The Efficacy of Oral 5-ASAs in the Treatment of Active Ulcerative Colitis: A Systematic Review

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The authors set out to critically review the current data on the efficacy of oral 5-aminosalicylic acid (5-ASA) agents for active ulcerative colitis (UC). Thirty-one studies were identified; 19 met entry criteria. Three trials with mesalamine showed statistical significance versus placebo; those with olsalazine or balsalazide did not. No agent was statistically different from sulfasalazine. In 2 of 3 trials of balsalazide versus mesalamine, results for defined primary and secondary endpoints failed to demonstrate statistically significant differences. Studies suggest that mesalamine is superior to placebo for treating active UC. Five-ASA products appear to be as effective as sulfasalazine, but available data do not suggest a difference in efficacy between any of the 5-ASA preparations. [Rev Gastroenterol Disord. 2003;3(4):210-218]

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Key words: 5-aminosalicylate • Mesalamine • Mesalazine • Ulcerative colitis

Ulcerative colitis (UC) is a chronic relapsing and remitting inflammatory disease of the colonic mucosa. The pathophysiology of this disorder is multifactorial and incompletely understood. It appears that the disease results from inappropriate activation of the mucosal immune system, resulting in the inflammatory response. Pharmacologic therapy for UC focuses on controlling this immune response, either with systemic agents, such as corticosteroi...
topical anti-inflammatories. Sulfasalazine has been a major agent in the therapy of mild to moderate UC for more than 50 years. In 1977, Azad Khan determined that 5-aminosalicylic acid (5-ASA) mesalamine was the therapeutically active compound in sulfasalazine. The knowledge that the sulfapyridine moiety was not required for clinical efficacy allowed the development of other 5-ASA compounds with the aim of maintaining efficacy, but avoiding the common side effects associated with sulfapyridine.

The exact mechanism of action of 5-ASA agents remains unknown but is thought to be related to a topical action on the GI mucosa rather than a systemic action. The clinical efficacy of oral 5-ASA compounds depends upon delivery of the intact molecule to the colonic mucosa without breakdown by the digestive process. In the case of sulfasalazine, the parent drug is delivered to the colon intact, where colonic bacteria cleave sulfapyridine from the 5-ASA, allowing for delivery of 5-ASA to the colonic mucosa. Newer preparations of 5-ASA, which are commercially available, differ in their mode of delivery throughout the small intestine and colon. Two forms of mesalamine exist that are not in the form of a pro-drug. One is a delayed-release form (Asacol, Procter and Gamble Pharmaceuticals, Cincinnati, OH) of 5-ASA in a tablet that is coated with an acrylic-based resin (Eudragit S) that dissolves at a pH ≥ 7, delivering the drug to the distal ileum and colon. The second is a controlled-release form (Pentasa, Shire US Inc, Somerville, NJ) of 5-ASA in microgranules that are coated with a semipermeable ethylcellulose membrane, allowing for a slow release of 5-ASA throughout the GI tract. Conjugation of two 5-ASA molecules with an azo bond delivered in a manner similar to that of sulfasalazine has been used to produce olsalazine (Dipentum, Celltech Pharmaceuticals, Inc., Rochester, NY). The most recently developed drug in this class is balsalazide (Colazal, Salix Pharmaceuticals, Raleigh, NC), a compound in which 5-ASA is conjugated to an inert carrier molecule (4-aminobenzoyl-ß-alanine) via an azo bond and is released by bacterial action in a manner similar to that of sulfasalazine.

Prior meta-analyses and systematic reviews of 5-ASA compounds have suggested that these drugs are more efficacious than placebo in the treatment of mild to moderately active UC and have an efficacy similar to that of sulfasalazine. Few data reviews including balsalazide (a compound only recently approved for use in the United States) have been published subsequent to these analyses. The most recent systematic review included one paper on balsalazide and concluded that: “The efficacy of 5-ASA in UC depending on the drug formulation is still unclear....” Nevertheless, the question of relative efficacy of balsalazide and mesalamine delivered in a pH-dependent release form has recently been raised in the literature. Our purpose in this article is to critically review the data on the efficacy of 5-ASAs and determine if any agent is superior in achieving clinical improvement or remission in patients with mild to moderate active UC.

Search Method

We elected to review the data comparing all 5-ASA agents to placebo, to sulfasalazine, and to other 5-ASA products for mild to moderate active UC. Separate MEDLINE and EMBASE searches of all articles (English and non-English language) from 1980-2002 were performed with different combinations of the following search terms: ulcerative colitis, 5-aminosalicylate, mesalamine, mesalazine, therapy, clinical trial, balsalazide, olsalazine, and randomized. The bibliographies of all studies that focused primarily on induction of remission were manually searched, as were the proceedings from the annual meetings of the American Gastroenterological Association and the American College of Gastroenterology from 1991-2002. Care was taken to exclude abstracts that were subsequently published in
full manuscript form. Multiple inflammatory bowel disease investigators and the manufacturers of all of the oral 5-ASA compounds available in the United States were contacted to identify any additional unpublished trials that compared 5-ASA with sulfasalazine, placebo, or other 5-ASA products.

**Study Selection Criteria**

Two investigators independently reviewed the titles and abstracts of all citations identified by the literature search. Both investigators independently retrieved and reviewed the manuscripts of potentially relevant studies and applied detailed selection criteria:

(a) randomized trials with a parallel group design;
(b) study population of adults with mild or moderate active UC;
(c) comparison of an oral 5-ASA (eg, mesalamine, balsalazide, or olsalazine) to placebo, sulfasalazine, or other 5-ASA products; and

(d) evaluation of clinical improvement or remission.

Studies on rectal preparations, combination therapies, maintenance of remission, or therapy of Crohn’s disease were excluded. The methodological quality and the results of each study were independently abstracted using a form that was developed by the investigators. Quality assessment was performed using standard criteria defined by Guyatt and colleagues. Results are reported according to the a priori definition of the primary endpoint described in the study. Post hoc and secondary analyses were noted as such and were not reported in the table. Disagreements were resolved by discussion and consensus.

**Results**

The initial literature search identified 31 potential studies for evaluation. Eighteen studies met the above criteria and were included in the review: seven comparing 5-ASA to placebo, seven comparing 5-ASA to sulfasalazine, and four comparing different 5-ASA preparations to each other. Discussions with Salix Pharmaceuticals led to the discovery of an unpublished trial of balsalazide versus placebo; thus the total number of studies included was nineteen. The methodological characteristics of each study are listed in Table 1.

**Delayed-release Mesalazine versus Placebo**

Both studies comparing delayed-release mesalazine to placebo in the treatment of active UC showed a significant benefit with the former. In a trial by Schroeder and colleagues, 87 patients with mild to moderate active UC were randomized to receive mesalamine 2.4 g/d (n = 38), 1.6 g/d (n = 53) or placebo (n = 52) for 6 weeks. The primary endpoint was clinical response at 6 weeks.

Both studies comparing delayed-release mesalazine to placebo in the treatment of active UC showed a significant benefit with the former.

Take placebo (24% vs 5%, \( P = .047 \)) as well as a higher partial response (50% vs 13%, \( P \) value not given). Those receiving mesalamine 4.8 g/d had a higher overall clinical response rate compared to those taking placebo (74% vs 18%, \( P < .001 \)). The absolute benefit increase (ABI) based on overall response for mesalamine 4.8 g/d over placebo was 56% with a number needed to treat (NNT) of two.

At a dose of 1.6 g/d, the overall clinical response rate was higher than that of placebo (27% vs 18%, \( P \) value not given); however, there was insufficient enrollment in the 1.6 g/d group to conclusively evaluate the efficacy at this dosage level. In the second trial, 158 patients were randomized to receive mesalamine 2.4 g/d (n = 53), 1.6 g/d (n = 53) or placebo (n = 52) for 6 weeks. The primary endpoint was clinical response at 6 weeks.
Table 1
Studies Fulfilling Entry Criteria

<table>
<thead>
<tr>
<th>Primary Author</th>
<th>Reference</th>
<th>Blinded</th>
<th>Concealed Allocation</th>
<th>ITT</th>
<th>Adequate Follow-Up</th>
<th>Comparisons</th>
<th>No. Patients</th>
<th>Duration (weeks)</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Withdrawals for Treatment Failure</th>
<th>Comments</th>
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<tr>
<td>Schroeder</td>
<td>N Engl J Med 1987;317:1625</td>
<td>Yes</td>
<td>No stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Mesalamine 1.6 g, 4.8 g, and placebo</td>
<td>87</td>
<td>6</td>
<td>Pre-defined clinical activity score</td>
<td>Greater complete and partial response w/ 4.8 g than placebo. No difference between 1.6 g and placebo, but study underpowered</td>
<td>3% with 4.8 g, 18% with 1.6 g, 34% with placebo</td>
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<tr>
<td>Satsky</td>
<td>Ann Intern Med 1991;115:350</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mesalamine 1.6 g, 2.4 g, and placebo</td>
<td>158</td>
<td>6</td>
<td>Pre-defined clinical criteria</td>
<td>Greater number of patients in remission of improved with both doses of mesalamine compared to placebo. No difference between mesalamine doses</td>
<td>7% with 2.4 g, 9% w/1.6 g, 34% w/placebo</td>
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<td>Hanauer</td>
<td>Am J Gastroenterol 1993;88:1088-1097</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mesalamine 1 g, 2 g, 4 g, and placebo</td>
<td>274</td>
<td>8</td>
<td>Remission by PICA, sigmoidoscopy, histology</td>
<td>2-4 g mesalamine was significantly better for induction of remission by strict criteria as compared to placebo. No difference between mesalamine doses</td>
<td>23% w/3 g, 16% w/2.4 g, 13% w/4 g, 30% w/placebo</td>
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<tr>
<td>Betzel</td>
<td>Scand J Gastroenterol 1988;23:61-69</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Olsalazine 1 g bid and placebo</td>
<td>30</td>
<td>6</td>
<td>Improvement by clinical parameters</td>
<td>&quot;Good&quot; clinical response was reported in 6 patients on olsalazine and 2 on placebo</td>
<td>13% w/olsalazine, 25% w/placebo</td>
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<td>Feurle</td>
<td>Gut 1989;30:1354-1361</td>
<td>Yes</td>
<td>No stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Mesalamine 2 g, 4 g, and sulfasalazine 1 g</td>
<td>105</td>
<td>4</td>
<td>Clinical improvement in 3 of 4 clinical parameters</td>
<td>A statistical difference in endoscopic findings, but no differences in other factors was found</td>
<td>12% w/olsalazine, 9% w/placebo</td>
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<td>Meyers</td>
<td>Gastroenterology 1987;93:1255-1262</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Olsalazine 0.75 g, 1.5 g, 3 g, or placebo</td>
<td>66</td>
<td>8</td>
<td>Improvement by clinical parameters</td>
<td>35% of ulcer patients improved vs 16% placebo patients. A dose-response was demonstrated at P = .04</td>
<td>4% w/olsalazine, 10% w/placebo</td>
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<td>Zinsstag</td>
<td>Am J Gastroenterol 1990;85:562-566</td>
<td>Yes</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Mesalamine 750 mg qid and placebo</td>
<td>15</td>
<td>4</td>
<td>Induction of remission by endoscopic and symptoms</td>
<td>4/7 of ulcer patients improved vs none in the placebo group</td>
<td>28% w/olsalazine, 50% w/placebo</td>
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<td>Riley</td>
<td>Gut 1988;29:669</td>
<td>Yes</td>
<td>No stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Mesalamine 2.4 g, 4.8 g, and sulfasalazine 1 g</td>
<td>60</td>
<td>4</td>
<td>Remission, bleeding, stool frequency</td>
<td>2.4 g mesalamine had greater remission, improvement in bleeding and reduced stool frequency than sulfasalazine. No difference between low-dose mesalamine and sulfasalazine</td>
<td>10% w/2.4 g mesalamine, 0% w/0.8 g mesalamine, 10% w/sulfasalazine</td>
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<td>Rachmilewitz</td>
<td>BMJ 1989;298:82-86</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Mesalamine 1.5 g and sulfasalazine 3 g</td>
<td>220</td>
<td>8</td>
<td>Remission by improvement of disease activity index</td>
<td>4.9% of mesalamine patients vs 36% of sulfasalazine patients achieved primary endpoint</td>
<td>24% w/olsalazine, 27% w/sulfasalazine</td>
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<td>Munakata</td>
<td>J Gastroenterol 1999;30:168-171</td>
<td>Yes</td>
<td>Not stated</td>
<td>No</td>
<td>No</td>
<td>Mesalamine 1.5 g and sulfasalazine 3 g</td>
<td>118</td>
<td>4</td>
<td>Improvement by clinical parameters</td>
<td>No difference in improvement and endoscopic findings between the groups</td>
<td>12% w/mesalamine, 3% w/sulfasalazine</td>
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<td>Mausfeld</td>
<td>Aliments Pharmacol Ther 2002;16:69</td>
<td>Yes</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Balsalazide 6.75 g, sulfasalazine 3 g</td>
<td>50</td>
<td>8</td>
<td>Symptom response, sigmoidoscopy, histology</td>
<td>No difference between sulfasalazine and balsalazide</td>
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<tr>
<td>Green</td>
<td>Aliments Pharmacol Ther 2002;16:61</td>
<td>Yes</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Balsalazide 6.75 g, sulfasalazine 3 g</td>
<td>87</td>
<td>12</td>
<td>Clinical response, symptomology, histology</td>
<td>No difference between sulfasalazine and balsalazide</td>
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<td>Willoughby</td>
<td>Scand J Gastroenterol 1988;148:40-44</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Olsalazine 3 g and sulfasalazine 1 g</td>
<td>56</td>
<td>5</td>
<td>Clinical response</td>
<td>No difference between sulfasalazine and placebo</td>
<td>15% w/olsalazine, 13% w/sulfasalazine</td>
<td></td>
<td></td>
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<tr>
<td>Rao</td>
<td>Gut 1989;30:525-530</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Olsalazine 2 g and sulfasalazine 1 g</td>
<td>39</td>
<td>4</td>
<td>Clinical improvement, sigmoidoscopy, histology</td>
<td>No difference between sulfasalazine and olsalazine</td>
<td>5% w/olsalazine, 5% w/sulfasalazine</td>
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<td>Krusis</td>
<td>Aliments Pharmacol Ther 1998;12:307-315</td>
<td>Yes</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Olsalazine 3 g and sulfasalazine 1 g</td>
<td>168</td>
<td>12</td>
<td>Endoscopic remission</td>
<td>No difference between olsalazine and sulfasalazine</td>
<td>26% w/olsalazine, 24% w/sulfasalazine</td>
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<td>Green</td>
<td>Gastroenterology 1998;104:35</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Balsalazide 6.75 g, mesalamine (Asacol) 2.4 g</td>
<td>99</td>
<td>12</td>
<td>Proportion of patients in complete remission</td>
<td>Balsalazide patients more likely to be in remission</td>
<td>12% w/balsalazide, 32% w/mesalamine</td>
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<td>Levine</td>
<td>Am J Gastroenterol 2002;97:1398</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Balsalazide 6.75 g, mesalamine (Asacol) 2.4 g</td>
<td>154</td>
<td>8</td>
<td>Improved rectal bleeding and other outcome</td>
<td>No difference between mesalamine and balsalazide in primary outcome or individual secondary outcomes at 6 weeks</td>
<td>4% w/6.75 g balsalazide, 16% w/2.25 g, 8% w/mesalamine</td>
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<td>Pratt</td>
<td>Am J Gastroenterol 2002;97:3070-3086</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Balsalazide 6.75 g, mesalamine (Asacol) 2.4 g</td>
<td>175</td>
<td>8</td>
<td>Symptomatic remission</td>
<td>All endpoints comparable at 6 weeks</td>
<td>Not stated</td>
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<td>N/A</td>
<td>Personal communication</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Balsalazide 6.75 g, 4.5 g, placebo</td>
<td>180</td>
<td>4</td>
<td>Symptomatic remission</td>
<td>No difference between balsalazide 6.75 and placebo</td>
<td>Not stated</td>
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5-ASAs and Active UC
Based on the per protocol analysis of complete or partial response, the ABI for 2.4 g of mesalamine compared to placebo was 26% with a NNT of 4.

Controlled-release Mesalamine versus Placebo
In the single published trial on controlled-release mesalamine versus placebo, 374 patients with mildly to moderately active UC were randomized to receive 1 g (n = 92), 2 g (n = 97), or 4 g (n = 95) of controlled-release mesalamine (Pentasa), or placebo (n = 90) for 8 weeks. The primary aim of the study was clinical improvement and induction of remission. Clinical improvement was assessed using PGA, assessment of treatment failure, sigmoidoscopic index, biopsy score, patient perceptions of severity of the four clinical symptoms (stool consistency, rectal bleeding, abdominal pain, and urgency), and trips to the toilet. Induction of remission was assessed by more stringent criteria for PGA, sigmoidoscopic index, and biopsy score. For the PGA assessment that measured treatment success 56 of 95 (59%), 55 of 97 (57%), and 41 of 92 (45%) patients receiving the 4 g, 2 g, and 1 g dose, respectively, achieved complete relief or marked improvement of symptoms compared to 32 of 90 (36%) patients on placebo. Both the 4 g and 2 g doses of mesalamine were significantly superior to placebo (P = .0012 and P = .0021, respectively). Remission, as defined by the PGA, was 11 of 90 (12%) in the placebo group, and 19 of 92 (21%), 28 of 97 (29%), and 28 of 95 (29%) for the 1 g, 2 g and 4 g groups, respectively. The placebo (n = 15) for 6 weeks. The primary endpoint was not clearly stated; however, patients were assessed clinically, endoscopically, and by histology. By ITT analysis, 6 of 15 (40%) olsalazine patients had “definite improvement” (a change of at least 2 grades in symptomatic well-being), versus 2 of 15 (13%) in the placebo arm, P = .11.

By ITT analysis, 6 of 15 (40%) olsalazine patients had “definite improvement” (a change of at least 2 grades in symptomatic well-being), versus 2 of 15 (13%) in the placebo arm, P = .11.

Olsalazine versus Placebo
There are four published trials of olsalazine versus placebo. In the first, by Hetzel and colleagues, 30 patients with mild to moderate proctitis or left-sided disease intolerant to sulfasalazine therapy were randomized to 1 g bid of olsalazine (n = 15) or placebo (n = 15) for 6 weeks. The primary endpoint was not clearly stated; however, patients were assessed clinically, endoscopically, and by histology. By ITT analysis, 6 of 15 (40%) olsalazine patients had “definite improvement” (a change of at least 2 grades in symptomatic well-being), versus 2 of 15 (13%) in the placebo arm, P = .11. Similar non-statistical differences were seen in sigmoidoscopy scores and histopathology.

In the second study, Feurle and colleagues reported on 105 patients with mild to moderate UC. Patients were randomized to 2 g of olsalazine daily (n = 52) or placebo (n = 53) for 4 weeks. Improvement was defined as 3 of 4 clinical parameters improving, which included number of stools, presence of blood in stool, stool consistency, and mucus in stool. After 4 weeks, there was a statistically significant improvement in the individual symptom of rectal mucus discharge (P = .004). No difference in improvement rates was seen between the two groups for other parameters assessed. Another endpoint of rectoscopy outcomes showed a decrease in inflammation in 61.7% of treatment patients and 46% of placebo patients (P = .0127). However, endoscopic findings in the sigma were not statistically different. It is difficult to interpret the results of this study however, as the authors present their data as percentages without absolute numbers, and the primary objective did not meet statistical significance.

Meyers and associates reported on 66 patients randomized to olsalazine 0.75 g/d (n = 15), 1.5 g/d (n = 16), 3 g/d (n = 15) or placebo (n = 20) in a 3-week dose response study in patients with mild, moderate, or severe UC. When comparing colitis activity at study entry to that at completion, 50% (7 of 14) of patients in the 3 g/d arm (P = .055) improved compared to 27% (4 of 15), 29% (4 of 14) and 16% (3 of 19) in the 1.5 g (P = .04), 0.75 g, and placebo groups, respectively.

The smallest but most recent trial was conducted by Zinberg and colleagues. In this trial, 15 patients with mild to moderate UC were randomized to olsalazone 3 g (n = 7) or placebo (n = 8) for 4 weeks. Four of the 7 in the treatment arm achieved symptomatic and colonoscopic improvement and no patients met these criteria in the placebo group (P < .05). Although these data are statistically significant, they are difficult to interpret given the small numbers of patients.

Balsalazide versus Placebo
There is a single phase 2 trial of balsalazide versus placebo in mild to moderate UC. The results have not been published in full form to date, and results are reported as disclosed by Salix. One hundred eighty patients were randomized to balsalazide 4.5 g,
6.75 g/d, or placebo in double-blinded fashion. The primary study endpoint was symptomatic improvement.

At the end of the 4-week trial, a response rate of 45% was seen in both the 6.75 g and placebo treatment arms; sigmoidoscopic improvement was seen in 45% of patients from each group.

Delayed-release Mesalazine versus Sulfasalazine

A single study compared delayed-release mesalamine (Asacol) at 800 mg/d (n = 20) or 2.4 g/d (n = 21) to 2 g/d of sulfasalazine (n = 19) for 4 weeks in patients with mild to moderate UC.14 The primary endpoint of the study was not defined. Multiple endpoints were reported separately, including symptomatic remission, stool frequency, rectal bleeding, sigmoidoscopy and histology. In a total of 60 patients, symptomatic remission, defined as resolution of rectal bleeding and 3 or fewer stools/day, was achieved in 21%, 30%, and 43%, with sulfasalazine, mesalazine 800 mg/d and mesalazine 2.4 g/d, respectively (P < .2). There was significantly greater improvement in rectal bleeding in the patients in the mesalazine 2.4 g/d arm compared to sulfasalazine (81% vs 47%, P < .05) and sigmoidoscopic appearance in the mesalazine 2.4 g group versus in the sulfasalazine group (33% vs 5%, P < .05). There was no significant difference between the 2.4 g/d mesalamine group and sulfasalazine in terms of stool frequency and histology.

Controlled-release Mesalamine versus Sulfasalazine

A Japanese trial published by Munakata and colleagues evaluated a Japanese controlled-release formulation of mesalamine (Pentasa) tablets versus sulfasalazine for 4 weeks in patients with mildly to moderately active UC.16 One hundred and eighteen patients were randomly assigned to receive either mesalamine 1500 mg/d or sulfasalazine 3000 mg/d. In the per protocol analysis, there was no difference in the improvement of clinical symptoms and endoscopic findings between the 48 patients in the mesalamine arm compared to the 52 in the sulfasalazine arm.

Balsalazide versus Sulfasalazine

Two recently published studies, which were reported simultaneously, compared patients taking balsalazide 6.75 g/d with patients taking sulfasalazine 3 g/d. The first study included 50 patients and was performed for 8 weeks in patients with mild to moderate active UC taking no other therapy for their ulcerative colitis.20 The primary endpoint was remission, defined as a stool frequency of two or fewer per day without blood and with a sigmoidoscopic appearance of normal rectal mucosa or minimal erythema. Twenty-six patients were randomized to the balsalazide arm and 24 to the sulfasalazine arm. While there was a trend in favor of balsalazide for rate of remission (50% vs 38%), this was not statistically different.

In the second trial, 57 patients (28 balsalazide and 29 sulfasalazine) with mild, moderate, or severe UC were studied for 12 weeks and were treated simultaneously with corticosteroids, as needed.21 Study outcome was defined in two ways: remission rates at the end of the study and treatment success or failure—patients who withdrew or completed the study without achieving remission. Again, while there was a trend for more patients in the balsalazide arm to achieve remission (75% vs 59%), this was not statistically significant (P = .19).

Olsalazine versus Sulfasalazine

In 1988, Willoughby and colleagues22 conducted a double-blind comparison of olsalazine 3 g/d (n = 26) to sulfasalazine 3 g/d (n = 30). The primary endpoint was improvement as defined by reduced stool frequency and loss of blood and mucus from the stools. Endoscopic improvement was also rated after the 5-week treatment course. Results for the intention-to-treat analysis were extracted from the paper. Twelve of 26 (46%) olsalazine patients versus 17 of 30 (56%) of sulfasalazine patients were found to be “better” at the end of the trial (P > .10). In the second trial, Rao and colleagues23 randomized 39 patients with various levels of disease severity to receive either olsalazine 2 g (n = 18) or sulfasalazine 3 g (n = 13) daily for 4 weeks. The majority of the patients who had baseline endoscopy had moderate or severe disease (34 of 37). The primary endpoint was overall improvement as defined by a positive change in sigmoidoscopic appearance, histology, or clinical parameters. By intention-to-treat analysis (not provided in the study results), 15 of 21 (71%) in the olsalazine arm and 11 of 18 (61%) in the sulfasalazine arm responded (P > .10).

Mesalazine versus Sulfasalazine

In a single study published by Rachmilewitz, 220 patients were randomized to receive either mesalazine 1.5 g or sulfasalazine 3 g...
daily for 8 weeks. The number of withdrawals in each group was identical (28) and only one third of patients from either arm completed the study. Remission rates were 74% and 81% for mesalazine and sulphasalazine, respectively; however, this was a per protocol analysis and it was not possible to determine remission by an intent-to-treat analysis.

**Olsalazine versus Mesalazine**

In a trial published by Kruis and colleagues, 168 patients were randomized to receive either mesalazine 3 g/d or olsalazine 3 g/d. The endpoint was endoscopic remission, as defined by the Rachmilewitz rating system. There was no difference between those who achieved the end point in the mesalazine group (46.2%) and in the olsalazine group (52.2%). The study was designed to be a non-inferiority study, but was not powered appropriately to achieve the primary aim.

**Asacol versus Balsalazide**

Three studies compared a non–FDA-approved formulation of Asacol (marketed in the United Kingdom) to balsalazide. In vitro dissolution studies have been performed, which showed that this formulation is not the same as the Asacol formulation that is FDA-approved and marketed in the United States. In 1998, Green and colleagues compared Asacol 2.4 g/d (n = 49) to balsalazide 6.75 g (n = 50) in patients with moderate to severe UC. The primary endpoint was the cumulative proportion of patients achieving complete remission by the end of the 12-week trial. For patients to be in “complete remission” they needed to have no symptoms or mild symptoms, a sigmoidoscopy score of 0 or 1, and no use of rectal steroids for the previous 4 days. Symptomatic remission was also analyzed and included patients with no/mild symptoms. In the 50 patients who received balsalazide, 62% achieved complete remission. In the 49 who received Asacol, 37% achieved complete remission (P < .05), with an ABI of 25%, and a NNT of four. The absolute number of responders was not reported.

In a more recently published trial, 154 patients with mildly to moderately active UC were randomized to receive the UK formulation of Asacol 2.4 g/d (n = 51), balsalazide 2.25 g/d (n = 50), or balsalazide 6.75 g/d (n = 53). The primary endpoint was improvement in rectal bleeding along with one other sign or symptom, as reported in patient diaries. Secondary measures included remission status, rectal biopsy score, and quality of life, determined by the Inflammatory Bowel Disease Questionnaire (IBDQ). Remission in this study was defined as normal stool frequency, no blood in stool for 48 hours, physician’s global assessment of “quiescent,” and a sigmoidoscopy score of normal or mild. The number of patients achieving the primary endpoint was not reported. The cumulative proportion of patients meeting all criteria for remission also did not differ significantly between any groups. At week 8, the proportion of patients achieving complete remission was 23% in the 6.75 g balsalazide group versus 19% in the Asacol group (P = NS). The other defined secondary endpoints did not differ significantly between balsalazide and Asacol.

In the third trial, all groups were comparable in all endpoints. The one with balsalazide did not. The 4 studies with olsalazine did not show consistent efficacy results versus placebo. None of the 6 trials of 5-ASA versus sulfasalazine showed a 5-ASA to be superior in efficacy. In most studies, sulfasalazine has had a numerical, if not statistical advantage. In 2 of 3 trials of balsalazide versus mesalamine, results for defined primary and secondary endpoints were comparable.
endpoints failed to demonstrate statistically significant differences.

Given the difficulties in assessing some of the results from these trials, it is worth reviewing some important points regarding appropriate data analysis in double-blind, randomized trials. Appropriate data analysis includes the appropriate comparison of medical therapies, including indicated patient population and indicated doses of medication.

In any clinical trial, there needs to be a well-defined primary endpoint. It is important to remember that if a trial does not meet its primary endpoint, then all other analyses become suspect, as the study was not powered to address alternative questions specifically. In addition, the more secondary endpoints there are in a study, the greater the chance of finding a spurious positive finding. In this scenario, appropriate steps to correct for multiple analyses are important. Finally, the authors need to prespecify which variables they are going to analyze, as post hoc, or post-trial, analysis is not a reasonable substitute for significant findings.

Historically, it has been difficult to agree upon a reproducible disease index for ulcerative colitis. There is no standard, validated scoring system for UC, which makes comparisons between various trials difficult. It was not possible to calculate in a quantitative manner a pooled odds ratio for the benefit of 5-ASA over placebo, sulfasalazine, or other 5-ASAs because of the differences in study endpoints and evaluation. Although we were able to calculate ABI and NNT for individual trials, it is confusing to use these statistics for direct comparison purposes, as endpoints for trials were so dissimilar.

Another problem with quantitative and, to some degree, qualitative comparisons is that some trials enrolled patients with moderate to severe disease. This is not currently an indication for this class of drugs and should not be compared to studies of patients with mild to moderate disease.

Specific comparisons of balsalazide and mesalamine are difficult to interpret due to the use of a different formulation of Asacol than that available in the United States and the use of differing endpoints and post hoc analyses. For the sake of completeness, those papers are included in the review but need to be kept in perspective. Balsalazide appears to have an efficacy that is similar to that of the non–FDA-approved formulation of Asacol. No efficacy and safety data are available comparing the US formulation of Asacol to balsalazide. Importantly, claims of superiority of balsalazide to Asacol in 2 of the 3 available studies are based on post hoc analyses in the setting of no difference in the primary and secondary endpoints between the drugs. The third trial was performed in a population of patients with more severe disease and used different endpoints. Since there is an absence of studies comparing the FDA-approved formulation of Asacol to balsalazide, it seems inappropriate to conclude that there is a clinically significant difference in efficacy between the two products.

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References

Main Points
- Although the exact mechanism of action of 5-ASA agents remains unknown, the hypothesized in vivo physiologic action of these compounds is to inhibit both the cyclo-oxygenase and 5-lipoxygenase pathways of arachidonic acid metabolism.
- Metaanalyses and systematic reviews of 5-ASA compounds have suggested that these drugs are more efficacious than placebo in the treatment of mild to moderately active UC and have an efficacy similar to that of sulfasalazine.
- Balsalazide appears to have an efficacy similar to that of the non–FDA-approved formulation of Asacol; however, efficacy and safety data comparing the US formulation of Asacol to balsalazide are not available.


10. Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA. 1994;271(1):59-63.


