASA and purine anti-metabolites were continued at stable dose, but corticosteroids and other immunosuppressants were not permitted. The primary end point was change in DAI at week 6. Secondary end points included change in DAI at other time points up to week 54, and rates of clinical improvement, clinical remission (DAI < 2, stool frequency <1, rectal bleeding = 0, endoscopy = 0, PAD = 1) and clinical relapse. At week 6 the mean percentage reduction in DAI was 40%, 41% and 50% on 120 mg alicaforsen, 240 mg alicaforsen and 5-ASA respectively (differences not statistically significant). At Week 18 a dose-response was observed with DAI decreases of 43% in the 240 mg alicoforsen group compared to 17% in the 120 mg alicaforsen group. There were a total of 306 adverse events (76 on alicaforsen 240 mg, 113 on alicaforsen 120 mg, 117 on 5-ASA), of which 17 were serious but not drug-related. The authors concluded that rectal alicaforsen was effective for treatment of distal UC and demonstrates a dose response relationship, but was not superior to rectal 5-ASA.

Moller 1978 randomised 30 patients with biopsy-confirmed UC extending no more than 15 cm from the anal verge to receive either 3 g sulphasalazine enema (n = 16) or placebo enema (n = 14) every night for 2 weeks. No other medications were permitted. Clinical assessments and proctoscopies were performed at 1 and 2 weeks with inflammation graded on a predefined 3 grade scale. Treatment response was defined as: Excellent

(full endoscopic remission with normalized symptoms); good (marked endoscopic improvement with normalized symptoms and/or less blood/mucus in the stool); and none (no endoscopic or symptomatic improvement). Demographic characteristics of the two groups were similar and only 1 patient (on placebo) withdrew due to lack of improvement. No adverse effects were reported. Due to the small sample size the outcomes "Good" and "None" were grouped together for statistical analysis when compared to the outcome "Excellent." At 2 weeks, 75% and 81% of sulphasalazine patients experienced "excellent" endoscopic and symptomatic responses, compared to 21% and 14% of placebo patients. These differences were statistically significant. The authors concluded that sulphasalazine enema was a useful short term treatment in ulcerative proctitis and can be used when oral therapy is not tolerated.

Mulder 1988 compared 3 g 5-ASA enemas to 30 mg prednisolone enemas in 29 patients with active UC within 20 cm of the anal verge. Sulphasalazine was continued at stable dose but no other medications were permitted, including steroids within one month of enrolment. Patients were randomised to 5-ASA (n = 15) or prednisolone (n = 14) enemas (40 ml) for 28 days, with improvement as the primary outcome. Clinical, endoscopic and histologic activity was assessed blindly using a predefined grading system according to Van der Heide 1988 at study entry and 28 days. Decreases of > 3 in endoscopic score, > 2 in clinical score and > 8 in histological score, were considered an improvement. The 2 groups were similar with respect to age, sex, disease duration and sulphasalazine therapy. Clinical, endoscopic and histological improvement was achieved by 73%, 73% and 73% at 28 days on 5-ASA compared to 79%, 86% and 57% on prednisolone. Clinical remission, defined as normalization of all variables, was not observed in either group. No adverse events were observed in either group. The authors concluded that 5-ASA enemas were a safe and effective treatment for distal UC and a reasonable alternative to rectal corticosteroids.

Mulder 1996 conducted a multicenter randomised double-blind trial comparing 3 mg beclomethasone dipropionate (BDP) enema (n = 20) with 2 g 5-ASA enema (n = 21) and an enema combination of BDP/5-ASA (3 mg/2 g; n = 19) for 4 weeks in 60 patients with active UC extending less than 20 cm from the anal verge. No corticosteroids or other topical therapies were permitted, but oral sulphasalazine and 5-ASA were continued at stable doses. Clinical, endoscopic and histologic activity was assessed at study entry and 4 weeks according to the Van der Heide 1988 scale. Clinical and endoscopic improvement was defined as a decrease in clinical score > 2 and a decrease in endoscopic score > 3. Histologic improvement was defined as a decrease in score > 2. All groups had similar demographics and compliance was greater than 95%. After 4 weeks, clinical improvement was seen in 70%, 76% and 100% of patients receiving BDP, 5-ASA and BDP + 5-ASA respectively. Endoscopic improvement was seen in 75%, 71% and 100%. Endoscopic healing was noted in 30%, 10% and 37%. Histologic improvement was seen in 50%, 48% and 100%. The difference in clinical improvement was statistically significant for the comparison of BDP+ 5-ASA versus BDP. The differences in endoscopic and histologic improvement was statistically significant for both BDP+ 5-ASA versus BDP and BDP+ 5-ASA versus 5-ASA. No adverse events were reported. The authors concluded that combination therapy with BDP + 5-ASA was superior to monotherapy with BDP or 5-ASA for treatment of active distal UC.

Palmer 1981 compared 2 weeks of treatment with sulphasalazine 3 g enemas (n = 17) or placebo (n = 23) in 40 patients with UC in a double-blind randomised trial. Oral sulphasalazine was continued at stable doses. Clinical, endoscopic and histologic activity was graded according to Wright 1966 as absent, mild, moderate or severe. Improvement and deterioration was defined as a one-grade change in each score. The treatment groups were similar at baseline. Adverse events occurred equally in both groups, and there was one withdrawal on sulphasalazine for non-compliance. At the end of 2 weeks, 65% on sulphasalazine improved compared to 9%

on placebo. The authors concluded that sulphasalazine enemas were effective treatment for active UC and should be considered for those intolerant of oral sulphasalazine.

Pokrotnieks 2000 randomised 111 patients with mild to moderately active UC distal to the splenic flexure to receive placebo (n = 57) or 2 g 5-ASA foam enemas (n = 54) for 6 weeks in a double-blind, parallel-group study. Subjects were required to have a CAI > 3 for proctosigmoiditis and > 4 for left-sided UC, and an Endoscopic Index (EI) > 4. Subjects were excluded if they had used steroids continually for 1 month, immunosuppressants for 3 months, or oral 5-ASA or NSAIDs within 2 weeks of study entry. Clinical and endoscopic activity was graded according to Rachmilewitz 1989, and histologic activity according to Floren 1987. Clinical remission was defined as a CAI < 4 with a decrease of at least 2 points from baseline. Endoscopic remission was defined as an EI < 3, and histologic improvement as a 1-point reduction in the histologic score from baseline. The two groups were similar at baseline. Compliance was near 90% for each group and each group had only 1 drop out, but adverse events were more common on placebo. There were 6 serious adverse events, 5 of which occurred in placebo patients and reflected deterioration of UC requiring hospitalization. Analysis was performed on an intention to treat basis. Of patients on 5-ASA, 65% experienced clinical remission, 57% achieved endoscopic remission and 59% had histologic improvement of their disease. This was compared to 40%, 37% and 41% on placebo. CAI scores were reduced by 4.7 and 3.5 points in 5-ASA patients compared to placebo. Differences in rates of clinical and endoscopic remission were statistically significant in favour of 5-ASA. The authors concluded that 5-ASA foam enema was well tolerated and superior to placebo for inducing clinical and endoscopic remission of distal UC.

Powell-Tuck 1986 conducted a 28 day randomised, double blind trial comparing 1 g (n = 12) and 2 g 5-ASA enemas (n = 13) in 25 patients with active ulcerative proctosigmoiditis. Sulphasalazine was continued at stable dose but no other therapies were permitted. Clinical, endoscopic and histological activity was assessed according to Powell-Tuck 1982 using a scale from 0 to 2. Remission was defined as a clinical score of 0, and an endoscopic score of 0 (non-friable mucosa). The groups were similar at baseline. One patient in the 2 g/day group withdrew for worsening diarrhoea but no other adverse events were noted. At 28 days, according to intention to treat analysis, 58% of those in the 1 g 5-ASA group achieved remission compared to 31% of the 2 g 5-ASA group. This difference was not statistically significant. The authors concluded that 1 g 5-ASA enemas were no less effective than 2 g 5-ASA enemas.

Prantera 2005 compared the efficacy of oral multi-matrix (MMx) 5-ASA 1.2 g three times daily to 4 g 5-ASA enemas in 79 patients with mild to moderately active distal UC in a randomised double-blind double-dummy trial for 8 weeks. The primary endpoint was clinical remission (CAI < 4) at week 8 according to Rachmilewitz 1989, with endoscopic remission (Rachmilewitz 1989 EI < 2) and histologic remission (Floren 1987) as secondary endpoints. Patients were enrolled if they were at least 18 years of age and had a CAI > 6 with disease extending at least 15 cm from the anal verge but not past the splenic flexure. No steroids or immunosuppressive agents were permitted within 4 weeks of study entry. The treatment groups were similar at baseline. There were 20 patient withdrawals (8 on oral MMx and 12 on 5-ASA enema) but no severe adverse events. Clinical remission was achieved by 60% in the oral MMx group compared to 49% of the 5-ASA enema group, with no statistically significant difference. Endoscopic and histologic remission was achieved by 45% and 15% of the oral MMx group, compared to 36% and 8% of the rectal 5-ASA group. The authors concluded that oral MMx 5-ASA was comparable to 5-ASA enema for inducing remission of distal UC.

Safdi 1997 reported a 6 week randomised, double-blind double-dummy comparison of oral 5-ASA (800 mg tid) versus rectal 5-ASA enema (4 g) versus combination therapy in patients with active UC extending between 5 and 50 cm from the anal verge. Eligible patients had a DAI between 4 and 10 at study entry (Sutherland 1987a). Those with previous bowel resections or who had used other topical or oral UC therapies within 1 week were excluded. Outcomes included clinical and endoscopic parameters of the DAI, a clinical global improvement (CGI) scale and a patient global improvement (PGI) scale. The treatment groups were similar at baseline. Completion rates were 82%, 94and and 95% for oral (n = 22), enema (n = 18) and combination therapy (n = 20) groups. Three patients in the oral 5-ASA group withdrew from the study, 1 patient in the enema group withdrew due to relapse and 1 patient in the combination therapy group was removed from the study due to a protocol violation. Adverse events were reported by 41%, 17% and 45% in the oral 5-ASA, rectal 5-ASA and combination groups, respectively. Most were minor (e.g. headache in 10%). Five were severe (2 oral, 1 rectal, 2 combination) but resolved by study completion. At 6 weeks, the mean decrease in DAI was 5.2 on combination therapy, 4.4 on enema therapy and 3.9 on oral therapy (no significant difference). Clinical improvement (cessation of rectal bleeding) was achieved by 89%, 69% and 46%, with a statistically significant difference between combination and oral therapy. Combination therapy was also superior to oral therapy for improving CGI scores at all visits and PGI scores at 3 weeks. The authors concluded that combination therapy with oral and rectal 5-ASA was more effective for treating mild to moderately active distal UC than either oral or rectal therapy alone.

Senagore 1992 randomised 45 patients with UC distal to the splenic flexure to treatment with hydrocortisone enemas (100 mg od; n = 12), 5-ASA enemas (4 g od; n = 19) or short-chain fatty acid (SCFA) enemas (bid; n = 14) for 6 weeks. No other therapies for UC were permitted. Outcomes included endoscopic and histologic activity. Endoscopic activity was scored as: normal (score

0); mucosal erythema, loss of vascularity and slight edema (score 1); contact friability (score 2); superficial with small amounts of mocopulent discharge (score 3); and large amounts of mucopurulent discharge with severe ulceration (score 4). Histology was scored as: normal (score 0); trace inflammation (score 1); mild inflammation (score 2); moderate inflammation (score 3) or severe inflammation (score 4). Treatment groups were similar at baseline. A large number of patients in all treatments groups experienced resolution of clinical symptoms and improved endoscopic and histologic scores. "Recovery" occurred in 83%, 89% and 86% of patients in the hydrocortisone, 5-ASA and SCFA groups respectively. A cost minimization analysis showed a significant saving with SCFA therapy. The authors concluded that SCFA enemas are an effective and cost-saving therapy for distal UC, and that a larger multicenter trial is necessary to confirm these results.

Sutherland 1987a randomised 153 patients with UC extending 5 to 50 cm from the anal verge to receive either 4 g 5-ASA (n = 76) enemas or placebo enemas (n = 77) for 6 weeks in a double-blind trial. The minimum DAI at entry was 3. Oral sulphasalazine and steroids (< 30 mg) were permitted if their dose had remained stable for 4 weeks but patient using rectal steroids were excluded. Clinical and endoscopic activity was assessed based on a predefined 12-point DAI with up to 3 points for each of: stool frequency; rectal bleeding; mucosal appearance; and physician rating of disease activity. Clinical, endoscopic and histologic activity was assessed at study entry, 3 weeks and 6 weeks. Subjects who deteriorated at 3 weeks were withdrawn and enrolled in a separate protocol. Treatment groups were similar at baseline. One subject dropped out early for non-compliance and was replaced. A further 20 subjects (6 in 5-ASA, 14 in placebo) dropped out due to poor response. Few adverse events were reported. Improvement in disease activity was achieved by 63% on 5-ASA compared to 29% on placebo. The DAI score was reduced by 55% in 5-ASA patients compared to 22% in placebo patients. Both differences were statistically significant. Treatment response was not influenced by co-treatment with oral sulphasalazine. The authors concluded that topical 5-ASA was an effective treatment for active distal UC.

Vecchi 2001 conducted a randomised multi-centre double-dummy trial comparing oral 5-ASA (4 g/day) with combined oral 5-ASA (2 g/day) and 5-ASA enemas (2 g/day) in 130 patients with mild to moderate UC, as defined by CAI between 4 and 12 (Rachmilewitz 1989). A total of 130 patients were enrolled, 67 were randomised to receive oral Mesalazine and 63 were allocated to receive a combined oral and topical therapy. The primary endpoint was clinical remission, defined as CAI < 4, and clinical improvement, defined as a decrease in CAI > 50%. A secondary endpoint was endoscopic remission, defined as an EI < 4 (Rachmilewitz 1989). No significant difference was observed between oral 5-ASA and combined oral/rectal 5-ASA for clinical remission (82% versus 87%) or endoscopic remission (58% versus 71%). The authors concluded that oral 5-ASA was as effective as combining oral with rectal 5-ASA for inducing remission in patients with mild to moderate UC.

Williams 1987 reported a randomised, double-blind 6 week trial comparing 5-ASA suppositories (500 mg tid, n = 14) to placebo (n = 13) in 27 patients with active UC extending less than 15 cm form the anal verge. Eligible patients had DAI greater than 3 on a 12 point scale at entry. Patients were excluded if they had taken 4-ASA or 5-ASA within 48 hours or rectal steroids within 2 weeks of study entry. Oral sulphasalazine and prednisone were permitted at stable dose. A subser of patients also received technetium-labelled 5-ASA to assess drug distribution. Response to treatment was assessed by change in the DAI and by endoscopy at 3 and 6 weeks on a predefined scale. Remission was defined as a DAI score of 0 . The treatment groups were similar at baseline. There were 2 withdrawals, both in the placebo group, 1 dropped out and the other had Salmonella. After 6 weeks, the mean DAI in the treatment group was 0.4 +/- 0.9, compared to 5.4 +/- 3.4 in the placebo group. Remission was achieved by 79% on 5-ASA compared to 8% on placebo after 6 weeks. No adverse events were reported. Technetium labelled 5-ASA remained in the rectum and sigmoid colon in all patients studied. The authors concluded that 5-ASA suppositories were safe, well tolerated and effective for distal UC. They also suggested that 5-ASA suppositories can be used as first line therapy for UC, or for UC resistant to oral sulphasalazine or prednisone.

Risk of bias in included studies

Study methodology was reviewed critically by two authors using the Jadad 1996 Scale and the 30-point scale developed and used previously by the authors. Overall methodologic quality was fair, with 28 of the 38 included studies scoring at least 3 points on the Jadad 1996 scale. Specifically, two studies scored 5 points (Campieri 1990a; Friedman 1986; a);9 studies scored 4 points (Campieri 1991b; Kam 1996; Moller 1978; Mulder 1996; Pokrotnieks 2000; Bianchi-Porro 1995; Prantera 2005; Safdi 1997; Sutherland 1987a) and 17 studies scored 3 points (Campieri 1984; Campieri 1990b; Campieri 1991b; Campieri 1993; Cortot 2008 Anonymous 1987; Eliakim 2007; Gionchetti 1997; Gionchetti 1998; Gionchetti 1999; Gionchetti 2005; Hanauer 1998; Lee 1996; Mulder 1988; Palmer 1981; Powell-Tuck 1986,Williams 1987). Of the remaining 10 studies, 9 studies scored 2 points (Andus 2008; Ardizzone 1999; Basilico 1987; Biancone 2007; Campieri 1988; Farup 1995; Lemann 1995; Miner 2006; Senagore 1992) and only one scored one point (Malchow 2002). Using the 30 point scale, the average score for included trials was 21.7 and ranged from 14 to 29 (See Additional Table 3). The Cochrane risk of bias tool indicates that the risk of bias was low for 13 of the 38 included studies (See Figure 1). The risk of bias in the other studies was high for blinding in 14 studies (due to single blind design) or unclear for some quality items in 11 studies (due to inadequate descriptions of methods used for sequence generation and allocation concealment or possible in-

complete outcome data or selective reporting).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

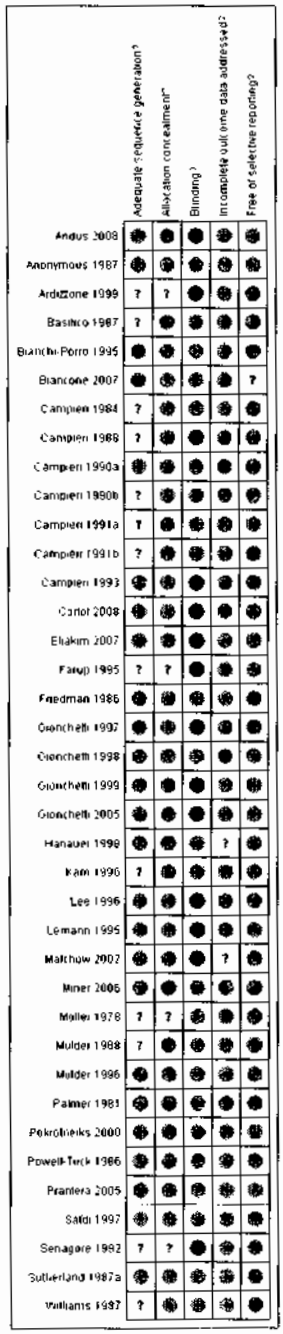


Table 3. Trial Quality Assessment

Author (Year of Pub)	Jadad Score	Quality Asess. score
Andus 2008	2	25
Ardizzone 1999	2	21
Basilisco 1987	2	16.5
Biancone L 2007	2	27
Campieri 1984	3	20
Campieri 1988	2	14
Campieri 1990	5	26
Campieri M 1990	3	19.5
Campieri 1991	3	19
Campieri M 1991	4	21.5
Campieri 1993	3	22.5
Corroc 2008	3	24
Danish 5-ASA Grp1987	3	20.5
Eliakim 2007	3	29
Farup 1995	2	23
Friedman 1986	5	23.5
Gionchetti 1997	3	24
Gionchetti 1998	3	23
Gionchetti 1999	3	24.5
Gionchetti 2005	3	25
Hanauer 1998	3	20
Kam 1996	4	23
Lee 1996	3	24.5

Table 3. Trial Quality Assessment *(Continued)*

Lemann 1995	2	21
Malchow 2002	1	19.5
Miner 2006	2	23.5
Moller 1978	4	18.5
Mulder 1988	3	20
Mulder 1996	4	22.5
Palmer 1981	3	17
Pokrotnieks 2000	4	23.5
Powell Tuck 1986	3	14.5
Porro-Bianchi 1995	4	19.5
Prantera 2005	4	27.5
Safdi 1997	4	18
Senagore 1992	2	19
Sutherland 1987	4	22.5
Williams 1987	3	20.5

Effects of interventions

Rectal 5-ASA was superior to placebo for inducing symptomatic, endoscopic and histological improvement and remission, with a POR for symptomatic improvement of 8.87 (8 trials, 95% CI: 5.30 to 14.83; P < 0.00001; See Figure 2), endoscopic improvement 11.18 (5 trials, 95% CI 5.99 to 20.88; P < 0.00001; See Figure 3), histologic improvement 7.69 (6 trials, 95% CI 3.26 to 18.12; P < 0.00001; See Figure 4), symptomatic remission 8.30 (8 trials, 95% CI 4.28 to 16.12; P < 0.00001; See Figure 5), endoscopic remission 5.31 (7 trials, 95% CI 3.15 to 8.92; P < 0.00001; See Figure 6), and histologic remission 6.28 (5 trials, 95% CI 2.74 to 14.40; P < 0.0001; See Figure 7).

Figure 2. Forest plot of comparison: 1 Rectal 5-ASA vs Placebo, outcome: 1.1 Symptomatic Improvement.

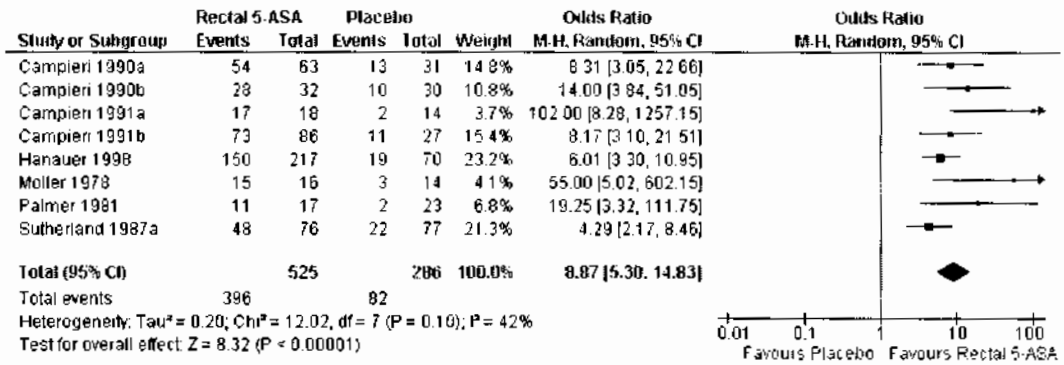


Figure 3. Forest plot of comparison: 1 Rectal 5-ASA vs Placebo, outcome: 1.2 Endoscopic Improvement.

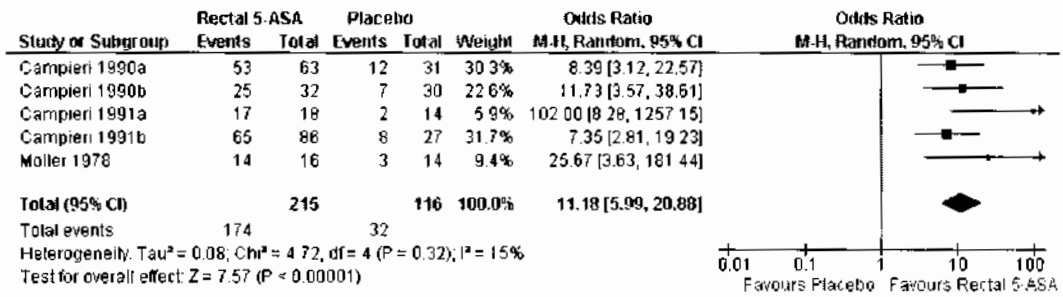


Figure 4. Forest plot of comparison: 1 Rectal 5-ASA vs Placebo, outcome: 1.3 Histologic Improvement.

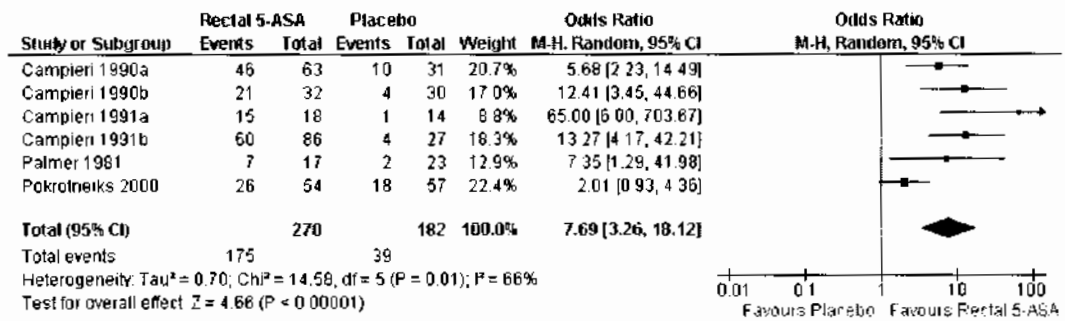


Figure 5. Forest plot of comparison: 1 Rectal 5-ASA vs Placebo, outcome: 1.4 Symptomatic Remission.

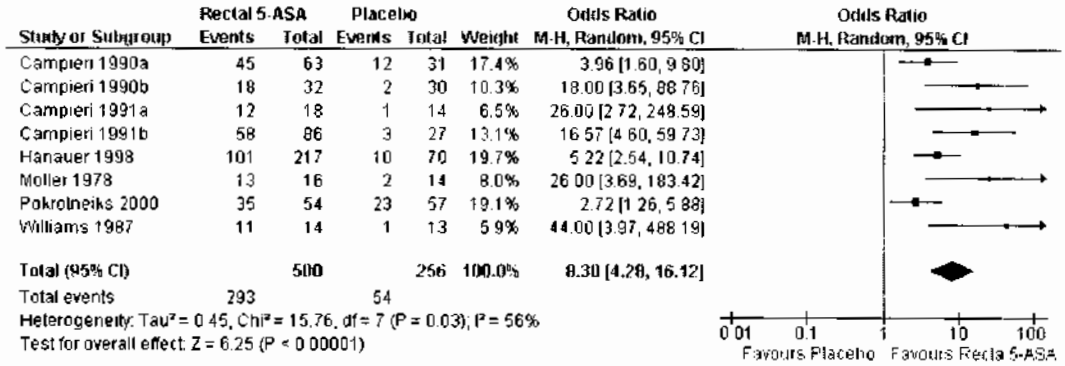


Figure 6. Forest plot of comparison: 1 Rectal 5-ASA vs Placebo, outcome: 1.5 Endoscopic Remission.

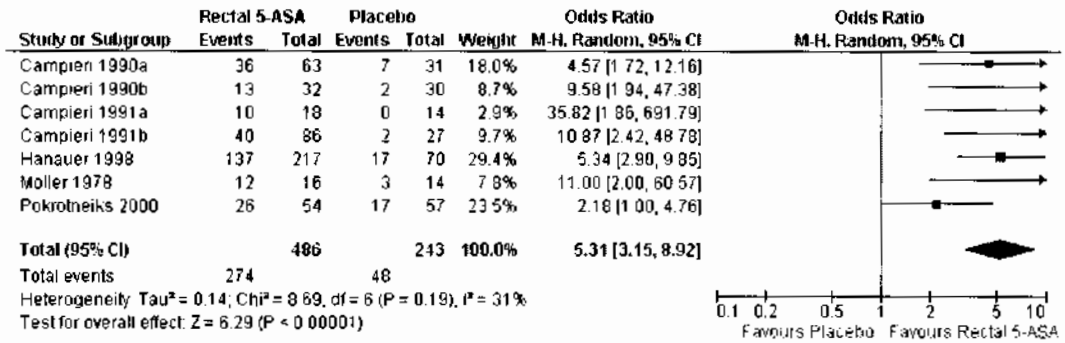
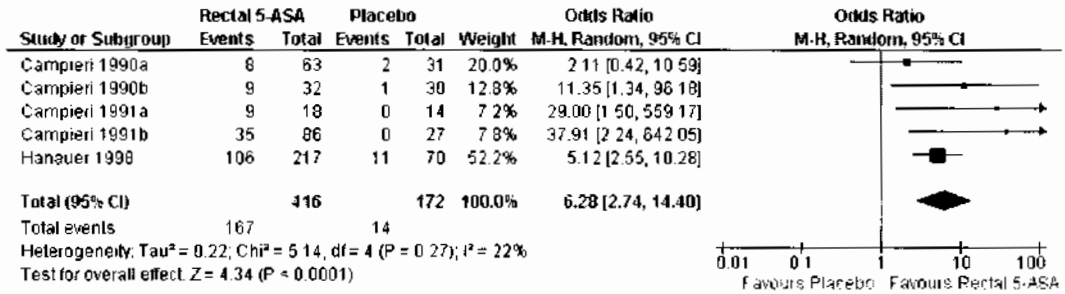


Figure 7. Forest plot of comparison: 1 Rectal 5-ASA vs Placebo, outcome: 1.6 Histologic Remission.



Rectal 5-ASA was superior to rectal corticosteroids for inducing symptomatic improvement and remission with PORs of 1.56 (6 trials, 95% CI 1.15 to 2.11; P = 0.004; See Figure 8), and 1.65 (6 trials, 95% CI 1.11 to 2.45; P = 0.01; See Figure 9) respectively with favourable non-significant trends for other endpoints.

Figure 8. Forest plot of comparison: 2 Rectal 5-ASA vs Rectal Corticosteroid, outcome: 2.1 Symptomatic Improvement.

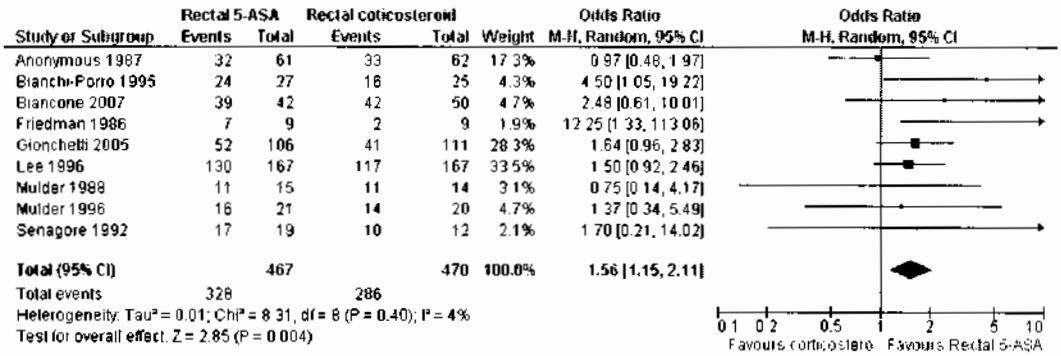
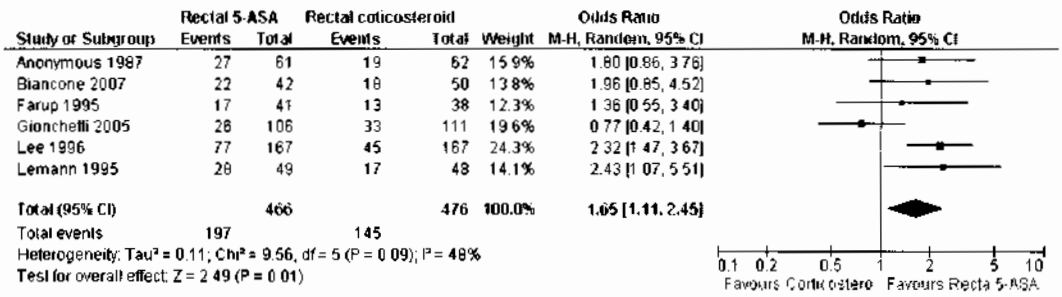
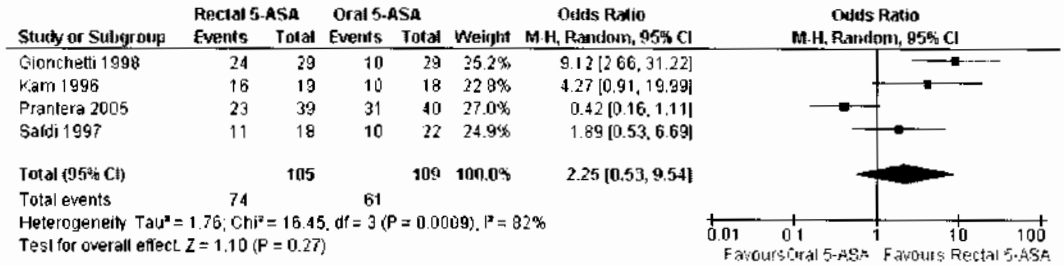


Figure 9. Forest plot of comparison: 2 Rectal 5-ASA vs Rectal Corticosteroid, outcome: 2.4 Symptomatic Remission.



Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement, with a POR of 2.25 (95% CI 0.53 to 9.54; P = 0.27; See Figure 10). Neither total daily dose nor 5-ASA form affected treatment response.

Figure 10. Forest plot of comparison: 3 Rectal 5-ASA Vs Oral 5-ASA, outcome: 3.1 Symptomatic Improvement.



No trial reported health-related quality of life as an outcome measure. Overall safety and tolerability for rectal 5-ASA was excellent with no apparent increase in adverse events relative to comparator therapies (See Additional Table 4). Few trials assessed patient preference for alternate rectal formulations. Among those that assessed preference, results were quite heterogeneous. Suppositories were generally preferred over foam and liquid enema formulations, while foam was generally preferred over liquid enemas (See Additional Table 4).

Table 4. Summary of Adverse Events and Patient Preference

Author Year	Reported Adverse Events:	Preference
Andus 2008	1g 5-ASA suppository OD (n=201): overall adverse events in 38 (19%); headache (n=5); nasopharyngytis (n= 5); ulcerative colitis (n= 3); constipation (n=2); increased lipase (n= 1); decrease platelet count (n=1); abdominal pain (n=1); nausea (n=1) 0.5g 5-ASA suppository TID (n=207): overall adverse events in 43 (21.2%); headache (n=11); nasopharyngytis (n=6); ulcerative colitis (n=5); constipation (n=1); increased lipase (n=1); decreased platelet count (n=1); pruritus (n=2); anal discomfort (n=1); back pain (n=1); defecation urgency (n=1); flatulence (n=1)	OD suppository (92.5%)
Ardizzone 1999	2g 5-ASA foam BID (n=97): overall adverse events in 6 (6.2%); perianal burning and meteorism (n=1); perianal burning and worsening of disease (n=1) 2g 5-ASA enema BID (n=98): overall adverse events in 2 (2%); perianal burning (n=1)	Enema (56%)
Basilisco 1987	1.5g 5-ASA enema BID (n=13): adverse events not reported 1.5g sulphasalazine enema BID (n=14): adverse events not reported	

Table 4. Summary of Adverse Events and Patient Preference (*Continued*)

Biancone L 2007	3mg beclomethasone dipropionate (n=50): overall adverse events in 17 (33%); drug discontinuation for bloody stools or diarrhoea (n=3 in foam group); abnormal cortisol level (n=2 in foam group and n=4 in enema group) 3g 5-ASA (n=22): overall adverse events in 10 (25%); drug discontinuation for abdominal pain or bowel tenderness (n=3 in foam group)	
Campieri 1984	2g 4ASA enema OD (n=31): adverse events not reported 2g 5-ASA enema OD (n=32): adverse events not reported	
Campieri 1988	2g 5-ASA enema OD (n=20): adverse events not reported 1g 5-ASA suppository BID (n=19): adverse events not reported	Suppository
Campieri 1990	1g 5-ASA suppository OD (n=32): facial erythema (n=1); mild fever (n=1) 1.5g 5-ASA suppository OD (n=31); worsening of symptoms (n=1) Placebo (n=31); overall adverse events in 6 (19.4%); worsening symptoms (n=5); headache (n=1)	
Campieri M 1990	0.5g 5-ASA suppository TID (n=32): adverse events not reported Placebo (n=30): adverse events not reported	
Campieri 1991	2g 5-ASA enema OD (n=18): adverse events not reported 10g sucralfate enema OD (n=18): overall adverse events in 3 (16.7%); constipation (n=1); worsening of symptoms (n=2) Placebo (n=14): overall adverse events in 4 (28.6%); worsening of symptoms in (n=4)	
Campieri M 1991	1g 5-ASA enema (n=27): adverse events not reported 2g 5-ASA enema (n=30): adverse events not reported 4g 5-ASA enema (n=29): adverse events not reported Placebo (n=27): adverse events not reported	

Table 4. Summary of Adverse Events and Patient Preference *(Continued)*

Campieri 1993	5-ASA foam (n=123); overall adverse events in 5 (4.1%); worsening of tenesmus and flatulence (n=1); occasional chills after administration (n=1); abdominal gas (n=3) 5-ASA enema (n=110); overall adverse events in 2 (1.8%); worsening tenesmus and flatulence (n=1); abdominal gas (n=1)	Foam
Cortot 2008	1g 5-ASA foam enema (n=191); overall adverse events in 52 (27.2%); gastrointestinal disorders (n=32); drug discontinuation in 4 (7.3%) 1g 5-ASA liquid enema (n=184); overall adverse events in 59 (32.4%); gastrointestinal disorders (n=37); drug discontinuation in 4 (6.6%)	
Danish 5-ASA Grp1987	1g 5-ASA enema OD (n=62): overall adverse events in 14 (22.9%); nausea or vomiting (n=2); abdominal distension (n=3); colic (n=3); fatigue (n=1); depression (n=1); difficulties in retaining enema (n=2); joint stiffness (n=1); minor complaints (n=1); withdrawal due to side effects (n=3) 25mg prednisolone enema OD (n=61); overall adverse events in 6 (9.7%); nausea or vomiting (n=2); abdominal distension (n=1); fatigue (n=1); minor complaints (n=2)	
Eliakim 2007	1g/30ml 5-ASA foam OD (n=163): overall adverse events in 63 (39%); gastrointestinal disorders (n=25); nervous system disorders (n=15); infections and infestations (n=18); general disorders and administration site conditions (n=7); musculoskeletal and connective tissue disorders (n=4); investigations (n=5); skin and subcutaneous tissue disorders (n=4); respiratory, thoracic and mediastinal disorders (n=2); reproductive system and breast disorders (n=1); hepatobiliary disorders (n=1); psychiatric disorders (n=1); renal and urinary disorders (n=1) 1g/60ml 5-ASA foam OD (n=167): overall adverse events in 62 (37%): gastrointestinal disorders (n=22); nervous system disorders (n=18); infections and infestations (n=10); general disorders and administration site conditions (n=8); musculoskeletal and connective tissue disorders (n=5); investigations (n=5); skin and subcutaneous tissue disorders (n=2); respiratory, thoracic and mediastinal disorders (n=4); reproductive system and breast disorders (n=4); hepatobiliary disorders (n=2); psychiatric disorders (n=2); injury poisoning and proce-	

Table 4. Summary of Adverse Events and Patient Preference *(Continued)*

	dural complications (n=2); cardiac disorders (n=1); surgical and medical procedures (n=1); vascular disorders (n=1)	
Farup 1995	0.5g 5-ASA suppository BID (n=41): overall adverse events in 6 (14.6%); rash and fever (n=1); exanthema (n=1); perianal burning (n=4) 178mg hydrocortisone foam BID (n=38): overall adverse events in 6 (15.8%); rash (n=1); perianal burning (n=1)	Suppository
Friedman 1986	4g 5-ASA enema OD (n=9): adverse events not reported 100mg hydrocortisone enema OD (n=9): adverse events not reported	
Gionchetti 1997	1g 5-ASA suppository OD (n=25): adverse events not reported 0.5g 5-ASA suppository BID (n=25): overall adverse events in 5 (20%); perianal irritation (n=5)	
Gionchetti 1998	0.8g 5-ASA tablets TID (n=29): overall adverse events in 6 (20.7%); headache (n=1); abdominal pain (n=2); nausea (n=3) 0.4g 5-ASA suppository TID (n=29): adverse events not reported	
Gionchetti 1999	2g 5-ASA enema OD (n=50): self limiting renal colic, insomnia and skin eruption (n=2); difficulty in retention (n=3); abdominal bloating (n=13); discomfort during administration (n=13) 2g 5-ASA foam OD (n=53): self limiting renal colic, insomnia and skin eruption (n=1); difficulty in retention (n=13); abdominal bloating (n=26); discomfort during administration (n=25)	
Gionchetti 2005	1g 5-ASA enema OD (n=106): overall adverse events in 13 (12.6%) 3mg BDP enema OD (n=111): overall adverse events in 12 (10.8%); pneumonia (n=1)	
Hanauer 1998	5-ASA enema OD (n=217): overall adverse events in 31 (14%); abdominal pain (n=7), diarrhoea (n=5) Placebo (n=70): overall adverse events in 7 (10%); abdominal pain (n=2); diarrhea (n=3)	
Kam 1996	4g 5-ASA enema OD (n=19): overall adverse events in 8 (42.1%): headache (n=3): abdominal pain (n=2); nausea (n=2); dizziness (n=1); flatulence	

Table 4. Summary of Adverse Events and Patient Preference *(Continued)*

	(n=1); back pain (n=1); constipation (n=1); rectal disorder (n=1) 1g sulphasalazine PO QID (n=19): overall adverse events in 15 (83%); headache (n=6); nausea (n=5); abdominal pain (n=1); dizziness (n=1); flatulence (n=1); dyspepsia (n=1); dysuria (n=1); general edema (n=1); menstrual disorder (n=1); pruritus (n=1); rash (n=1); sweat (n=1); urinary abnormality (n=1); peripheral vascular disease (n=1); vasodilation (n=1); vertigo (n=1)	
Lee 1996	2g 5-ASA foam OD (n=167): overall adverse events in 57 (34%): headache (n=7); abdominal pain (n=12); nausea and vomiting (n=5); bloating (n=10); worsening disease (n=5) 20mg prednisolone foam OD (n=167): overall adverse events in 43 (26%): headache (n=4); abdominal pain (n=7); nausea and vomiting (n=7); bloating (n=2); worsening disease (n=7)	
Lemann 1995	1g 5-ASA enema OD (n=49): overall adverse events in 1 (0.2%): 2mg budesonide enema OD (n=48): overall adverse events in 4 (8.3%): acne (n=2); disease deterioration (n=1)	
Malchow 2002	2g 5-ASA foam OD (n=133): flatulence, nausea, abdominal pain and diarrhoea (n=3) 4g 5-ASA enema OD (n=167): flatulence, nausea, abdominal pain and diarrhoea (n=1)	East Europe sites preferred foam while German sites preferred enema. Foam was preferred overall.
Miner 2006	4g 5-ASA enema OD (n=54): overall adverse events in 40 (63.5%); gastrointestinal disorders (n=19); infections and infestations (n=14); infections and infestation (n=10); arthralgia (n=1); sinus congestion (n=2); skin disorders (n=3) 120mg alicaforsen enema OD (n=55): overall adverse events in 40 (61.5%); gastrointestinal disorders (n=13); infections and infestations (n=9); headache (n=4); arthralgia (n=3); sinus congestion (n=3) 240mg alicaforsen enema OD (n=50): overall adverse events in 35 (57.4%); gastrointestinal disorders (n=16); infections and infestations (n=14); arthralgia (n=2); skin disorders (n=1); headache (n=1)	

Table 4. Summary of Adverse Events and Patient Preference *(Continued)*

Moller 1978	3g sulphasalazine enema OD (n=16): adverse events not reported Placebo (n=14): adverse events not reported
Mulder 1988	3g 5-ASA enema OD (n=15): marked deterioration in 2 (1.3%) 30mg prednisolone phosphate sodium enema OD (n=14): adverse events not reported
Mulder 1996	2g 5-ASA enema OD (n=21): marked deterioration (n=2) 3mg BDP enema OD (n=20): marked deterioration (n=3) 3mg BDP OD + 2g 5-ASA enema OD (n=19): adverse events not reported
Palmer 1981	3g sulphasalazine enema OD (n=17): overall adverse events in 8 (47.1%); lower abdominal discomfort (n=8) Placebo (n=23): overall adverse events in 7 (30.4%): lower abdominal pain (n=6); headaches (n=1)
Pokrotnieks 2000	2g 5-ASA foam OD (n=54): overall adverse events in 6 (11%); deterioration of ulcerative colitis (n=1); hallucination (n=1) Placebo (n=57): overall adverse events in 11 (19%); deterioration of ulcerative colitis (n=4); decompensation of diabetes mellitus (n=1); diarrhoea and abdominal cramps (n=1)
Porro-Bianchi 1995	1g 5-ASA enema OD (n=27): (microscopic hematuria (n=2); proteinuria (n=2); increased alkaline phosphate (n=1) 100mg hydrocortisone enema OD (n=25): worsening of clinical activity (n=1); microscopic hematuria (n=1); proteinuria (n=1); increased serum transaminases (n=3)
Powell Tuck 1986	1g 5-ASA enema OD (n=12): adverse events not reported 2g 5-ASA enema OD (n=13): worsening diarrhoea (n=1)
Prantera 2005	1.2g 5-ASA PO TID (n=40): overall adverse events in 6 (15.0%); increased serum lipase (n=1); increased serum creatinine (n=1) 4g 5-ASA enema OD (n=39): overall adverse events in 11 (28%): abdominal and anal pain and headache

Table 4. Summary of Adverse Events and Patient Preference *(Continued)*

	(n=1); increased blood urea nitrogen (n=1)
Safdi 1997	4g 5-ASA enema OD (n=18): overall adverse events in 4 (17%); headache (n=2) 0.4g 5-ASA PO TID (n=22): overall adverse events in 10 (41%); headache, chest pain and heartburn (n=1); increased platelet count and decreased erythrocyte count (n=2) 4g 5-ASA enema OD + 0.4g 5-ASA PO TID (n=20): overall adverse events in 9 (45%); headache and urinary tract infection (n=2)
Senagore 1992	4g 5-ASA enema OD (n=19): allergic rash (n=1) 100mg hydrocortisone enema OD (n=12): adverse events not reported 120mg short chain fatty acid enema BID (n=14): disease progression (n=1)
Sutherland 1987	4g 5-ASA enema OD (n=76): headache (n=7); hair loss (n=1) Placebo (n=77): headache (n=4); rash (n=2); nausea and vomiting (n=2); arthralgia (n=1); periorbital edema (n=1); diarrhoea (n=1)
Williams 1987	0.5g 5-ASA suppository TID (n=14): adverse events not reported Placebo (n=13): adverse events not reported

DISCUSSION

This systematic review confirms the efficacy of rectal 5-ASA for inducing remission of mild to moderate ulcerative colitis and updates previously published meta analyses (Marshall 1995; Marshall 1997; Marshall 2000) with an increased sample size and Cochrane Collaboration formatting. Among 10 placebo-controlled trials, rectal 5-ASA was superior to placebo for symptomatic, endoscopic and histological improvement or remission. Rectal 5-ASA was also superior to rectal corticosteroids for inducing symptomatic remission, with favourable non significant trends for endoscopic and histologic outcomes.

No 5-ASA dose response relationship was observed, with no significant differences in outcomes among 5-ASA dose strata. This confirms observations made by individual trials, and supports the poor dose response seen in clinical trials of oral 5-ASA for induction of remission. However, the absence of a dose response must be reconciled with observations that the combination of oral and rectal 5-ASA appears to be more effective than either given as monotherapy, even in subjects with extensive UC (Marteau 2005; Vecchi 2001; Safdi 1997). One possible explanation is that, rather than increasing local drug concentrations, combination therapy promotes more homogeneous drug distribution across affected segments in patients with active disease. This would suggest that geographic coverage is a more important determinant of response than local drug concentration. More studies comparing rectal monotherapy to combination oral and rectal 5-ASA are needed (Safdi 1997).

Within the definition of distal ulcerative colitis are patients with limited proctitis and those with disease extending as far as the splenic flexure. We planned a priori to conduct subgroup anal-

yses of efficacy by proximal disease margin but were unable to extract sufficient subject-level information. Accordingly, it is unclear whether patients with proctitis and proctosigmoiditis respond equally to rectal 5-ASA therapy. Further studies comparing oral, rectal and combination therapy with adequate power to assess such subgroups should be considered.

No consistent difference in efficacy was noted among the various rectal 5-ASA formulations (liquid enema, foam enema or suppository) but comparative data are limited. This is consistent with scintigraphic studies showing that suppositories distribute drug to the rectum, foam enemas to the sigmoid colon and liquid enemas to the splenic flexure. However, it should be noted that most trials evaluating suppositories restricted enrolment to patients with only proctitis, while studies of foam and liquid enemas more often included patients with more extensive left-sided disease. Farup 1995 found suppositories to be superior to foam enemas in patients with proctitis and also to be preferred by patients. For patients with disease extending more proximally, foam and liquid enemas appear equally effective but patients generally prefer foam because of easier administration and more comfortable retention. While 5-ASA foam is arguably the preferred first-line therapy for patients with mild to moderately active proctosigmoiditis, it is not available in all jurisdictions.

A considerable challenge to producing summary evaluations of efficacy data in active ulcerative colitis is the heterogeneity of outcome definitions across clinical trials. For quantitative pooling of results, the original authors' definitions of outcomes were accepted, if they were established a priori. With sufficient individual subject data, it would have been preferable to transpose each trial's outcomes to common definitions of response and remission. This would likely have reduced inter-study heterogeneity and improved the precision of the point estimates of response and remission. The standardization of outcome measurement in clinical trials for ulcerative colitis is required (Cooney 2007; D'Haens 2007), to facilitate quantitative pooling and comparisons of efficacy across therapies.

AUTHORS' CONCLUSIONS

Implications for practice

Rectal 5-ASA should be considered the first-line therapy for patients with mild to moderately active distal ulcerative colitis who are willing to use rectal therapies and who do not have clinically important contraindications to 5-ASA therapy. The optimal total daily dose and dose frequency remains to be defined.

Implications for research

Future research should consider further evaluation of the relative efficacies of rectal 5-ASA delivery systems, and better comparison of efficacy across patient subgroups defined by proximal disease margin and disease activity. There is a strong need for consensus standardization of outcome measurements for clinical trials in ulcerative colitis.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Andus 2008

Methods	Multicentre single-blind randomised controlled trial
Participants	Patients with active ulcerative proctitis, confirmed by endoscopy and histology
Interventions	5-ASA suppositories 1g OD vs 0.5g TiD for 6 weeks
Outcomes	Clinical, histologic and endoscopic remission and Endoscopic/histologic improvement
Notes	Abstract

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind (investigator)
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Anonymous 1987

Methods	Randomized multicenter double-blind randomised controlled trial
Participants	Patients with mild to moderately active ulcerative proctosigmoiditis
Interventions	5-ASA enema 1g OD vs. prednisolone enema 25 mg OD for 2 weeks
Outcomes	Clinical and endoscopic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description

Anonymous 1987 *(Continued)*

Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	8 patients in the 5-ASA group did not complete the study compared to 1 in the prednisolone group
Free of selective reporting?	Yes	The published report includes all expected outcomes

Ardizzone 1999

Methods	Multicentre randomised controlled trial
Participants	Patients with active left-sided ulcerative colitis with Clinical Activity Index (CAI) > or = 4 and Endoscopic Index (EI) > or = 6
Interventions	5-ASA enema 2g BID vs. 5-ASA foam 2g BID for 3 weeks
Outcomes	Clinical and endoscopic remission
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	No	Open study
Incomplete outcome data addressed? All outcomes	Yes	9 patients withdrew from enema group compared to 16 from the foam group
Free of selective reporting?	Yes	The published report includes all expected outcomes

Basilico 1987

Methods	Single center double-blind randomised controlled trial
Participants	Patients age 20 to 71 years with ulcerative proctosigmoiditis confirmed clinically, endoscopically and histologically
Interventions	5-ASA enema 1.5g BID vs. SAS enema 1.5g BID for 28 days
Outcomes	Clinical and endoscopic remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Two patients in the 5-ASA group and one in the SAS group dropped out
Free of selective reporting?	Yes	The published report includes all expected outcomes

Bianchi-Porro 1995

Methods	Single centre double-blind randomised controlled trial
Participants	Patients age 16 to 67 with endoscopically confirmed mild to moderately active ulcerative proctitis
Interventions	5-ASA enema 1g OD vs. hydrocortisone enema 100mg OD for 3 weeks
Outcomes	Clinical, endoscopic, and histologic improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate

Bianchi-Porro 1995 *(Continued)*

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	One patient withdrew from the hydrocortisone group due to worsening disease
Free of selective reporting?	Yes	The published report includes all expected outcomes

Biancone 2007

Methods	Multicenter double-blind, randomised controlled trial
Participants	Patients age 18 years or older with endoscopically confirmed mild to moderately active ulcerative proctosigmoiditis
Interventions	5-ASA enema 2g OD enema vs. 5-ASA foam 2g OD vs. BDP enema 3mg OD vs. BDP foam 3mg OD for 8 weeks
Outcomes	Clinical and endoscopic remission and improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Seven patients were excluded due to protocol violations before week 4 assessment (1 in BDP group and 6 in 5-ASA)
Free of selective reporting?	Unclear	Additional outcomes that were not prespecified appear to be reported

Campieri 1984

Methods	Single centre double-blind randomised controlled trial
Participants	Patients age 22 to 60 years with endoscopically confirmed mild to moderately active left-sided ulcerative colitis

Campieri 1984 *(Continued)*

Interventions	5-ASA enema 2g OD vs. 4ASA enema 2g OD for 15 days
Outcomes	Clinical, endoscopic and histologic improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	No drop outs were reported
Free of selective reporting?	Yes	The published report includes all expected outcomes

Campieri 1988

Methods	Single centre randomised controlled trial
Participants	Patients with mild to moderately active ulcerative proctosigmoiditis
Interventions	5-ASA enema 2g OD vs. 5-ASA suppository 1g BID for 1 month
Outcomes	Clinical, endoscopic, and histologic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind

Campieri 1988 *(Continued)*

Incomplete outcome data addressed? All outcomes	Yes	No drop outs were reported
Free of selective reporting?	Yes	The published report includes all expected outcomes

Campieri 1990a

Methods	Multicentre double-blind randomised placebo-controlled trial
Participants	Patients age 18 to 75 years with endoscopically confirmed mild to moderately active proctosigmoiditis
Interventions	5-ASA suppositories 1.5g OD vs. 1g OD vs. placebo for 4 weeks
Outcomes	Clinical, endoscopic, and histologic improvement and remission
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Nine patients in the placebo group dropped out mostly due to worsening symptoms compared to 2 5-ASA patients
Free of selective reporting?	Yes	The published report includes all expected outcomes

Campieri 1990b

Methods	Single centre double-blind randomised, placebo-controlled trial
Participants	Patients with endoscopically confirmed mild to moderately active ulcerative colitis
Interventions	5-ASA suppositories 0.5g TID vs. placebo for 1 month
Outcomes	Clinical, endoscopic, and histologic improvement and remission

Campieri 1990b *(Continued)*

Notes		

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	No drop outs were reported
Free of selective reporting?	Yes	The published report includes all expected outcomes

Campieri 1991a

Methods	Randomized double-blind placebo-controlled trial
Participants	Patients age 18 years or older with endoscopically confirmed mild to moderately active ulcerative colitis
Interventions	5-ASA enema 2g OD vs. sulcrafate enema 10g OD vs. placebo for 4 weeks
Outcomes	Clinical, endoscopic, and histologic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	There were no drop outs

Campieri 1991a *(Continued)*

Free of selective reporting?	Yes	The published report includes all expected outcomes

Campieri 1991b

Methods	Randomized, double-blind placebo-controlled trial
Participants	Patients age 18 years or older with endoscopically confirmed mild to moderately active ulcerative colitis
Interventions	5-ASA enemas 1g OD vs. 2g OD vs. 4g OD vs. placebo for 4 weeks
Outcomes	Clinical, endoscopic, and histologic improvement and remission
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	There were no drop outs
Free of selective reporting?	Yes	The published report includes all expected outcomes

Campieri 1993

Methods	Multicenter single-blind randomised controlled trial
Participants	Patients age 18 to 75 years with endoscopically confirmed mild to moderately active ulcerative colitis
Interventions	5-ASA foam 2g OD vs. 5-ASA enema 2g OD vs. 5-ASA enema 4g OD vs. 5-ASA foam 4g OD for 3 weeks
Outcomes	Clinical, endoscopic, and histologic improvement and remission
Notes	

Campieri 1993 *(Continued)*

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind (investigator)
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Cortot 2008

Methods	Multicenter randomised controlled investigator-blinded trial
Participants	Patients aged 18 years or older with mild to moderate left sided active ulcerative colitis with disease extension at least 5cm from the anal verge but not above the splenic flexure
Interventions	Mesalamine 5-ASA foam enema 1g/80ml OD vs.Mesalamine 5-ASA liquid enema 1g/100ml for 4 weeks
Outcomes	Clinical and endoscopic remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Investigator-blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups

Cortot 2008 *(Continued)*

Free of selective reporting?	Yes	The published report includes all expected outcomes

Eliakim 2007

Methods	Multicentre single-blind randomised controlled trial
Participants	Patients age 18 to 75 years with endoscopically and histologically confirmed ulcerative colitis extending no more than 40cm from the anal verge
Interventions	5-ASA foam 1g/30ml OD vs. 1g/60ml OD for 6 weeks
Outcomes	Clinical, endoscopic, and histologic remission
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Investigator-blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Farup 1995

Methods	Multicentre double-blind randomised controlled trial
Participants	Patients age 19 to 70 years with endoscopically confirmed ulcerative proctosigmoiditis
Interventions	5-ASA suppositories 0.5g BID vs. hydrocortisone foam 178mg BID for 4 weeks
Outcomes	Clinical and histologic improvement and remission
Notes	

Risk of bias

Farup 1995 *(Continued)*

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	No	Open trial
Incomplete outcome data addressed? All outcomes	Yes	There were no drop outs
Free of selective reporting?	Yes	The published report includes all expected outcomes

Friedman 1986

Methods	Randomized, double-blind controlled trial
Participants	Patients age 18 years or older with endoscopically confirmed ulcerative colitis
Interventions	5-ASA enema 4g OD vs. hydrocortisone enema 100mg OD for 3 weeks
Outcomes	Clinical, endoscopic and histologic improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Adequate
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	One patient dropped out from each group
Free of selective reporting?	Yes	The published report includes all expected outcomes

Gionchetti 1997

Methods	Single-centre randomised, single-blind controlled trial
Participants	Patients age 18 years or older with endoscopically and histologically confirmed ulcerative proctosigmoiditis
Interventions	5-ASA suppositories 1g OD vs. 0.5g BID for 4 weeks
Outcomes	Clinical, endoscopic, and histologic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind (investigator)
Incomplete outcome data addressed? All outcomes	Yes	There were no drop outs
Free of selective reporting?	Yes	The published report includes all expected outcomes

Gionchetti 1998

Methods	Single-centre single-blind randomised controlled trial
Participants	Patients age 18 years or older with endoscopically and histologically confirmed ulcerative proctitis extending no more than 15cm from the anal verge
Interventions	5-ASA suppositories 0.4g TID vs. oral 5-ASA 0.8g TID for 4 weeks
Outcomes	Clinical, endoscopic and histologic remission and clinical improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate

Gionchetti 1998 *(Continued)*

Blinding? All outcomes	Yes	Single blind (investigator)
Incomplete outcome data addressed? All outcomes	Yes	There were no drop outs
Free of selective reporting?	Yes	The published report includes all expected outcomes

Gionchetti 1999

Methods	Multicenter, single-blind randomised controlled trial
Participants	Patients age 18 to 70 years with endoscopically confirmed mild to moderately active ulcerative colitis
Interventions	5-ASA gel enema 2g OD vs. 5-ASA foam 2g OD for 4 weeks
Outcomes	Clinical, endoscopic and histologic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind
Incomplete outcome data addressed? All outcomes	Yes	6 patients were excluded from the foam group and 1 from the gel group
Free of selective reporting?	Yes	The published report includes all expected outcomes

Gionchetti 2005

Methods	Multicentre single-blind randomised controlled trial
Participants	Patients age 18 to 70 years with endoscopically and histologically confirmed ulcerative colitis
Interventions	5-ASA enema 1g OD vs. BDP enema 3mg OD for 6 weeks

Gionchetti 2005 *(Continued)*

Outcomes	Clinical improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Hanauer 1998

Methods	Multicenter double-blind randomised placebo-controlled trial
Participants	Patients with mild to moderately active ulcerative proctosigmoiditis
Interventions	5-ASA 1g OD vs. 2g OD vs. 4g OD vs. placebo for 8 weeks
Outcomes	Clinical , endoscopic, and histologic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Unclear	37% of placebo patients dropped out due to treatment failure compared to compared

Hanauer 1998 (*Continued*)

		to 8 to 10% of 5-ASA patients. No other description of drop outs was provided
Free of selective reporting?	Yes	The published report includes all expected outcomes

Kam 1996

Methods	Multicenter, double-blind randomised, double-dummy controlled trial
Participants	Patients age 18 years or older with endoscopically confirmed distal ulcerative colitis
Interventions	5-ASA enema 4g OD vs. oral SAS 1g QID for 6 weeks
Outcomes	Clinical and endoscopic improvement and remission
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind, double dummy
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Lee 1996

Methods	Multicenter, single-blind randomised, controlled trial
Participants	Patients age 18 years and older with ulcerative colitis distal to the splenic flexure
Interventions	5-ASA foam 2g OD vs. prednisolone foam 20mg OD for 4 weeks
Outcomes	Clinical, endoscopic, and histologic improvement and remission
Notes	

Lee 1996 *(Continued)*

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Lemann 1995

Methods	Multicenter, single-blind randomised controlled trial
Participants	Patients age 18 years and older with endoscopically and histologically confirmed distal ulcerative colitis
Interventions	5-ASA enema 1g OD vs. budesonide enema 2mg OD for 4 weeks
Outcomes	Endoscopic and histologic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Single blind (investigator)
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups

Free of selective reporting?	Yes	The published report includes all expected outcomes

Malchow 2002

Methods	Multicenter double-blind randomised controlled trial
Participants	Patients age 18 to 75 years with endoscopically and histologically confirmed distal ulcerative colitis
Interventions	5-ASA foam 2g OD vs. 5-ASA enema 4g OD for 4 weeks
Outcomes	Clinical and endoscopic improvement and remission
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	No	Investigator blinded
Incomplete outcome data addressed? All outcomes	Unclear	A similar proportion of patients dropped out from each group. However, reasons for withdrawal are not adequately explained
Free of selective reporting?	Yes	The published report includes all expected outcomes

Miner 2006

Methods	Multicentre double-blind randomised controlled trial
Participants	Patients age 18 years and older with ulcerative colitis extending 5 to 50cm from the anal verge and DAI 4 to 10
Interventions	5-ASA enema 4g OD vs. alicaforsen enema 120mg vs. 240mg OD for 6 weeks
Outcomes	Clinical and endoscopic improvement and remission
Notes	

Miner 2006 *(Continued)*

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Moller 1978

Methods	Single center single-blind randomised placebo-controlled trial
Participants	Patients with ulcerative proctitis
Interventions	SAS enema 3g OD vs. placebo for 2 weeks
Outcomes	Clinical and endoscopic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	One placebo patient dropped out due to lack of benefit
Free of selective reporting?	Yes	The published report includes all expected outcomes

Mulder 1988

Methods	Single centre single-blind randomised controlled trial
Participants	Patients with ulcerative proctitis extending no more than 20cm from the anal verge
Interventions	5-ASA enema 3g OD vs. prednisolone enema 30mg OD for 28 days
Outcomes	Clinical, endoscopic, and histologic improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	No drop outs were described
Free of selective reporting?	Yes	The published report includes all expected outcomes

Mulder 1996

Methods	Multicentre, double-blind controlled trial
Participants	Patients age 18 years and older with ulcerative proctitis extending no more than 20 cm from the anal verge
Interventions	5-ASA enema 2 g OD vs. beclomethasone enema 3 mg OD vs. both for 4 weeks
Outcomes	Clinical, endoscopic or histologic improvement and remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate

Mulder 1996 *(Continued)*

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	No drop outs were described
Free of selective reporting?	Yes	The published report includes all expected outcomes

Palmer 1981

Methods	Randomized double-blind placebo-controlled trial
Participants	Patients with endoscopically and histologically confirmed ulcerative colitis
Interventions	SAS enema 3g OD vs. placebo for 2 weeks
Outcomes	Clinical and histologic improvement
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	One patient was withdrawn from the treatment group due to non compliance
Free of selective reporting?	Yes	The published report includes all expected outcomes

Pokrotnieks 2000

Methods	Multicenter double-blind randomised placebo-controlled trial
Participants	Patients age 19 to 69 years with mild to moderately active left-sided ulcerative colitis
Interventions	5-ASA enema 2g OD vs. placebo for 6 weeks
Outcomes	Clinical, endoscopic and histologic improvement and remission

Pokrotneiks 2000 *(Continued)*

Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Powell-Tuck 1986

Methods	Single centre randomised controlled trial
Participants	Patients with endoscopically and histologically confirmed ulcerative colitis
Interventions	5-ASA enema 1g OD vs. 2g OD for 28 days
Outcomes	Clinical, endoscopic, and histologic remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Adequate
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	One patient was withdrawn from the 2 g group for worsening diarrhea

Powell-Tuck 1986 *(Continued)*

Free of selective reporting?	Yes	The published report includes all expected outcomes

Prantera 2005

Methods	Multicenter, double-blind randomised double-dummy controlled trial
Participants	Patients with mild to moderately active left-sided ulcerative colitis
Interventions	5-ASA enema 4g OD vs. oral 5-ASA MMX 1.2g TID for 8 weeks
Outcomes	Clinical, endoscopic, and histologic improvement and remission
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind, double dummy
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Safdi 1997

Methods	Multicenter double-blind randomised controlled trial
Participants	Patients with endoscopically confirmed ulcerative colitis
Interventions	5-ASA enema 4g OD vs. oral 5-ASA 0.8g TID vs. both for 6 weeks
Outcomes	Clinical improvement
Notes	

Risk of bias

Safdi 1997 *(Continued)*

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind, double dummy
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups
Free of selective reporting?	Yes	The published report includes all expected outcomes

Senagore 1992

Methods	Single center, randomised controlled trial
Participants	Patients with endoscopically and histologically confirmed ulcerative proctosigmoiditis
Interventions	5-ASA enema 4g OD vs. hydrocortisone enema 100mg OD vs. short chain fatty acid enema 120ml OD for 6 weeks
Outcomes	Clinical improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	No	Single blind
Incomplete outcome data addressed? All outcomes	Yes	No drop outs
Free of selective reporting?	Yes	The published report includes all expected outcomes

Sutherland 1987a

Methods	Multicentre double-blind randomised placebo-controlled trial
Participants	Patients with active ulcerative colitis extending no more than 50 cm from the anal verge
Interventions	5-ASA enema 4g OD vs. placebo for 6 weeks
Outcomes	Clinical improvement
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Table of random numbers
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	6 patients dropped out of the 5-ASA group for worsening disease or unsatisfactory response compared to 14 placebo patients
Free of selective reporting?	Yes	The published report includes all expected outcomes

Williams 1987

Methods	Single centre double-blind placebo-controlled trial
Participants	Patients and 18 and older with endoscopically confirmed ulcerative proctitis extending no more than 15cm from the anal verge
Interventions	5-ASA suppositories 0.5g TID vs. placebo for 6 weeks
Outcomes	Clinical remission
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequare sequence generation?	Unclear	Not described
Allocation concealment?	Yes	Adequate

Williams 1987 *(Continued)*

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	There were 2 drop outs in the placebo group
Free of selective reporting?	Yes	The published report includes all expected outcomes

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

Barber 1985	Case reports, not randomised, disease extent not described, symptom score not an outcome
Biddle 1990	Not a randomised trial, retrospective study
Bresci 1997	Not randomised, some patients with pancolitis
Campieri 1981	Some patient less than 12 years of age
Campieri 1987	Limited information about study design (randomisation not stated)
Campieri 1989	Analysis based on cycles without definition of cycle
D'Arienzo 1987	Not a randomised trial, single arm trial
Fedotin 1985	Not a randomised trial, no symptom-based outcome
Fruhmorgen 1980	Results for some patients not evaluable, treatment allocation unclear, lacks methodological rigour.
Guarino 1987	Not a randomised trial
Kandel 1987	Not a randomised trial
Klotz 1980	Some subjects with extensive ulcerative colitis and Crohn's disease
Lucidarme 1997	Some subjects with Crohn's disease
Marteau 2005	Some patients with extensive colitis
McPhee 1987	Not a randomised trial
Paolozi 2002	Not a randomised trial, some patients with pancolitis
Pullan 1993	Some patients withdrew after randomise without description of treatment allocation
Robinson 1990	Not a randomised trial, some patients with Crohn's disease
Serebro 1977	Not a randomised trial, age of subjects not reported
Sutherland 1987b	Duplicate publication (reports single-centre results from Multicentre trial)
Van Bodegraven 1996	Some subject with pancolitis
Van Hees 1980	Some subjects included twice (crossed over during relapse)
van Hogezand 1988	Some subjects included twice

(*Continued*)

Vecchi 2001	Some patients had disease extending to ascending and transverse colon
Willoughby 1980	Treatment drug N-Acetyl-5-ASA rather than 5-ASA
Willoughby 1986	Some subjects with extensive colitis
Yokoyama H 2007	Some subjects with pancolitis, minimal duration of remission prior to randomisation less than 4 weeks

DATA AND ANALYSES

Comparison 1. Rectal 5-ASA vs Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic Improvement	8	811	Odds Ratio (M-H, Random, 95% CI)	8.87 [5.30, 14.83]
2 Endoscopic Improvement	5	331	Odds Ratio (M-H, Random, 95% CI)	11.18 [5.99, 20.88]
3 Histologic Improvement	6	452	Odds Ratio (M-H, Random, 95% CI)	7.69 [3.26, 18.12]
4 Symptomatic Remission	8	756	Odds Ratio (M-H, Random, 95% CI)	8.30 [4.28, 16.12]
5 Endoscopic Remission	7	729	Odds Ratio (M-H, Random, 95% CI)	5.31 [3.15, 8.92]
6 Histologic Remission	5	588	Odds Ratio (M-H, Random, 95% CI)	6.28 [2.74, 14.40]

Comparison 2. Rectal 5-ASA vs Rectal Corticosteroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic Improvement	9	937	Odds Ratio (M-H, Random, 95% CI)	1.56 [1.15, 2.11]
2 Endoscopic Improvement	6	360	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.71, 1.72]
3 Histologic Improvement	6	316	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.95, 2.34]
4 Symptomatic Remission	6	942	Odds Ratio (M-H, Random, 95% CI)	1.65 [1.11, 2.45]
5 Endoscopic Remission	4	595	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.69, 1.94]
6 Histologic Remission	2	431	Odds Ratio (M-H, Random, 95% CI)	1.46 [0.90, 2.37]

Comparison 3. Rectal 5-ASA vs Oral 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic Improvement	4	214	Odds Ratio (M-H, Random, 95% CI)	2.25 [0.53, 9.54]
2 Symptomatic Remission	3	174	Odds Ratio (M-H, Random, 95% CI)	1.94 [0.35, 10.72]
3 Endoscopic Remission	3	174	Odds Ratio (M-H, Random, 95% CI)	1.45 [0.41, 5.10]
4 Histologic Remission	2	137	Odds Ratio (M-H, Random, 95% CI)	1.98 [0.13, 31.23]

Comparison 4. Rectal 5-ASA vs Oral + Rectal 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic Improvement	1	38	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.09, 1.67]

Comparison 5. Rectal 5-ASA vs Rectal 4-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic Improvement	1	63	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.37, 4.30]
2 Endoscopic Improvement	1	63	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.32, 3.42]
3 Histologic Improvement	1	63	Odds Ratio (M-H, Random, 95% CI)	1.22 [0.45, 3.31]

Comparison 6. Frequency of Rectal 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic Improvement Once daily vs more than one daily	2	89	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.20, 3.23]
2 Endoscopic Improvement once a day vs more than once a day	2	447	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.62, 1.77]
3 Histologic Improvement once a day vs more than once a day	2	447	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.82, 1.76]
4 Symptomatic Remission Once daily vs More than once a day	3	497	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.54, 1.47]
5 Endoscopic Remission once daily vs More than once a day	3	497	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.55, 1.34]
6 Histologic Remission	2	89	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.33, 1.90]

Comparison 7. Dose of 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic Improvement 5-ASA vs Placebo	8	811	Odds Ratio (M-H, Random, 95% CI)	7.62 [5.26, 11.04]
1.1 0-1g 5-ASA vs Placebo	3	179	Odds Ratio (M-H, Random, 95% CI)	6.25 [2.96, 13.19]
1.2 >1g-2g 5-ASA vs Placebo	5	274	Odds Ratio (M-H, Random, 95% CI)	10.22 [4.75, 21.98]
1.3 >2g-4g 5-ASA vs Placebo	5	358	Odds Ratio (M-H, Random, 95% CI)	8.73 [4.12, 18.49]
2 Endoscopic Improvement 5-ASA vs Placebo	5	331	Odds Ratio (M-H, Random, 95% CI)	10.70 [6.12, 18.69]
2.1 0-1g 5-ASA vs Placebo	2	83	Odds Ratio (M-H, Random, 95% CI)	8.78 [2.90, 26.53]
2.2 >1g-2g 5-ASA vs Placebo	4	180	Odds Ratio (M-H, Random, 95% CI)	11.41 [4.73, 27.49]
2.3 >2g-4g 5-ASA vs Placebo	2	68	Odds Ratio (M-H, Random, 95% CI)	12.68 [3.59, 44.78]
3 Histologic Improvement 5-ASA vs Placebo	6	452	Odds Ratio (M-H, Random, 95% CI)	7.60 [3.81, 15.15]
3.1 0-1g 5-ASA vs Placebo	2	83	Odds Ratio (M-H, Random, 95% CI)	6.60 [2.12, 20.55]
3.2 >1g-2g 5-ASA vs Placebo	5	291	Odds Ratio (M-H, Random, 95% CI)	8.63 [2.70, 27.64]
3.3 >2g-4g 5-ASA vs Placebo	2	78	Odds Ratio (M-H, Random, 95% CI)	8.95 [2.57, 31.15]
4 Symptomatic Remission 5-ASA vs placebo	8	756	Odds Ratio (M-H, Random, 95% CI)	6.98 [4.29, 11.38]
4.1 0-1g 5-ASA vs Placebo	3	179	Odds Ratio (M-H, Random, 95% CI)	5.13 [2.21, 11.91]
4.2 >1g-2g 5-ASA vs Placebo	7	412	Odds Ratio (M-H, Random, 95% CI)	8.13 [3.73, 17.70]
4.3 >2g-4g 5-ASA vs Placebo	3	165	Odds Ratio (M-H, Random, 95% CI)	10.07 [2.66, 38.18]
5 Endoscopic Remission 5-ASA vs Placebo	7	729	Odds Ratio (M-H, Random, 95% CI)	4.80 [3.27, 7.07]
5.1 0-1g 5-ASA vs Placebo	3	179	Odds Ratio (M-H, Random, 95% CI)	5.52 [2.45, 12.45]
5.2 >1g-2g 5-ASA vs Placebo	6	385	Odds Ratio (M-H, Random, 95% CI)	4.22 [2.31, 7.69]
5.3 >2g-4g 5-ASA vs Placebo	3	165	Odds Ratio (M-H, Random, 95% CI)	7.53 [3.21, 17.63]
6 Histologic Remission 5-ASA vs Placebo	5	588	Odds Ratio (M-H, Random, 95% CI)	5.78 [3.28, 10.20]
6.1 0-1g 5-ASA vs Placebo	3	179	Odds Ratio (M-H, Random, 95% CI)	4.76 [1.66, 13.60]
6.2 >1g-2g 5-ASA vs Placebo	5	274	Odds Ratio (M-H, Random, 95% CI)	5.98 [2.53, 14.11]
6.3 >2g-4g 5-ASA vs Placebo	2	135	Odds Ratio (M-H, Random, 95% CI)	6.77 [2.29, 20.04]
7 Symptomatic Improvement Comparison of Dose of 5-ASA	4	802	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.53, 1.14]
7.1 1g 5-ASA Vs 2g 5-ASA	2	150	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.53, 2.42]
7.2 2g 5-ASA vs 4g 5-ASA	4	652	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.43, 1.16]
8 Endoscopic Improvement Comparison of Dose of 5-ASA	2	319	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.57, 1.56]
8.1 1g 5-ASA Vs 2g 5-ASA	1	42	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.25, 4.35]
8.2 2g 5-ASA vs 4g 5-ASA	2	277	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.54, 1.60]
9 Histologic Improvement Comparison of Dose of 5-ASA	2	319	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.24]
9.1 1g 5-ASA Vs 2g 5-ASA	1	42	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.23, 3.21]
9.2 2g 5-ASA vs 4g 5-ASA	2	277	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.46, 1.27]
10 Symptomatic Remission Comparison of Dose of 5-ASA	6	827	Odds Ratio (M-H, Random, 95% CI)	1.37 [0.67, 2.78]
10.1 1g 5-ASA Vs 2g 5-ASA	3	175	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.58, 2.06]
10.2 2g 5-ASA vs 4g 5-ASA	4	652	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.50, 4.13]

11 Endoscopic Remission	5	827	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.76, 2.01]
Comparison of Dose of 5-ASA				
11.1 1g 5-ASA Vs 2g 5-ASA	3	175	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.52, 2.48]
11.2 2g 5-ASA vs 4g 5-ASA	4	652	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.64, 2.42]
12 Histologic Remission	5	827	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.73, 1.84]
Comparison of Dose of 5-ASA				
12.1 1g 5-ASA Vs 2g 5-ASA	3	175	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.44, 4.16]
12.2 2g 5-ASA vs 4g 5-ASA	4	652	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.65, 1.99]

Comparison 8. Drug formulation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptomatic Improvement 5-ASA foam vs Enema	4	644	Odds Ratio (M-H, Random, 95% CI)	2.07 [0.88, 4.84]
2 Endoscopic Improvement 5-ASA Foam vs Enema	2	336	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.48, 4.71]
3 Histologic Improvement 5-ASA Foam vs Enema	2	336	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.41, 1.00]
4 Symptomatic Remission 5-ASA Foam vs Enema	5	1172	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.43, 1.66]
5 Endoscopic Remission 5-ASA Enema vs 5-ASA Foam	5	1172	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.59, 1.11]
6 Histologic Remission 5-ASA Enema vs 5-ASA Foam	3	602	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.67, 1.33]
7 Symptomatic Improvement 5-ASA enema vs Suppository	1	40	Odds Ratio (M-H, Fixed, 95% CI)	1.59 [0.24, 10.70]
8 Endoscopic Improvement 5-ASA Enema vsSuppository	1	49	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.03, 0.79]
9 Histological Improvement 5-ASA enema vs Suppository	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.14, 3.90]
10 Symptomatic Remission 5-ASA enema vs Suppository	1	39	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.23, 5.05]
11 Endoscopic Remission 5-ASA enema vs Suppository	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.17, 2.62]
12 Histologic Remission 5-ASA enema vs Suppository	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.13, 1.72]

Analysis 1.1. Comparison 1 Rectal 5-ASA vs Placebo, Outcome 1 Symptomatic Improvement.

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

Comparison: 1 Rectal 5-ASA vs Placebo

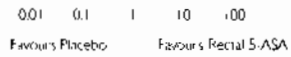
Outcome: 1 Symptomatic Improvement

Study or subgroup	Rectal 5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1990a	54/63	13/31		14.8 %	8.31 [3.05, 22.66]
Campieri 1990b	28/32	10/30		10.8 %	14.00 [3.84, 51.05]
Campieri 1991a	17/18	2/14		3.7 %	102.00 [8.28, 1257.15]
Campieri 1991b	73/86	11/27		15.4 %	8.17 [3.10, 21.51]
Hanauer 1998	150/217	19/70		23.2 %	6.01 [3.30, 10.95]
Moller 1978	15/16	3/14		4.1 %	55.00 [5.02, 602.15]
Palmer 1981	11/17	2/23		6.8 %	19.25 [3.32, 111.75]
Sutherland 1987a	48/76	22/77		21.3 %	4.29 [2.17, 8.46]
Total (95% CI)	**525**	**286**		**100.0 %**	**8.87 [5.30, 14.83]**

Total events: 396 (Rectal 5-ASA), 82 (Placebo)

Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 12.02$, df = 7 ($P = 0.10$); $I^2 = 42\%$

Test for overall effect: $Z = 8.32$ ($P < 0.00001$)



Analysis 1.2. Comparison 1 Rectal 5-ASA vs Placebo, Outcome 2 Endoscopic Improvement.

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

Comparison: 1 Rectal 5-ASA vs Placebo

Outcome: 2 Endoscopic Improvement

Study or subgroup	Rectal 5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1990a	53/63	12/31		30.3 %	8.39 [3.12, 22.57]
Campieri 1990b	25/32	7/30		22.6 %	11.73 [3.57, 38.61]
Campieri 1991a	17/18	2/14		5.9 %	102.00 [8.28, 1257.15]
Campieri 1991b	65/86	8/27		31.7 %	7.35 [2.81, 19.23]
Moller 1978	14/16	3/14		9.4 %	25.67 [3.63, 181.44]
Total (95% CI)	**215**	**116**		**100.0 %**	**11.18 [5.99, 20.88]**
Total events 174 (Rectal 5-ASA), 32 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 4.72, df = 4 (P = 0.32), I^2 = 15%					
Test for overall effect Z = 7.57 (P < 0.00001)					

0.01 0.1 1 10 100

Favours Placebo Favours Rectal 5-ASA

Analysis 1.3. Comparison 1 Rectal 5-ASA vs Placebo, Outcome 3 Histologic Improvement.

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

Comparison: 1 Rectal 5-ASA vs Placebo

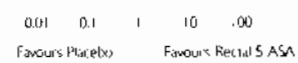
Outcome: 3 Histologic Improvement

Study or subgroup	Rectal 5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1990a	46/63	10/31		20.7 %	5.68 [2.23, 14.49]
Campieri 1990b	21/32	4/30		17.0 %	12.41 [3.45, 44.66]
Campieri 1991a	15/18	1/14		8.8 %	65.00 [6.00, 703.67]
Campieri 1991b	60/86	4/27		18.3 %	13.27 [4.17, 42.21]
Palmer 1981	7/17	2/23		12.9 %	7.35 [1.29, 41.98]
Pokrotnieks 2000	26/54	18/57		22.4 %	2.01 [0.93, 4.36]
Total (95% CI)	**270**	**182**		**100.0 %**	**7.69 [3.26, 18.12]**

Total events: 175 (Rectal 5-ASA), 39 (Placebo)

Heterogeneity: $Tau^2 = 0.70$, $Chi^2 = 14.58$, df = 5 (P = 0.01); $I^2 = 66\%$

Test for overall effect: Z = 4.66 (P < 0.00001)



Analysis 1.4. Comparison 1 Rectal 5-ASA vs Placebo, Outcome 4 Symptomatic Remission.

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

Comparison: 1 Rectal 5-ASA vs Placebo

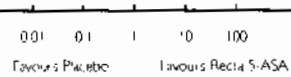
Outcome: 4 Symptomatic Remission

Study or subgroup	Rectal 5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1990a	15/63	12/31		17.4 %	3.96 [1.60, 9.80]
Campieri 1990b	18/32	2/30		10.3 %	18.00 [3.65, 88.76]
Campieri 1991a	12/18	1/14		6.5 %	26.00 [2.72, 248.59]
Campieri 1991b	58/86	3/27		13.1 %	16.57 [4.60, 59.73]
Hanauer 1998	101/217	10/70		19.7 %	5.22 [2.54, 10.74]
Moller 1978	13/16	2/14		8.0 %	26.00 [3.69, 183.42]
Pokrotnieks 2000	35/54	23/57		19.1 %	2.72 [1.26, 5.88]
Williams 1987	11/14	1/13		5.9 %	44.00 [3.97, 488.19]
Total (95% CI)	**500**	**256**		**100.0 %**	**8.30 [4.28, 16.12]**

Total events: 293 (Rectal 5-ASA), 54 (Placebo)

Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 15.76$, df = 7 (P = 0.03); $I^2 = 56\%$

Test for overall effect: Z = 6.25 (P < 0.00001)



Analysis 1.5. Comparison 1 Rectal 5-ASA vs Placebo, Outcome 5 Endoscopic Remission.

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

Comparison: 1 Rectal 5-ASA vs Placebo

Outcome: 5 Endoscopic Remission

Study or subgroup	Rectal 5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1990a	36/63	7/31		18.0 %	4.57 [1.72, 12.16]
Campieri 1990b	13/32	2/30		8.7 %	9.58 [1.94, 47.38]
Campieri 1991a	10/18	0/14		2.9 %	35.82 [1.86, 691.79]
Campieri 1991b	40/86	2/27		9.7 %	10.87 [2.42, 48.78]
Hanauer 1998	137/217	17/70		29.4 %	5.34 [2.90, 9.85]
Moller 1978	12/16	3/14		7.8 %	11.00 [2.00, 60.57]
Pokrotnieks 2000	26/54	17/57		23.5 %	2.18 [1.00, 4.76]
Total (95% CI)	**486**	**243**		**100.0 %**	**5.31 [3.15, 8.92]**

Total events: 274 (Rectal 5-ASA), 48 (Placebo)

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 8.69$, df = 6 (P = 0.19); $I^2 = 31\%$

Test for overall effect: Z = 6.29 (P < 0.00001)

0.1 0.2 0.5 1 2 5 10

Favours Placebo Favours Rectal 5-ASA

Analysis 1.6. Comparison 1 Rectal 5-ASA vs Placebo, Outcome 6 Histologic Remission.

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

Comparison: 1 Rectal 5-ASA vs Placebo

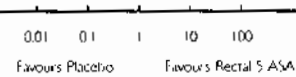
Outcome: 6 Histologic Remission

Study or subgroup	Rectal 5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1990a	8/63	2/31		20.0 %	2.11 [0.42, 10.59]
Campieri 1990b	9/32	1/30		12.8 %	11.35 [1.34, 96.18]
Campieri 1991a	9/18	0/14		7.2 %	29.00 [1.50, 559.17]
Campieri 1991b	35/86	0/27		7.8 %	37.91 [2.24, 642.05]
Hanauer 1998	106/217	11/70		52.2 %	5.12 [2.55, 10.28]
Total (95% CI)	**416**	**172**		**100.0 %**	**6.28 [2.74, 14.40]**

Total events: 167 (Rectal 5-ASA), 14 (Placebo)

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 5.14$, df = 4 (P = 0.27); $I^2 = 22\%$

Test for overall effect: Z = 4.34 (P = 0.000014)



Analysis 2.1. Comparison 2 Rectal 5-ASA vs Rectal Corticosteroid, Outcome 1 Symptomatic Improvement.

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

Comparison: 2 Rectal 5-ASA vs Rectal Corticosteroid

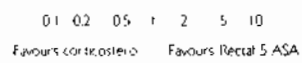
Outcome: 1 Symptomatic Improvement

Study or subgroup	Rectal 5-ASA n/N	Rectal coticosteroid n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Anonymous 1987	32/61	33/62		17.3 %	0.97 [0.48, 1.97]
Bianchi-Porro 1995	24/27	16/25		4.3 %	4.50 [1.05, 19.22]
Biancone 2007	39/42	42/50		4.7 %	2.48 [0.61, 10.01]
Friedman 1986	7/9	2/9		1.9 %	12.25 [1.33, 113.06]
Gionchetti 2005	52/106	44/111		28.3 %	1.64 [0.96, 2.83]
Lee 1996	130/167	117/167		33.5 %	1.50 [0.92, 2.46]
Mulder 1988	11/15	11/14		3.1 %	0.75 [0.14, 4.17]
Mulder 1996	16/21	14/20		4.7 %	1.37 [0.34, 5.49]
Senagore 1992	17/19	10/12		2.1 %	1.70 [0.21, 14.02]
Total (95% CI)	**467**	**470**		**100.0 %**	**1.56 [1.15, 2.11]**

Total events: 328 (Rectal 5-ASA), 286 (Rectal coticosteroid)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.31$, df = 8 (P = 0.40); $I^2 = 4\%$

Test for overall effect: Z = 2.85 (P = 0.0044)



Analysis 2.2. Comparison 2 Rectal 5-ASA vs Rectal Corticosteroid, Outcome 2 Endoscopic Improvement.

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

Comparison: 2 Rectal 5-ASA vs Rectal Corticosteroid

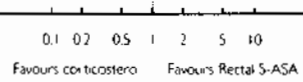
Outcome: 2 Endoscopic Improvement

Study or subgroup	Rectal 5-ASA n/N	Rectal coticosteroid n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Anonymous 1987	34/61	40/62		46.9 %	0.69 [0.34, 1.43]
Bianchi-Porro 1995	20/27	14/25		10.1 %	2.24 [0.70, 7.22]
Friedman 1986	6/9	2/9		1.8 %	7.00 [0.86, 56.89]
Lemann 1995	38/49	34/48		20.6 %	1.42 [0.57, 3.55]
Mulder 1988	11/15	12/14		8.8 %	0.46 [0.07, 3.02]
Mulder 1996	15/21	15/20		11.7 %	0.83 [0.21, 3.33]
Total (95% CI)	**182**	**178**		**100.0 %**	**1.11 [0.71, 1.72]**

Total events: 124 (Rectal 5-ASA), 117 (Rectal coticosteroid)

Heterogeneity: $Chi^2 = 7.28$, df = 5 (P = 0.20); $I^2 = 31\%$

Test for overall effect: Z = 0.45 (P = 0.65)



Analysis 2.3. Comparison 2 Rectal 5-ASA vs Rectal Corticosteroid, Outcome 3 Histologic Improvement.

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

Comparison: 2 Rectal 5-ASA vs Rectal Corticosteroid

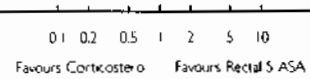
Outcome: 3 Histologic Improvement

Study or subgroup	Rectal 5-ASA n/N	Rectal coticosteroid n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bianchi-Porro 1995	15/27	15/25		22.4 %	0.83 [0.28, 2.51]
Farup 1995	31/41	22/38		18.0 %	2.25 [0.86, 5.89]
Friedman 1986	6/9	2/9		2.2 %	7.00 [0.86, 56.89]
Lemann 1995	30/49	26/48		32.9 %	1.34 [0.60, 3.00]
Mulder 1988	11/15	8/14		7.1 %	2.06 [0.43, 9.80]
Mulder 1996	10/21	10/20		17.4 %	0.91 [0.27, 3.10]
Total (95% CI)	**162**	**154**		**100.0 %**	**1.49 [0.95, 2.34]**

Total events: 103 (Rectal 5-ASA), 83 (Rectal coticosteroid)

Heterogeneity: Chi^2 = 4.74, df = 5 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 1.73 (P = 0.084)



Analysis 2.4. Comparison 2 Rectal 5-ASA vs Rectal Corticosteroid, Outcome 4 Symptomatic Remission.

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

Comparison: 2 Rectal 5-ASA vs Rectal Corticosteroid

Outcome: 4 Symptomatic Remission

Study or subgroup	Rectal 5-ASA n/N	Rectal coticosteroid n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Anonymous 1987	27/61	19/62		15.9 %	1.80 [0.86, 3.76]
Biancone 2007	22/42	18/50		13.8 %	1.96 [0.85, 4.52]
Farup 1995	17/41	13/38		12.3 %	1.36 [0.55, 3.40]
Gionchetti 2005	26/106	33/111		19.6 %	0.77 [0.42, 1.40]
Lee 1996	77/167	45/167		24.3 %	2.32 [1.47, 3.67]
Lemann 1995	28/49	17/48		14.1 %	2.43 [1.07, 5.51]
Total (95% CI)	**466**	**476**		**100.0 %**	**1.65 [1.11, 2.45]**

Total events: 197 (Rectal 5-ASA), 145 (Rectal coticosteroid)

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 9.56$, df = 5 (P = 0.09); $I^2 = 48\%$

Test for overall effect: Z = 2.49 (P = 0.013)

0.1 0.2 0.5 1 2 5 10

Favours Corticostero Favours Recta 5-ASA

Analysis 2.5. Comparison 2 Rectal 5-ASA vs Rectal Corticosteroid, Outcome 5 Endoscopic Remission.

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

Comparison: 2 Rectal 5-ASA vs Rectal Corticosteroid

Outcome: 5 Endoscopic Remission

Study or subgroup	Rectal 5-ASA n/N	Rectal coticosteroid n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Anonymous 1987	17/61	15/62		27.5 %	1.21 [0.54, 2.71]
Lee 1996	59/167	44/167		49.5 %	1.53 [0.96, 2.44]
Lemann 1995	6/49	6/48		15.0 %	0.98 [0.29, 3.27]
Mulder 1996	2/21	6/20		8.0 %	0.25 [0.04, 1.40]
Total (95% CI)	**298**	**297**		**100.0 %**	**1.16 [0.69, 1.94]**

Total events: 84 (Rectal 5-ASA), 71 (Rectal coticosteroid)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 4.21$, df = 3 (P = 0.24); $I^2 = 29\%$

Test for overall effect: Z = 0.56 (P = 0.58)

0.1 0.2 0.5 1 2 5 10

Favours Corticostero Favours Rectal 5-ASA

Analysis 2.6. Comparison 2 Rectal 5-ASA vs Rectal Corticosteroid, Outcome 6 Histologic Remission.

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

Comparison 2 Rectal 5-ASA vs Rectal Corticosteroid

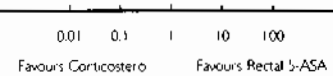
Outcome 6 Histologic Remission

Study or subgroup	Rectal 5-ASA n/N	Rectal Coticosteroid n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Lee 1996	40/167	31/167		83.2 %	1.38 [0.82, 2.34]
Lemann 1995	9/49	5/48		16.8 %	1.94 [0.60, 6.27]
Total (95% CI)	**216**	**215**		**100.0 %**	**1.46 [0.90, 2.37]**

Total events: 49 (Rectal 5-ASA), 36 (Rectal Coticosteroid)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 1.55 (P = 0.12)



Analysis 3.1. Comparison 3 Rectal 5-ASA vs Oral 5-ASA, Outcome 1 Symptomatic Improvement.

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

Comparison 3 Rectal 5-ASA vs Oral 5-ASA

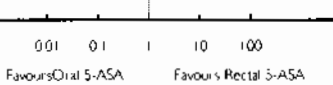
Outcome: 1 Symptomatic Improvement

Study or subgroup	Rectal 5-ASA n/N	Oral 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Gionchetti 1998	24/29	10/29		25.2 %	9.12 [2.66, 31.22]
Kam 1996	16/19	10/18		22.8 %	4.27 [0.91, 19.99]
Prantera 2005	23/39	31/40		27.0 %	0.42 [0.16, 1.11]
Safdi 1997	11/18	10/22		24.9 %	1.89 [0.53, 6.69]
Total (95% CI)	**105**	**109**		**100.0 %**	**2.25 [0.53, 9.54]**

Total events: 74 (Rectal 5-ASA), 61 (Oral 5-ASA)

Heterogeneity: $Tau^2 = 1.76$; $Chi^2 = 16.45$, df = 3 (P = 0.00092); $I^2 = 82\%$

Test for overall effect: Z = 1.10 (P = 0.27)



Analysis 3.2. Comparison 3 Rectal 5-ASA vs Oral 5-ASA, Outcome 2 Symptomatic Remission.

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

Comparison: 3 Rectal 5-ASA vs Oral 5-ASA

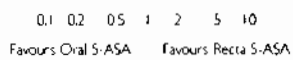
Outcome: 2 Symptomatic Remission

Study or subgroup	Rectal 5-ASA n/N	Oral 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Gionchetti 1998	26/29	12/29		31.5 %	12.28 [3.01, 50.04]
Kam 1996	9/19	8/18		32.5 %	1.13 [0.31, 4.10]
Prantera 2005	19/39	24/40		36.0 %	0.63 [0.26, 1.54]
Total (95% CI)	**87**	**87**		**100.0 %**	**1.94 [0.35, 10.72]**

Total events: 54 (Rectal 5-ASA), 44 (Oral 5-ASA)

Heterogeneity: $Tau^2 = 1.90$; $Chi^2 = 12.47$, df = 2 (P = 0.002); $I^2 = 84\%$

Test for overall effect: Z = 0.76 (P = 0.45)



Analysis 3.3. Comparison 3 Rectal 5-ASA vs Oral 5-ASA, Outcome 3 Endoscopic Remission.

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

Comparison: 3 Rectal 5-ASA vs Oral 5-ASA

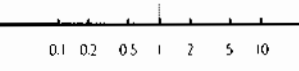
Outcome: 3 Endoscopic Remission

Study or subgroup	Rectal 5-ASA n/N	Oral 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Gionchetti 1998	21/29	10/29		33.3 %	4.99 [1.63, 15.25]
Kam 1996	7/19	7/18		30.0 %	0.92 [0.24, 3.46]
Prantera 2005	14/39	18/40		36.7 %	0.68 [0.28, 1.69]
Total (95% CI)	**87**	**87**		**100.0 %**	**1.45 [0.41, 5.10]**

Total events: 42 (Rectal 5-ASA), 35 (Oral 5-ASA)

Heterogeneity: $Tau^2 = 0.91$; $Chi^2 = 7.75$, df = 2 (P = 0.02); $I^2 = 74\%$

Test for overall effect: Z = 0.58 (P = 0.56)



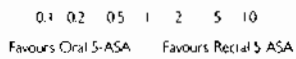
Analysis 3.4. Comparison 3 Rectal 5-ASA vs Oral 5-ASA, Outcome 4 Histologic Remission.

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

Comparison: 3 Rectal 5-ASA vs Oral 5-ASA

Outcome: 4 Histologic Remission

Study or subgroup	Rectal 5-ASA n/N	Oral 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Gionchetti 1998	18/29	5/29		51.1 %	7.85 [2.32, 26.63]
Prantera 2005	3/39	6/40		48.9 %	0.47 [0.11, 2.04]
Total (95% CI)	**68**	**69**		**100.0 %**	**1.98 [0.13, 31.23]**
Total events: 21 (Rectal 5-ASA), 11 (Oral 5-ASA)					
Heterogeneity: Tau^2 = 3.48; Chi^2 = 8.37, df = 1 (P = 0.004), I^2 =88%					
Test for overall effect: Z = 0.49 (P = 0.63)					



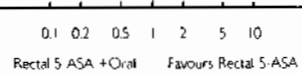
Analysis 4.1. Comparison 4 Rectal 5-ASA vs Oral + Rectal 5-ASA, Outcome 1 Symptomatic Improvement.

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

Comparison: 4 Rectal 5-ASA vs Oral + Rectal 5-ASA

Outcome: 1 Symptomatic Improvement

Study or subgroup	Rectal 5-ASA n/N	Oral + Rectal 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Safdi 1997	11/18	16/20		100.0 %	0.39 [0.09, 1.67]
Total (95% CI)	**18**	**20**		**100.0 %**	**0.39 [0.09, 1.67]**
Total events: 11 (Rectal 5-ASA), 16 (Oral + Rectal 5-ASA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.26 (P = 0.21)					



Analysis 5.1. Comparison 5 Rectal 5-ASA vs Rectal 4-ASA, Outcome 1 Symptomatic Improvement.

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

Comparison: 5 Rectal 5-ASA vs Rectal 4-ASA

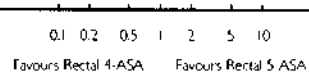
Outcome: 1 Symptomatic Improvement

Study or subgroup	Rectal 5-ASA n/N	Rectal 4-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1984	26/32	24/31		100.0 %	1.26 [0.37, 4.30]
Total (95% CI)	**32**	**31**		**100.0 %**	**1.26 [0.37, 4.30]**

Total events: 26 (Rectal 5-ASA), 24 (Rectal 4-ASA)

Heterogeneity: not applicable

Test for overall effect: Z = 0.38 (P = 0.71)



Analysis 5.2. Comparison 5 Rectal 5-ASA vs Rectal 4-ASA, Outcome 2 Endoscopic Improvement.

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

Comparison: 5 Rectal 5-ASA vs Rectal 4-ASA

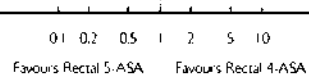
Outcome: 2 Endoscopic Improvement

Study or subgroup	Rectal 5-ASA n/N	Rectal 4-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1984	25/32	24/31		100.0 %	1.04 [0.32, 3.42]
Total (95% CI)	**32**	**31**		**100.0 %**	**1.04 [0.32, 3.42]**

Total events: 25 (Rectal 5-ASA), 24 (Rectal 4-ASA)

Heterogeneity: not applicable

Test for overall effect: Z = 0.07 (P = 0.95)



Analysis 5.3. Comparison 5 Rectal 5-ASA vs Rectal 4-ASA, Outcome 3 Histologic Improvement.

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

Comparison: 5 Rectal 5-ASA vs Rectal 4-ASA

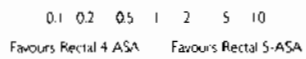
Outcome: 3 Histologic Improvement

Study or subgroup	Rectal 5-ASA n/N	Rectal 4-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1984	15/32	13/31		100.0 %	1.22 [0.45, 3.31]
Total (95% CI)	**32**	**31**		**100.0 %**	**1.22 [0.45, 3.31]**

Total events: 15 (Rectal 5-ASA), 13 (Rectal 4-ASA)

Heterogeneity: not applicable

Test for overall effect: Z = 0.39 (P = 0.69)



Analysis 6.1. Comparison 6 Frequency of Rectal 5-ASA, Outcome 1 Symptomatic Improvement Once daily vs more than one daily.

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

Comparison: 6 Frequency of Rectal 5-ASA

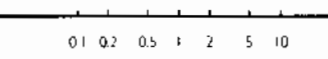
Outcome: 1 Symptomatic Improvement Once daily vs more than one daily

Study or subgroup	Once daily n/N	More than Once a day n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1988	18/20	17/19		45.3 %	1.06 [0.13, 8.38]
Gionchetti 1997	22/25	23/25		54.7 %	0.64 [0.10, 4.19]
Total (95% CI)	**45**	**44**		**100.0 %**	**0.80 [0.20, 3.23]**

Total events: 40 (Once daily), 40 (More than Once a day)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 0.31 (P = 0.76)

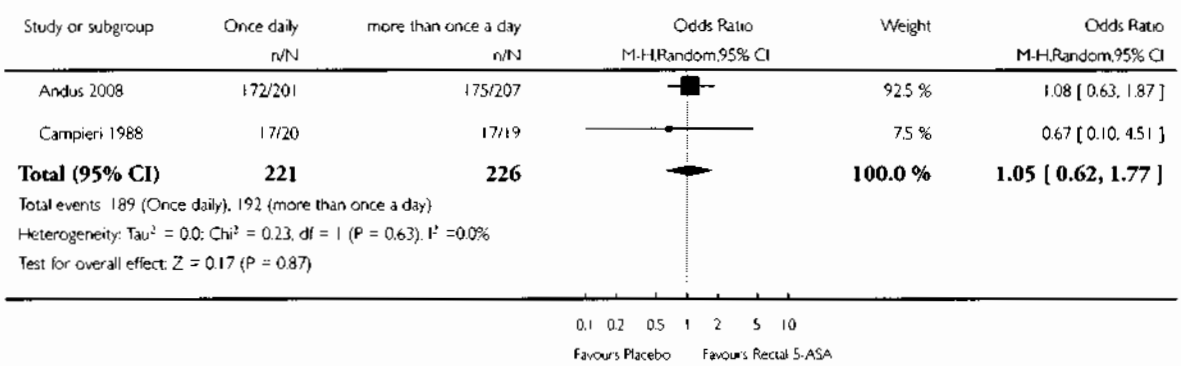


Analysis 6.2. Comparison 6 Frequency of Rectal 5-ASA, Outcome 2 Endoscopic Improvement once a day vs more than once a day.

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

Comparison: 6 Frequency of Rectal 5-ASA

Outcome: 2 Endoscopic Improvement once a day vs more than once a day

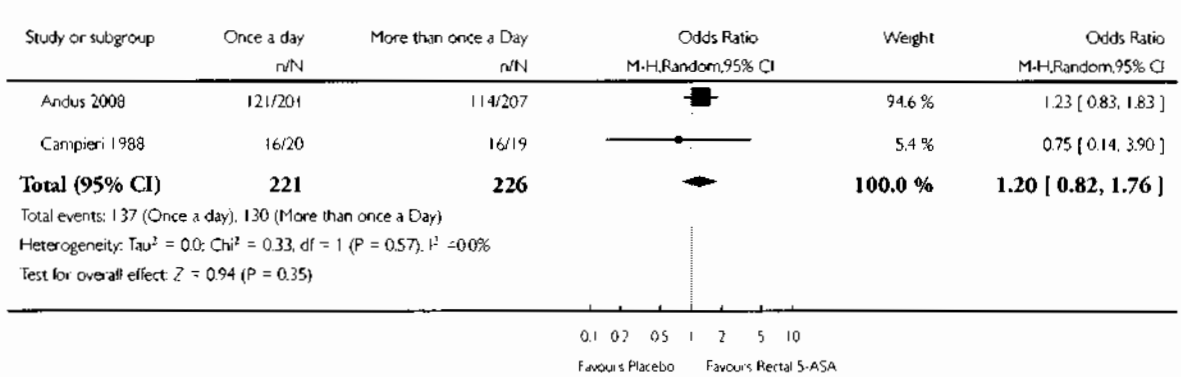


Analysis 6.3. Comparison 6 Frequency of Rectal 5-ASA, Outcome 3 Histologic Improvement once a day vs more than once a day.

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

Comparison: 6 Frequency of Rectal 5-ASA

Outcome: 3 Histologic Improvement once a day vs more than once a day



Analysis 6.4. Comparison 6 Frequency of Rectal 5-ASA, Outcome 4 Symptomatic Remission Once daily vs More than once a day.

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

Comparison: 6 Frequency of Rectal 5-ASA

Outcome: 4 Symptomatic Remission Once daily vs More than once a day

Study or subgroup	Once a day n/N	More than once a day n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Andus 2008	171/201	182/207		77.0 %	0.78 [0.44, 1.38]
Campieri 1988	16/20	15/19		10.4 %	1.07 [0.23, 5.05]
Gionchetti 1997	21/25	19/25		12.6 %	1.66 [0.41, 6.78]
Total (95% CI)	**246**	**251**		**100.0 %**	**0.89 [0.54, 1.47]**

Total events: 208 (Once a day), 216 (More than once a day)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.99$, df = 2 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 0.46 (P = 0.64)

Analysis 6.5. Comparison 6 Frequency of Rectal 5-ASA, Outcome 5 Endoscopic Remission once daily vs More than once a day.

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

Comparison: 6 Frequency of Rectal 5-ASA

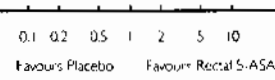
Outcome: 5 Endoscopic Remission once daily vs More than once a day

Study or subgroup	Once a day n/N	more than once a day n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Andus 2008	161/201	172/207		78.1 %	0.82 [0.50, 1.35]
Campieri 1988	13/20	14/19		10.4 %	0.66 [0.17, 2.62]
Gionchetti 1997	20/25	18/25		11.4 %	1.56 [0.42, 5.78]
Total (95% CI)	**246**	**251**		**100.0 %**	**0.86 [0.55, 1.34]**

Total events: 194 (Once a day), 204 (more than once a day)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.66 (P = 0.51)



Analysis 6.6. Comparison 6 Frequency of Rectal 5-ASA, Outcome 6 Histologic Remission.

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

Comparison: 6 Frequency of Rectal 5-ASA

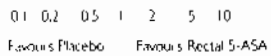
Outcome: 6 Histologic Remission

Study or subgroup	Once a day n/N	Twice a day n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1988	9/20	12/19		43.3 %	0.48 [0.13, 1.72]
Gionchetti 1997	13/25	12/25		56.7 %	1.17 [0.39, 3.56]
Total (95% CI)	**45**	**44**		**100.0 %**	**0.79 [0.33, 1.90]**

Total events: 22 (Once a day), 24 (Twice a day)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 1.08$, df = 1 (P = 0.30); $I^2 = 8\%$

Test for overall effect: Z = 0.52 (P = 0.61)



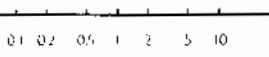
Analysis 7.1. Comparison 7 Dose of 5-ASA, Outcome 1 Symptomatic Improvement 5-ASA vs Placebo.

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

Comparison: 7 Dose of 5-ASA

Outcome: 1 Symptomatic Improvement 5-ASA vs Placebo

Study or subgroup	5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 0-1g 5-ASA vs Placebo					
Campieri 1990a	26/32	6/15		6.9 %	6.50 [1.66, 25.38]
Campieri 1991b	23/27	4/9		4.6 %	7.19 [1.33, 38.95]
Hanauer 1998	49/73	6/23		11.2 %	5.78 [2.02, 16.55]
Subtotal (95% CI)	**132**	**47**		**22.7 %**	**6.25 [2.96, 13.19]**
Total events: 98 (5-ASA), 16 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 2 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: $Z = 4.81$ (P < 0.00001)					
2 >1g-2g 5-ASA vs Placebo					
Campieri 1990a	28/31	7/16		5.5 %	12.00 [2.55, 56.37]
Campieri 1990b	28/32	10/30		7.6 %	14.00 [3.84, 51.05]



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Study or subgroup	5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1991a	17/18	2/14		2.1 %	102.00 [8.28, 1257.15]
Campieri 1991b	25/30	4/9		5.0 %	6.25 [1.23, 31.84]
Hanauer 1998	46/71	6/23		11.2 %	5.21 [1.82, 14.90]
Subtotal (95% CI)	**182**	**92**		**31.4 %**	**10.22 [4.75, 21.98]**
Total events: 141 (5-ASA), 29 (Placebo)					
Heterogeneity: Tau^2 = 0.20; Chi^2 = 5.39, df = 4 (P = 0.25); I^2 =26%					
Test for overall effect: Z = 5.95 (P < 0.00001)					
3 >2g-4g 5-ASA vs Placebo					
Campieri 1991b	25/29	3/9		4.3 %	12.50 [2.19, 71.36]
Hanauer 1998	55/73	7/24		11.6 %	7.42 [2.65, 20.76]
Moller 1978	15/16	3/14		2.3 %	55.00 [5.02, 602.15]
Palmer 1981	11/17	2/23		4.3 %	19.25 [3.32, 111.75]
Sutherland 1987a	48/76	22/77		23.4 %	4.29 [2.17, 8.46]
Subtotal (95% CI)	**211**	**147**		**45.9 %**	**8.73 [4.12, 18.49]**
Total events: 154 (5-ASA), 37 (Placebo)					
Heterogeneity: Tau^2 = 0.27; Chi^2 = 6.56, df = 4 (P = 0.16); I^2 =39%					
Test for overall effect: Z = 5.66 (P < 0.00001)					
Total (95% CI)	**525**	**286**		**100.0 %**	**7.62 [5.26, 11.04]**
Total events: 396 (5-ASA), 82 (Placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 12.91, df = 12 (P = 0.38); I^2 =7%					
Test for overall effect: Z = 10.73 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours Placebo Favours Rectal 5-ASA

Analysis 7.2. Comparison 7 Dose of 5-ASA, Outcome 2 Endoscopic Improvement 5-ASA vs Placebo.

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

Comparison: 7 Dose of 5-ASA

Outcome: 2 Endoscopic Improvement 5-ASA vs Placebo

Study or subgroup	5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 0-1g 5-ASA vs Placebo					
Campieri 1990a	27/32	6/15		15.7 %	8.10 [1.98, 33.05]
Campieri 1991b	20/27	2/9		9.7 %	10.00 [1.67, 60.00]
Subtotal (95% CI)	**59**	**24**		**25.4 %**	**8.78 [2.90, 26.53]**
Total events: 47 (5-ASA), 8 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.03, df = 1 (P = 0.86); I² =0.0%					
Test for overall effect: Z = 3.85 (P = 0.00012)					
2 >1g-2g 5-ASA vs Placebo					
Campieri 1990a	26/31	6/16		16.0 %	8.67 [2.15, 34.90]
Campieri 1990b	25/32	7/30		21.9 %	11.73 [3.57, 38.61]
Campieri 1991a	17/18	2/14		4.9 %	102.00 [8.28, 1257.15]
Campieri 1991b	22/30	3/9		12.1 %	5.50 [1.11, 27.37]
Subtotal (95% CI)	**111**	**69**		**55.0 %**	**11.41 [4.73, 27.49]**
Total events: 90 (5-ASA), 18 (Placebo)					
Heterogeneity: Tau² = 0.19; Chi² = 3.88, df = 3 (P = 0.27); I² =23%					
Test for overall effect: Z = 5.42 (P < 0.00001)					
3 >2g-4g 5-ASA vs Placebo					
Campieri 1991b	23/29	3/9		11.4 %	7.67 [1.47, 39.99]
Moller 1978	14/16	3/14		8.1 %	25.67 [3.63, 181.44]
Subtotal (95% CI)	**45**	**23**		**19.5 %**	**12.68 [3.59, 44.78]**
Total events: 37 (5-ASA), 6 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.86, df = 1 (P = 0.35); I² =0.0%					
Test for overall effect: Z = 3.95 (P = 0.000080)					
Total (95% CI)	**215**	**116**		**100.0 %**	**10.70 [6.12, 18.69]**
Total events: 174 (5-ASA), 32 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 4.97, df = 7 (P = 0.66); I² =0.0%					
Test for overall effect: Z = 8.33 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours Placebo Favours Rectal 5-ASA

Analysis 7.3. Comparison 7 Dose of 5-ASA, Outcome 3 Histologic Improvement 5-ASA vs Placebo.

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

Comparison: 7 Dose of 5-ASA

Outcome: 3 Histologic Improvement 5-ASA vs Placebo

Study or subgroup	5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 0-1g 5-ASA vs Placebo					
Campieri 1990a	23/32	5/15		13.4 %	5.11 [1.36, 19.16]
Campieri 1991b	17/27	1/9		7.1 %	13.60 [1.48, 125.31]
Subtotal (95% CI)	**59**	**24**		**20.4 %**	**6.60 [2.12, 20.55]**
Total events: 40 (5-ASA), 6 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.56, df = 1 (P = 0.45); I² =0.0%					
Test for overall effect: Z = 3.26 (P = 0.0011)					
2 >1g-2g 5-ASA vs Placebo					
Campieri 1990a	23/31	5/16		13.3 %	6.33 [1.68, 23.88]
Campieri 1990b	21/32	4/30		13.8 %	12.41 [3.45, 44.66]
Campieri 1991a	15/18	1/14		6.4 %	65.00 [6.00, 703.67]
Campieri 1991b	21/30	1/9		7.1 %	18.67 [2.03, 171.99]
Pokrotnieks 2000	26/54	18/57		19.8 %	2.01 [0.93, 4.36]
Subtotal (95% CI)	**165**	**126**		**60.3 %**	**8.63 [2.70, 27.64]**
Total events: 106 (5-ASA), 29 (Placebo)					
Heterogeneity: Tau² = 1.14; Chi² = 13.27, df = 4 (P = 0.01); I² =70%					
Test for overall effect: Z = 3.63 (P = 0.00028)					
3 >2g-4g 5-ASA vs Placebo					
Campieri 1991b	22/29	2/9		9.5 %	11.00 [1.84, 65.68]
Palmer 1981	7/17	2/23		9.8 %	7.35 [1.29, 41.98]
Subtotal (95% CI)	**46**	**32**		**19.3 %**	**8.95 [2.57, 31.15]**
Total events: 29 (5-ASA), 4 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.10, df = 1 (P = 0.75); I² =0.0%					
Test for overall effect: Z = 3.44 (P = 0.00058)					
Total (95% CI)	**270**	**182**		**100.0 %**	**7.60 [3.81, 15.15]**
Total events: 175 (5-ASA), 39 (Placebo)					
Heterogeneity: Tau² = 0.47; Chi² = 14.79, df = 8 (P = 0.06); I² =46%					
Test for overall effect: Z = 5.77 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours Placebo Favours Rectal 5-ASA

Analysis 7.4. Comparison 7 Dose of 5-ASA, Outcome 4 Symptomatic Remission 5-ASA vs placebo.

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

Comparison: 7 Dose of 5-ASA

Outcome: 4 Symptomatic Remission 5-ASA vs placebo

Study or subgroup	5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 0-1g 5-ASA vs Placebo					
Campieri 1990a	22/32	6/15		9.9 %	3.30 [0.92, 11.81]
Campieri 1991b	17/27	1/9		4.2 %	13.60 [1.48, 125.31]
Hanauer 1998	34/73	3/23		9.7 %	5.81 [1.59, 21.28]
Subtotal (95% CI)	**132**	**47**		**23.8 %**	**5.13 [2.21, 11.91]**
Total events: 73 (5-ASA), 10 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 1.25, df = 2 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 3.81 (P = 0.00014)					
2 >1g-2g 5-ASA vs Placebo					
Campieri 1990a	23/31	6/16		9.7 %	4.79 [1.32, 17.46]
Campieri 1990b	18/32	2/30		7.2 %	18.00 [3.65, 88.76]
Campieri 1991a	12/18	1/14		4.1 %	26.00 [2.72, 248.59]
Campieri 1991b	20/30	1/9		4.2 %	16.00 [1.75, 146.31]
Hanauer 1998	35/71	3/23		9.7 %	6.48 [1.77, 23.77]
Pokrotnieks 2000	35/54	23/57		17.4 %	2.72 [1.26, 5.88]
Williams 1987	11/14	1/13		3.6 %	44.00 [3.97, 488.19]
Subtotal (95% CI)	**250**	**162**		**55.8 %**	**8.13 [3.73, 17.70]**
Total events: 154 (5-ASA), 37 (Placebo)					
Heterogeneity: Tau² = 0.47; Chi² = 11.12, df = 6 (P = 0.08); I² =46%					
Test for overall effect: Z = 5.28 (P < 0.00001)					
3 >2g-4g 5-ASA vs Placebo					
Campieri 1991b	21/29	1/9		4.1 %	21.00 [2.25, 195.82]
Hanauer 1998	32/73	4/24		11.1 %	3.90 [1.21, 12.56]
Moller 1978	13/16	2/14		5.2 %	26.00 [3.69, 183.42]
Subtotal (95% CI)	**118**	**47**		**20.4 %**	**10.07 [2.66, 38.18]**
Total events: 66 (5-ASA), 7 (Placebo)					
Heterogeneity: Tau² = 0.62; Chi² = 3.56, df = 2 (P = 0.17); I² =44%					
Test for overall effect: Z = 3.40 (P = 0.00068)					
Total (95% CI)	**500**	**256**		**100.0 %**	**6.98 [4.29, 11.38]**
Total events: 293 (5-ASA), 54 (Placebo)					
Heterogeneity: Tau² = 0.20; Chi² = 16.39, df = 12 (P = 0.17); I² =27%					
Test for overall effect: Z = 7.80 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours Placebo Favours Rectal 5-ASA

Analysis 7.5. Comparison 7 Dose of 5-ASA, Outcome 5 Endoscopic Remission 5-ASA vs Placebo.

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

Comparison: 7 Dose of 5-ASA

Outcome: 5 Endoscopic Remission 5-ASA vs Placebo

Study or subgroup	5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 0-1g 5-ASA vs Placebo					
Campieri 1990a	19/32	3/15		7.1 %	5.85 [1.37, 24.89]
Campieri 1991b	12/27	1/9		3.0 %	6.40 [0.70, 58.52]
Hanauer 1998	43/73	5/23		12.4 %	5.16 [1.73, 15.42]
Subtotal (95% CI)	**132**	**47**		**22.5 %**	**5.52 [2.45, 12.45]**
Total events: 74 (5-ASA), 9 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.04, df = 2 (P = 0.98); I² =0.0%					
Test for overall effect: Z = 4.12 (P = 0.000037)					
2 >1g-2g 5-ASA vs Placebo					
Campieri 1990a	17/31	4/16		8.4 %	3.64 [0.96, 13.84]
Campieri 1990b	13/32	2/30		5.8 %	9.58 [1.94, 47.38]
Campieri 1991a	10/18	0/14		1.7 %	35.82 [1.86, 691.79]
Campieri 1991b	13/30	1/9		3.1 %	6.12 [0.68, 55.25]
Hanauer 1998	46/71	6/23		13.5 %	5.21 [1.82, 14.90]
Pokrotnieks 2000	26/54	17/57		24.5 %	2.18 [1.00, 4.76]
Subtotal (95% CI)	**236**	**149**		**56.9 %**	**4.22 [2.31, 7.69]**
Total events: 125 (5-ASA), 30 (Placebo)					
Heterogeneity: Tau² = 0.10; Chi² = 6.09, df = 5 (P = 0.30); I² =18%					
Test for overall effect: Z = 4.69 (P < 0.000001)					
3 >2g-4g 5-ASA vs Placebo					
Campieri 1991b	15/29	0/9		1.7 %	20.31 [1.08, 381.35]
Hanauer 1998	48/73	6/24		13.7 %	5.76 [2.03, 16.34]
Moller 1978	12/16	3/14		5.1 %	11.00 [2.00, 60.57]
Subtotal (95% CI)	**118**	**47**		**20.5 %**	**7.53 [3.21, 17.63]**
Total events: 75 (5-ASA), 9 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 0.90, df = 2 (P = 0.64); I² =0.0%					
Test for overall effect: Z = 4.65 (P < 0.000001)					
Total (95% CI)	**486**	**243**		**100.0 %**	**4.80 [3.27, 7.07]**
Total events: 274 (5-ASA), 48 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 8.86, df = 11 (P = 0.63); I² =0.0%					
Test for overall effect: Z = 7.98 (P < 0.00001)					

0.1 0.2 0.5 1 2 5 10

Favours Placebo Favours Rectal 5-ASA

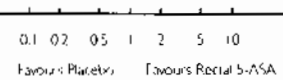
Analysis 7.6. Comparison 7 Dose of 5-ASA, Outcome 6 Histologic Remission 5-ASA vs Placebo.

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

Comparison: 7 Dose of 5-ASA

Outcome: 6 Histologic Remission 5-ASA vs Placebo

Study or subgroup	5-ASA n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 0-1g 5-ASA vs Placebo					
Campieri 1990a	5/32	1/15		6.4 %	2.59 [0.28, 24.40]
Campieri 1991b	10/27	0/9		3.7 %	11.40 [0.60, 216.71]
Hanauer 1998	31/73	3/23		19.0 %	4.92 [1.34, 18.04]
Subtotal (95% CI)	**132**	**47**		**29.1 %**	**4.76 [1.66, 13.60]**
Total events: 46 (5-ASA), 4 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.63, df = 2 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 2.91 (P = 0.0036)					
2 >1g-2g 5-ASA vs Placebo					
Campieri 1990a	3/31	1/16		5.8 %	1.61 [0.15, 16.83]
Campieri 1990b	9/32	1/30		7.0 %	11.35 [1.34, 96.18]
Campieri 1991a	9/18	0/14		3.7 %	29.00 [1.50, 559.17]
Campieri 1991b	13/30	0/9		3.7 %	14.66 [0.78, 274.80]
Hanauer 1998	35/71	4/23		23.3 %	4.62 [1.43, 14.94]
Subtotal (95% CI)	**182**	**92**		**43.6 %**	**5.98 [2.53, 14.11]**
Total events: 69 (5-ASA), 6 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.28, df = 4 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 4.08 (P = 0.000045)					
3 >2g-4g 5-ASA vs Placebo					
Campieri 1991b	12/29	0/9		3.7 %	13.57 [0.72, 255.43]
Hanauer 1998	40/73	4/24		23.5 %	6.06 [1.88, 19.49]
Subtotal (95% CI)	**102**	**33**		**27.3 %**	**6.77 [2.29, 20.04]**
Total events: 52 (5-ASA), 4 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 3.45 (P = 0.00056)					
Total (95% CI)	**416**	**172**		**100.0 %**	**5.78 [3.28, 10.20]**
Total events: 167 (5-ASA), 14 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.36, df = 9 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 6.07 (P < 0.00001)					



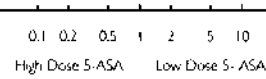
Analysis 7.7. Comparison 7 Dose of 5-ASA, Outcome 7 Symptomatic Improvement Comparison of Dose of 5-ASA.

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

Comparison: 7 Dose of 5-ASA

Outcome: 7 Symptomatic Improvement Comparison of Dose of 5-ASA

Study or subgroup	Low Dose 5-ASA n/N	High Dose 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 1g 5-ASA Vs 2g 5-ASA					
Campieri 1991b	23/27	12/15		5.2 %	1.44 [0.28, 7.50]
Hanauer 1998	49/73	23/35		17.7 %	1.07 [0.45, 2.50]
Subtotal (95% CI)	**100**	**50**		**22.9 %**	**1.13 [0.53, 2.42]**
Total events: 72 (Low Dose 5-ASA), 35 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 2g 5-ASA vs 4g 5-ASA					
Campieri 1991b	13/15	25/29		4.3 %	1.04 [0.17, 6.45]
Campieri 1993	102/117	98/116		22.5 %	1.25 [0.60, 2.62]
Hanauer 1998	23/36	55/73		17.3 %	0.58 [0.24, 1.37]
Malchow 2002	93/133	110/133		33.0 %	0.49 [0.27, 0.87]
Subtotal (95% CI)	**301**	**351**		**77.1 %**	**0.71 [0.43, 1.16]**
Total events: 231 (Low Dose 5-ASA), 288 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 4.21, df = 3 (P = 0.24); I^2 =29%					
Test for overall effect: Z = 1.37 (P = 0.17)					
Total (95% CI)	**401**	**401**		**100.0 %**	**0.78 [0.53, 1.14]**
Total events: 303 (Low Dose 5-ASA), 323 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 5.67, df = 5 (P = 0.34); I^2 =12%					
Test for overall effect: Z = 1.28 (P = 0.20)					



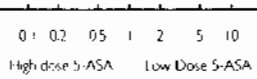
Analysis 7.8. Comparison 7 Dose of 5-ASA, Outcome 8 Endoscopic Improvement Comparison of Dose of 5-ASA.

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

Comparison: 7 Dose of 5-ASA

Outcome: 8 Endoscopic Improvement Comparison of Dose of 5-ASA

Study or subgroup	Low Dose 5-ASA n/N	High Dose 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 1g 5-ASA Vs 2g 5-ASA					
Campieri 1991b	20/27	11/15		12.5 %	1.04 [0.25, 4.35]
Subtotal (95% CI)	**27**	**15**		**12.5 %**	**1.04 [0.25, 4.35]**
Total events: 20 (Low Dose 5-ASA), 11 (High Dose 5-ASA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.05 (P = 0.96)					
2 2g 5-ASA vs 4g 5-ASA					
Campieri 1991b	11/15	23/29		12.1 %	0.72 [0.17, 3.07]
Campieri 1993	86/117	86/116		75.3 %	0.97 [0.54, 1.74]
Subtotal (95% CI)	**132**	**145**		**87.5 %**	**0.93 [0.54, 1.60]**
Total events: 97 (Low Dose 5-ASA), 109 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.27 (P = 0.79)					
Total (95% CI)	**159**	**160**		**100.0 %**	**0.94 [0.57, 1.56]**
Total events: 117 (Low Dose 5-ASA), 120 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.16, df = 2 (P = 0.92), I^2 =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					



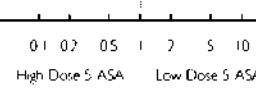
Analysis 7.9. Comparison 7 Dose of 5-ASA, Outcome 9 Histologic Improvement Comparison of Dose of 5-ASA.

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

Comparison: 7 Dose of 5-ASA

Outcome: 9 Histologic Improvement Comparison of Dose of 5-ASA

Study or subgroup	Low Dose 5-ASA n/N	High Dose 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 1g 5-ASA Vs 2g 5-ASA					
Campieri 1991b	17/27	10/15		12.6 %	0.85 [0.23, 3.21]
Subtotal (95% CI)	**27**	**15**		**12.6 %**	**0.85 [0.23, 3.21]**
Total events: 17 (Low Dose 5-ASA), 10 (High Dose 5-ASA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.24 (P = 0.81)					
2 2g 5-ASA vs 4g 5-ASA					
Campieri 1991b	11/15	22/29		10.9 %	0.88 [0.21, 3.64]
Campieri 1993	72/117	79/116		76.4 %	0.75 [0.44, 1.29]
Subtotal (95% CI)	**132**	**145**		**87.4 %**	**0.76 [0.46, 1.27]**
Total events: 83 (Low Dose 5-ASA), 101 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 1.05 (P = 0.30)					
Total (95% CI)	**159**	**160**		**100.0 %**	**0.77 [0.48, 1.24]**
Total events: 100 (Low Dose 5-ASA), 111 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.0, Chi^2 = 0.06, df = 2 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 1.06 (P = 0.29)					



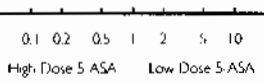
Analysis 7.10. Comparison 7 Dose of 5-ASA, Outcome 10 Symptomatic Remission Comparison of Dose of 5-ASA.

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

Comparison: 7 Dose of 5-ASA

Outcome: 10 Symptomatic Remission Comparison of Dose of 5-ASA

Study or subgroup	Low Dose 5-ASA n/N	High Dose 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 1g 5-ASA Vs 2g 5-ASA					
Campieri 1991a	17/27	10/15		11.7 %	0.85 [0.23, 3.21]
Hanauer 1998	34/73	17/35		15.8 %	0.92 [0.41, 2.07]
Powell-Tuck 1986	7/12	4/13		9.6 %	3.15 [0.61, 16.31]
Subtotal (95% CI)	**112**	**63**		**37.0 %**	**1.09 [0.58, 2.06]**
Total events: 58 (Low Dose 5-ASA), 31 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.90, df = 2 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 0.26 (P = 0.79)					
2 2g 5-ASA vs 4g 5-ASA					
Campieri 1991b	10/15	21/29		11.5 %	0.76 [0.20, 2.93]
Campieri 1993	92/117	19/116		17.5 %	5.03 [2.83, 8.95]
Hanauer 1998	18/36	32/73		15.8 %	1.28 [0.58, 2.85]
Malchow 2002	72/133	82/133		18.1 %	0.73 [0.45, 1.20]
Subtotal (95% CI)	**301**	**351**		**63.0 %**	**1.43 [0.50, 4.13]**
Total events: 192 (Low Dose 5-ASA), 184 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.99; Chi^2 = 26.35, df = 3 (P<0.00001); I^2 =89%					
Test for overall effect: Z = 0.67 (P = 0.50)					
Total (95% CI)	**413**	**414**		**100.0 %**	**1.37 [0.67, 2.78]**
Total events: 250 (Low Dose 5-ASA), 215 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.66; Chi^2 = 29.05, df = 6 (P = 0.00006); I^2 =79%					
Test for overall effect: Z = 0.87 (P = 0.39)					



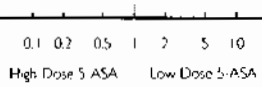
Analysis 7.11. Comparison 7 Dose of 5-ASA, Outcome 11 Endoscopic Remission Comparison of Dose of 5-ASA.

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

Comparison: 7 Dose of 5-ASA

Outcome: 11 Endoscopic Remission Comparison of Dose of 5-ASA

Study or subgroup	Low Dose 5-ASA n/N	High Dose 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 1g 5-ASA Vs 2g 5-ASA					
Campieri 1991b	12/27	6/15		9.7 %	1.20 [0.33, 4.32]
Hanauer 1998	43/73	23/35		15.5 %	0.75 [0.32, 1.73]
Powell-Tuck 1986	9/12	6/13		6.4 %	3.50 [0.64, 19.19]
Subtotal (95% CI)	**112**	**63**		**31.6 %**	**1.14 [0.52, 2.48]**
Total events: 64 (Low Dose 5-ASA), 35 (High Dose 5-ASA)					
Heterogeneity: Tau² = 0.12; Chi² = 2.59, df = 2 (P = 0.27); I² =23%					
Test for overall effect: Z = 0.32 (P = 0.75)					
2 2g 5-ASA vs 4g 5-ASA					
Campieri 1991b	7/15	15/29		10.0 %	0.82 [0.23, 2.85]
Campieri 1993	71/117	42/116		21.4 %	2.72 [1.60, 4.62]
Hanauer 1998	23/36	48/73		15.6 %	0.92 [0.40, 2.12]
Malchow 2002	37/133	40/133		21.4 %	0.90 [0.53, 1.52]
Subtotal (95% CI)	**301**	**351**		**68.4 %**	**1.24 [0.64, 2.42]**
Total events: 138 (Low Dose 5-ASA), 145 (High Dose 5-ASA)					
Heterogeneity: Tau² = 0.31; Chi² = 10.42, df = 3 (P = 0.02); I² =71%					
Test for overall effect: Z = 0.63 (P = 0.53)					
Total (95% CI)	**413**	**414**		**100.0 %**	**1.23 [0.76, 2.01]**
Total events: 202 (Low Dose 5-ASA), 180 (High Dose 5-ASA)					
Heterogeneity: Tau² = 0.22; Chi² = 13.51, df = 6 (P = 0.04); I² =56%					
Test for overall effect: Z = 0.84 (P = 0.40)					



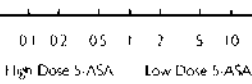
Analysis 7.12. Comparison 7 Dose of 5-ASA, Outcome 12 Histologic Remission Comparison of Dose of 5-ASA.

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

Comparison: 7 Dose of 5-ASA

Outcome: 12 Histologic Remission Comparison of Dose of 5-ASA

Study or subgroup	Low Dose 5-ASA n/N	High Dose 5-ASA n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 1g 5-ASA Vs 2g 5-ASA					
Campieri 1991b	10/27	6/15		9.0 %	0.88 [0.24, 3.22]
Hanauer 1998	31/73	17/35		15.9 %	0.78 [0.35, 1.76]
Powell-Tuck 1986	9/12	4/13		5.7 %	6.75 [1.16, 39.20]
Subtotal (95% CI)	**112**	**63**		**30.5 %**	**1.36 [0.44, 4.16]**
Total events: 50 (Low Dose 5-ASA), 27 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.58; Chi^2 = 4.89, df = 2 (P = 0.09); I^2 =59%					
Test for overall effect: Z = 0.53 (P = 0.60)					
2 2g 5-ASA vs 4g 5-ASA					
Campieri 1991b	7/15	12/29		9.4 %	1.24 [0.35, 4.35]
Campieri 1993	47/117	28/116		21.1 %	2.11 [1.20, 3.71]
Hanauer 1998	18/36	40/73		16.0 %	0.83 [0.37, 1.84]
Malchow 2002	51/133	59/133		22.9 %	0.78 [0.48, 1.27]
Subtotal (95% CI)	**301**	**351**		**69.5 %**	**1.14 [0.65, 1.99]**
Total events: 123 (Low Dose 5-ASA), 139 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.19; Chi^2 = 7.54, df = 3 (P = 0.06); I^2 =60%					
Test for overall effect: Z = 0.46 (P = 0.65)					
Total (95% CI)	**413**	**414**		**100.0 %**	**1.16 [0.73, 1.84]**
Total events: 173 (Low Dose 5-ASA), 166 (High Dose 5-ASA)					
Heterogeneity: Tau^2 = 0.18; Chi^2 = 12.44, df = 6 (P = 0.05), I^2 =52%					
Test for overall effect: Z = 0.63 (P = 0.53)					



Analysis 8.1. Comparison 8 Drug formulation, Outcome 1 Symptomatic Improvement 5-ASA foam vs Enema.

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

Comparison: 8 Drug formulation

Outcome: 1 Symptomatic Improvement 5-ASA foam vs Enema

Study or subgroup	5-ASA Enema n/N	5-ASA Foam n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Biancone 2007	22/22	17/20		6.7 %	9.00 [0.44, 185.96]
Campieri 1993	93/110	107/123		33.0 %	0.82 [0.39, 1.71]
Gionchetti 1999	46/50	37/53		23.8 %	4.97 [1.53, 16.15]
Malchow 2002	110/133	93/133		36.4 %	2.06 [1.15, 3.68]
Total (95% CI)	**315**	**329**		**100.0 %**	**2.07 [0.88, 4.84]**
Total events: 271 (5-ASA Enema), 254 (5-ASA Foam)					
Heterogeneity: Tau^2 = 0.43; Chi^2 = 8.56, df = 3 (P = 0.04); I^2 =65%					
Test for overall effect: Z = 1.67 (P = 0.095)					

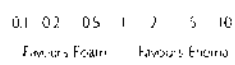
Analysis 8.2. Comparison 8 Drug formulation, Outcome 2 Endoscopic Improvement 5-ASA Foam vs Enema.

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

Comparison: 8 Drug formulation

Outcome: 2 Endoscopic Improvement 5-ASA Foam vs Enema

Study or subgroup	5-ASA Enema n/N	5-ASA Foam n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1993	80/110	92/123		56.0 %	0.90 [0.50, 1.61]
Gionchetti 1999	43/50	36/53		44.0 %	2.90 [1.08, 7.77]
Total (95% CI)	**160**	**176**		**100.0 %**	**1.51 [0.48, 4.71]**
Total events: 123 (5-ASA Enema), 128 (5-ASA Foam)					
Heterogeneity: Tau^2 = 0.52; Chi^2 = 4.02, df = 1 (P = 0.04); I^2 =75%					
Test for overall effect: Z = 0.70 (P = 0.48)					



Analysis 8.3. Comparison 8 Drug formulation, Outcome 3 Histologic Improvement 5-ASA Foam vs Enema.

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

Comparison: 8 Drug formulation

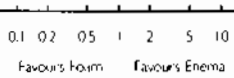
Outcome: 3 Histologic Improvement 5-ASA Foam vs Enema

Study or subgroup	5-ASA Enema n/N	5-ASA Foam n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1993	73/123	78/110		67.8 %	0.60 [0.35, 1.03]
Gionchetti 1999	30/53	32/50		32.2 %	0.73 [0.33, 1.62]
Total (95% CI)	**176**	**160**		**100.0 %**	**0.64 [0.41, 1.00]**

Total events: 103 (5-ASA Enema), 110 (5-ASA Foam)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.17$, df = 1 (P = 0.68); $I^2 = 0.0\%$

Test for overall effect: Z = 1.95 (P = 0.051)



Analysis 8.4. Comparison 8 Drug formulation, Outcome 4 Symptomatic Remission 5-ASA Foam vs Enema.

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

Comparison: 8 Drug formulation

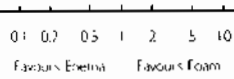
Outcome: 4 Symptomatic Remission 5-ASA Foam vs Enema

Study or subgroup	5-ASA Foam n/N	5-ASA Enema n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Ardizzone 1999	55/97	74/98		19.8 %	0.42 [0.23, 0.78]
Campieri 1993	90/123	51/110		20.4 %	3.16 [1.83, 5.45]
Cortot 2008	126/191	126/184		21.5 %	0.89 [0.58, 1.37]
Gionchetti 1999	29/53	37/50		17.4 %	0.42 [0.18, 0.98]
Malchow 2002	72/133	82/133		21.0 %	0.73 [0.45, 1.20]
Total (95% CI)	**597**	**575**		**100.0 %**	**0.84 [0.43, 1.66]**

Total events: 372 (5-ASA Foam), 370 (5-ASA Enema)

Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 29.79$, df = 4 (P<0.00001); $I^2 = 87\%$

Test for overall effect: Z = 0.50 (P = 0.62)



Analysis 8.5. Comparison 8 Drug formulation, Outcome 5 Endoscopic Remission 5-ASA Enema vs 5-ASA Foam.

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

Comparison: 8 Drug formulation

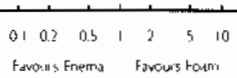
Outcome: 5 Endoscopic Remission 5-ASA Enema vs 5-ASA Foam

Study or subgroup	5-ASA Foam n/N	5-ASA Enema n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Ardizzone 1999	51/97	67/98		18.7 %	0.51 [0.29, 0.92]
Campieri 1993	64/123	49/110		21.7 %	1.35 [0.81, 2.26]
Cortot 2008	121/191	130/184		26.1 %	0.72 [0.47, 1.11]
Gionchetti 1999	22/53	25/50		12.5 %	0.71 [0.33, 1.55]
Malchow 2002	37/133	40/133		21.0 %	0.90 [0.53, 1.52]
Total (95% CI)	**597**	**575**		**100.0 %**	**0.81 [0.59, 1.11]**

Total events: 295 (5-ASA Foam), 311 (5-ASA Enema)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 6.67$, df = 4 (P = 0.15); $I^2 = 40\%$

Test for overall effect: Z = 1.31 (P = 0.19)



Analysis 8.6. Comparison 8 Drug formulation, Outcome 6 Histologic Remission 5-ASA Enema vs 5-ASA Foam.

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

Comparison: 8 Drug formulation

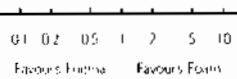
Outcome: 6 Histologic Remission 5-ASA Enema vs 5-ASA Foam

Study or subgroup	5-ASA Foam n/N	5-ASA Enema n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Campieri 1993	42/123	33/110		37.9 %	1.21 [0.70, 2.10]
Gionchetti 1999	12/53	12/50		13.8 %	0.93 [0.37, 2.31]
Malchow 2002	51/133	59/133		48.3 %	0.78 [0.48, 1.27]
Total (95% CI)	**309**	**293**		**100.0 %**	**0.94 [0.67, 1.33]**

Total events: 105 (5-ASA Foam), 104 (5-ASA Enema)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.36$, df = 2 (P = 0.51); $I^2 = 0.0\%$

Test for overall effect: Z = 0.34 (P = 0.74)



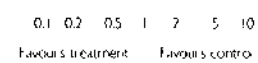
Analysis 8.7. Comparison 8 Drug formulation, Outcome 7 Symptomatic Improvement 5-ASA enema vs Suppository.

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

Comparison: 8 Drug formulation

Outcome: 7 Symptomatic Improvement 5-ASA enema vs Suppository

Study or subgroup	Enema n/N	Suppository n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Campieri 1988	18/20	17/20		100.0 %	1.59 [0.24, 10.70]
Total (95% CI)	**20**	**20**		**100.0 %**	**1.59 [0.24, 10.70]**
Total events: 18 (Enema), 17 (Suppository)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.48 (P = 0.63)					



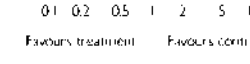
Analysis 8.8. Comparison 8 Drug formulation, Outcome 8 Endoscopic Improvement 5-ASA Enema vsSuppository.

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

Comparison: 8 Drug formulation

Outcome: 8 Endoscopic Improvement 5-ASA Enema vsSuppository

Study or subgroup	Enema n/N	Suppository n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Campieri 1988	17/30	17/19		100.0 %	0.15 [0.03, 0.79]
Total (95% CI)	**30**	**19**		**100.0 %**	**0.15 [0.03, 0.79]**
Total events: 17 (Enema), 17 (Suppository)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.25 (P = 0.025)					



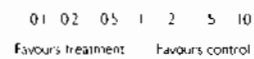
Analysis 8.9. Comparison 8 Drug formulation, Outcome 9 Histological Improvement 5-ASA enema vs Suppository.

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

Comparison: 8 Drug formulation

Outcome: 9 Histological Improvement 5-ASA enema vs Suppository

Study or subgroup	Enema n/N	Suppository n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Campieri 1988	16/20	16/19		100.0 %	0.75 [0.14, 3.90]
Total (95% CI)	**20**	**19**		**100.0 %**	**0.75 [0.14, 3.90]**
Total events: 16 (Enema), 16 (Suppository)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.73)					



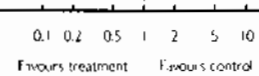
Analysis 8.10. Comparison 8 Drug formulation, Outcome 10 Symptomatic Remission 5-ASA enema vs Suppository.

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

Comparison: 8 Drug formulation

Outcome: 10 Symptomatic Remission 5-ASA enema vs Suppository

Study or subgroup	Enema n/N	Suppository n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Campieri 1988	16/20	15/19		100.0 %	1.07 [0.23, 5.05]
Total (95% CI)	**20**	**19**		**100.0 %**	**1.07 [0.23, 5.05]**
Total events: 16 (Enema), 15 (Suppository)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.94)					



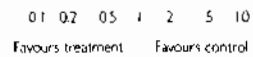
Analysis 8.11. Comparison 8 Drug formulation, Outcome 11 Endoscopic Remission 5-ASA enema vs Suppository.

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

Comparison: 8 Drug formulation

Outcome: 11 Endoscopic Remission 5-ASA enema vs Suppository

Study or subgroup	Enema n/N	Suppository n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Campieri 1988	13/20	14/19		100.0 %	0.66 [0.17, 2.62]
Total (95% CI)	**20**	**19**		**100.0 %**	**0.66 [0.17, 2.62]**
Total events: 13 (Enema), 14 (Suppository)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.56)					



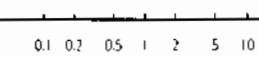
Analysis 8.12. Comparison 8 Drug formulation, Outcome 12 Histologic Remission 5-ASA enema vs Suppository.

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

Comparison: 8 Drug formulation

Outcome: 12 Histologic Remission 5-ASA enema vs Suppository

Study or subgroup	Enema n/N	Suppository n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Campieri 1988	9/20	12/19		100.0 %	0.48 [0.13, 1.72]
Total (95% CI)	**20**	**19**		**100.0 %**	**0.48 [0.13, 1.72]**
Total events: 9 (Enema), 12 (Suppository)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.13 (P = 0.26)					



WHAT'S NEW

Last assessed as up-to-date: 8 October 2008.

2 November 2009	New citation required and conclusions have changed	Substantive amendment

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 1, 2010

DECLARATIONS OF INTEREST

None known.