

ORIGINAL ARTICLES

Oral Pentasa in the Treatment of Active Crohn's Disease: A Meta-Analysis of Double-Blind, Placebo-Controlled Trials

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Background & Aims: The aim of this study was to perform a meta-analysis of the efficacy results from 3 placebo-controlled multicenter clinical trials of slow-release mesalamine (Pentasa) for the acute treatment of mild to moderate Crohn's disease. **Methods:** Three trials fulfilled the selection criteria (double-blind, placebo-controlled, randomized studies in adult patients treated with Pentasa 4 g/day for active Crohn's disease). The efficacy and safety was evaluated in these trials by using the Crohn's Disease Activity Index (CDAI) as the primary efficacy variable. The study duration was 16 weeks in all 3 trials. The total numbers of patients were 304 in the Pentasa 4-g/day treatment groups and 311 in the placebo groups. A meta-analysis was performed based on the study reports. **Results:** For the intent-to-treat patients in the Pentasa groups, the overall mean reduction of the CDAI from baseline to the final visit was -63 points. The corresponding CDAI change in the placebo groups was -45 points; the net difference was -18 points. Compared with placebo, the 4-g/day dose of Pentasa was associated with a statistically significant overall improvement in the CDAI from baseline to the final visit ($P = 0.04$). When the meta-analysis was restricted to protocol correct patients, the effect of Pentasa became more pronounced (overall mean reduction of -83 CDAI points; $P = 0.02$, compared with placebo). Contrary to the consistent effects with Pentasa, the trial-specific reductions of the CDAI with placebo differed significantly between the trials. **Conclusions:** The meta-analysis of 3 large, double-blind, randomized studies in the treatment of active Crohn's disease confirms that Pentasa 4 g/day is superior to placebo in reducing the CDAI but the clinical significance of the magnitude of this difference is not clear.

rations consist of ethyl cellulose-coated microgranules of mesalamine that, by diffusion, allow a continuous release of mesalamine throughout the entire gastrointestinal tract at all enteral pH values.

Although only one placebo-controlled trial using the oral Pentasa formulation of slow-release mesalamine has been published in its entirety,³ the efficacy and safety of oral Pentasa capsules, 4 g/day, in the treatment of active Crohn's disease have been studied in 2 additional, similarly designed, double-blind, randomized, placebo-controlled trials conducted in North America that have yet to be published in their entirety.^{6,7}

The present study was undertaken to analyze the efficacy results of these 3 similarly designed trials by means of a meta-analysis. The Crohn's Disease Activity Index (CDAI) was considered as the primary efficacy response variable of the meta-analysis.

Meta-analyses attempt to analyze and combine the results of clinical trials to increase statistical power for primary endpoints and for subgroups, to resolve uncertainty when reports disagree, and to improve estimates of effect size.⁸ The main objective in this study was to assess the overall efficacy of Pentasa 4 g/day in active Crohn's disease. Although the response to Pentasa was fairly consistent in each of the trials considered, the individual efficacy results have been inconsistent, possibly owing to different placebo effects. Further, it was of interest to examine whether the overall difference between responses to Pentasa and placebo, respectively, was modified by certain factors. Therefore, complementary meta-analyses were performed, based on relevant subgroups of patients.

Mesalamine has become a widely recommended and used first-line agent for patients with mild to moderately active Crohn's disease^{1,2} based on a series of published controlled clinical trials.³⁻⁵ Pentasa (Shire Pharmaceutical, Newport, KY) oral slow-release prepa-

Table 1. Pentasa: Efficacy and Safety Studies in Active Crohn's Disease

Dosage	No. of patients	Duration	Method of evaluation	Reference
Randomized, double-blind, placebo-controlled studies				
1.5 g/day dosed 3 × day	67	16 wk	CDAI	Rasmussen et al. ⁵
1.5 g/day	12	10 days	CDAI	Saverymattu SH et al. <i>Digestion</i> 33(2):89–91, 1986
1–2–4 g/day dosed 4 × day	310	16 wk	CDAI	Singleton et al: <i>Dig Dis Sci</i> 40(5):931–935, 1995 and <i>Gastroenterology</i> 104(5):1293–1301, 1993
1.5 g/day dosed 3 × day	40	6 wk	Harvey-Bradshaw	Mahida YR et al. <i>Digestion</i> 45(2):88–92, 1990
2–4 g/day dosed 4 × day	232	16 wk	CDAI	Singleton J, <i>Gastroenterology</i> 107(2):632–633, 1994 (letter to the editor); Internal study report
3 g/day dosed 3 × day	33	24 wk	CDAI	Internal study report
4 g/day dosed 4 × day	310	16 wk	CDAI	Internal study report
Children, randomized, double-blind, placebo-controlled studies				
50 mg/kg/day maximum	13	8 wk	CDAI	Griffiths AM, <i>J Pediatr Gastroenterol Nutr</i> 17(2):186–192, 1993
3 g/day dosed 3 × day				
Comparative, double-blind studies				
Pentasa 1.5 g/day vs. sulfasalazine 3 g/day dosed 3 × day	34	16 wk	CDAI	Brillanti S, <i>Scand J Gastroenterol</i> 24 (suppl. 158):129–130, 1989 (abstract)
Pentasa 4 g/day dosed 2 × day vs. Entocort ^a 9 mg every morning	182	16 wk	CDAI	Thomsen OO, <i>N Engl J Med</i> 339(6):370–374, 1998
Open comparative studies				
Pentasa 4 g/day 2 × day vs. 1 g ciprofloxacin/day	40	6 wk	CDAI	Colombel et al., <i>Gastroenterology</i> 112(4):A951, 1997 (abstract)
Open uncontrolled studies				
1.5 g/day dosed 3 × day	18	10 wk	CDAI	Rasmussen SN, <i>Gastroenterology</i> 85(6):1350–1353, 1983
Individual dosages up to 4 g/day	333	Individual, up to 458 days	CDAI	Hanauer et al., <i>Am J Gastroenterol</i> 88(9):1343–1351, 1993
4 g/day	14	No information	Clinical symptoms	Barreiro MA et al., <i>Gastroenterology</i> 100 (5, part 2):A195, 1991 (Abstract)
3 g/day dosed 3 × day	19	6 wk	CDAI	Piodi LP, <i>Patologia del Colon</i> 19–21, 1990
Mean: 1.86 g/day dosed 4 × day	116	16 wk	Clinical symptoms	Internal report
Open uncontrolled studies, children				
30.6 ± 9 g/kg/day	14	8.1 ± 3.9 wk (2–15 wk)	CDAI	Griffiths AM, <i>J Pediatr Gastroenterol Nutr</i> 17(2):186–192, 1993

^aAstraZeneca Pharmaceutical, Wilmington, DE.

Materials and Methods

Selected Trials

Several efficacy and safety studies of Pentasa tablets/capsules have been performed. Table 1 provides an overview of such studies. Criteria for selection in the current meta-analysis were that the studies should be double-blind, placebo-controlled, randomized studies in adult patients with active Crohn's disease using 4 g of Pentasa and with the CDAI score as the primary effect variable.

By literature search in Medline (1986–1998) and by review of internal files of the marketing authorization holders in the United States and Europe (Hoechst Marion Roussel, now Shire and Ferring A/S), 3 trials, here referred to as Crohn's I, II, and III,^{3,6,7} respectively, fulfilled the selection criteria. They were multicenter trials and took place in Canada and the

United States. The total numbers of patients were 304 in the Pentasa 4-g/day treatment groups and 311 in the placebo groups. Crohn's I included 75 patients in the Pentasa 4-g/day treatment group and 80 patients in the placebo group.^{3,9} Crohn's II included 75 patients in each corresponding group.^{6,10} In the Crohn's III trial there were 154 patients in the Pentasa 4-g/day treatment group and 156 patients in the placebo group.⁷

With the exception of a few minor changes, the study designs of the trials were identical. For example, Crohn's I included patients in 2 additional treatment groups (Pentasa 1 g/day and Pentasa 2 g/day), and Crohn's II included patients receiving Pentasa 2 g/day; data obtained from these patients were not taken into account in the present analysis. The entry criteria for mild to moderately active patients differed somewhat in the 3 trials, indicated by a CDAI at baseline between

Table 2. Baseline Characteristics, Intent-to-Treat Data

Baseline characteristic	Crohn's I		Crohn's II		Crohn's III	
	Pentasa 4 g (N = 75)	Placebo (N = 80)	Pentasa 4 g (N = 75)	Placebo (N = 75)	Pentasa 4 g (N = 154)	Placebo (N = 156)
Sex						
Male % (N)	27% (20)	41% (33)	35% (26)	39% (29)	40% (61)	37% (58)
Age (yr)						
Mean \pm SD	37 \pm 13	37 \pm 13	37 \pm 13	38 \pm 11	42 \pm 13	39 \pm 12
Range	19–76	16–75	19–70	19–72	19–82	18–74
Weight (lb)						
Mean \pm SD	142 \pm 30	148 \pm 33	144 \pm 32	147 \pm 36	152 \pm 37	152 \pm 39
Range	86–216	93–250	89–219	83–266	83–300	77–295
Disease location						
Colitis % (N)	19% (14)	19% (14)	25% (19)	27% (20)	25% (38)	32% (50)
Ileocolitis % (N)	36% (26)	36% (26)	31% (23)	35% (26)	33% (50)	31% (48)
Ileitis % (N)	44% (32)	45% (33)	44% (33)	38% (28)	42% (64)	36% (56)
Unknown extent ^a (N)	(2)	(3)	(0)	(1)	(2)	(1)
No disease ^b (N)	(1)	(4)	(0)	(0)	(0)	(1)
Duration of disease (yr)						
Mean \pm SD	10 \pm 9	10 \pm 8	8 \pm 8	9 \pm 6	10 \pm 9	9 \pm 9
Range	0–45	0–38	0–37	0–23	0–37	0–42
Duration of current episode						
Acute % (N) (<28 days)	25% (19)	28% (22)	32% (24)	31% (23)	31% (47)	32% (47)
Chronic % (N) (\geq 28 days)	75% (56)	72% (58)	68% (51)	69% (52)	69% (104)	68% (102)
Unknown (N)	(0)	(0)	(0)	(0)	(3)	(7)
Abdominal mass definite or questionable						
Yes % (N)	28% (21)	21% (17)	28% (21)	29% (22)	29% (45)	27% (42)
Oral steroid use in prior 30 days						
Yes % (N)	20% (15)	26% (21)	16% (12)	24% (18)	4% (6)	9% (14)
Sulfasalazine use in prior 30 days						
Yes % (N)	17% (13)	25% (20)	19% (14)	19% (14)	17% (26)	12% (19)
Response to prior oral steroid use ^c						
Remission or benefit % (N)	60% (45)	53% (42)	45% (34)	55% (41)	25% (38)	27% (42)
No benefit % (N)	7% (5)	10% (8)	5% (4)	4% (3)	3% (4)	3% (4)
Not applicable or unknown % (N)	33% (25)	38% (30)	49% (37)	41% (31)	73% (112)	71% (110)
Response to prior sulfasalazine use ^c						
Remission or benefit % (N)	39% (29)	30% (24)	31% (23)	36% (27)	17% (26)	19% (29)
No benefit % (N)	19% (14)	36% (29)	23% (17)	21% (16)	8% (12)	4% (7)
Not applicable or unknown % (N)	43% (32)	34% (27)	47% (35)	43% (32)	75% (116)	77% (120)
CDAI						
Mean \pm SD	260 \pm 64	277 \pm 66	248 \pm 76	255 \pm 79	265 \pm 53	265 \pm 58
Range	86–381	112–460	129–474	67–440	136–431	118–428

^aComplete examination of either ileum or colon was not performed.

^bReview of endoscopic and radiologic studies of these patients failed to show evidence of active disease. Participating investigators entered them on basis of clinical findings.

^cIn the Crohn's III trial, response to steroid/sulfasalazine use was restricted to prior 365 days.

151–400 (Crohn's I), or between 200–400 (Crohn's II and III). Each patient gave written informed consent before entry into the trials. Patients with Crohn's disease of the small intestine, colon, or both, diagnosed according to specified criteria¹¹ were randomized to one dosage group and were evaluated at months 0 (baseline), 1, 2, 3, and 4. Baseline characteristics of the patients are presented in Table 2. The CDAI was calculated at the baseline visit by using the patients' diary data collected throughout the preceding week. The CDAI also was calculated at months 1, 2, 3, and 4. If patients failed to complete the 4-month follow-up period, observations made at a patient's last clinic visit were used as that patient's final visit evaluation (Table 3). Some patients had no postbase-

line measurement recorded in which case zero change from baseline was assumed.

Table 4 shows the numbers of patients with protocol violations, according to the 3 protocol guidelines.

Statistical Methods

Individual study reports. Statistical analyses of the patient data from each trial were performed in a consistent manner.^{6–9} Missing data at baseline or endpoint were imputed as follows: if data were missing at baseline, the mean of all patients at baseline was used for continuous variables, and the

Table 3. Early Termination of Study Patients

	Crohn's I		Crohn's II		Crohn's III	
	Pentasa 4 g N	Placebo N	Pentasa 4 g N	Placebo N	Pentasa 4 g N	Placebo N
Randomized and consumed study medication	75	80	75	75	154	156
Completed month 1	67 (89%)	72 (90%)	62 (83%)	63 (84%)	131 (85%)	133 (85%)
Completed month 2	55 (73%)	59 (74%)	52 (69%)	50 (67%)	116 (75%)	112 (72%)
Completed month 3	50 (67%)	48 (60%)	43 (57%)	41 (55%)	109 (71%)	101 (65%)
Completed month 4	49 (65%)	39 (49%)	40 (53%)	41 (55%)	104 (68%)	96 (62%)
Reasons for early termination						
Side effects caused by study medication	8	13	12	10	25	14
Development of an intercurrent condition that would affect validity of assessments	2	1	2	4	0	0
Noncompliance with study procedures	1	4	3	1	0	0
Patient elected to discontinue study	3	3	1	2	4	5
Insufficient therapeutic effect ^a	10	16	12	14	14	32
Other	2	4	5	5	7	9
Total	26 (35%)	41 (51%)	35 (47%)	34 ^b (45%)	50 (32%)	60 (38%)

^aAs determined by individual investigators or defined by treatment failure criteria.

^bSome patients had more than one reason for early termination.

mode of all patients at baseline was used for categoric variables. For such patients, change from baseline was calculated as postbaseline value minus imputed baseline value.

The CDAI was treated as a continuous response variable and analyzed by using analysis of covariance techniques.¹² Changes from baseline were estimated with corrections for baseline CDAI, which was incorporated as a continuous variable in the statistical model, and study center, which was incorporated as a categoric variable. Treatment by center interaction was included in the statistical model if it proved significant at a level of 0.05. Subgroup analyses were performed in a consistent manner. Because the impact of the baseline and study center corrections differed between subgroups, in some subgroup analyses the estimated group-specific mean change from baseline was smaller than the total mean change.

Meta-analyses. In the present study, meta-analyses were performed according to the fixed-effects model.¹² An overall effect estimate for the 3 trials was obtained by calculating a weighted sum of the trial-specific effect estimates; an individual trial weight was set to the inverse squared standard

error of the corresponding effect estimate. A 95% confidence interval for an overall effect estimate was provided by a normal approximation. Under the fixed-effects model, it is assumed that the relevant effect measure is homogeneous across the trials; homogeneity was tested by using an appropriate statistical test.¹²

To examine whether the overall difference in CDAI change between Pentasa and placebo was modified by certain factors, complementary meta-analyses were performed based on relevant subgroups with respect to the following: response to prior oral steroid use, response to prior sulfasalazine use, duration of disease, duration of current episode, and sex. These subgroup analyses were considered because the individual reports⁶⁻⁹ provide indications of effect modification by the corresponding factors (when at least one of the related trial-specific tests for consistency of treatment effect implied a *P* value less than 0.10). The individual reports do not indicate any effect modification by disease location, prior surgical resection, abdominal mass, recent oral steroid use, recent sulfasalazine use, age, and smoking status.

Table 4. Protocol Violations; Patients Excluded From Protocol Correct End-Point Analysis

	Crohn's I		Crohn's II		Crohn's III	
	Pentasa 4 g N (%)	Placebo N (%)	Pentasa 4 g N (%)	Placebo N (%)	Pentasa 4 g N (%)	Placebo N (%)
Incomplete data available to calculate baseline or end-point CDAI	13 (62)	14 (67)	17 (50)	22 (69)	0 (0)	1 (2)
Patient off study drug more than 5 days before final visit	10 (48)	11 (52)	9 (26)	3 (9)	11 (32)	23 (56)
Patient on study drug <7 days	6 (29)	4 (19)	5 (15)	5 (16)	9 (26)	8 (20)
Medication noncompliant	7 (33)	5 (24)	5 (15)	5 (16)	16 (47)	15 (37)
Use of prescribed medications for Crohn's disease	3 (14)	1 (5)	3 (9)	5 (16)	7 (21)	8 (20)
Failed entry criteria	6 (29)	10 (48)	9 (26)	11 (34)	8 (24)	11 (27)
Administrative discretion	0 (0)	0 (0)	0 (0)	0 (0)	5 (15)	2 (5)
Total ^a	21	21	34	32	34	41

^aColumns do not sum to total because some patients had more than one violation. Percentages in this table are computed using these totals.

Table 5. Summary of Intent-to-Treat Endpoint Analysis of the CDAI Score, With Corresponding Meta-Analysis Results

Trial	Pentasa 4 g ^a		Placebo ^a		Pentasa 4 g – placebo ^a		
	N	Mean ± SE	N	Mean ± SE	Mean ± SE	95% confidence interval	P value
Crohn's I	75	-72 ± 13	80	-21 ± 13	-52 ± 18	(-88, -16)	0.005
Crohn's II	75	-41 ± 12	75	-35 ± 12	-6 ± 17	(-40, 27)	0.7
Crohn's III	154	-72 ± 9	156	-64 ± 9	-8 ± 13	(-33, 16)	0.5
Overall effect ^b		-63 ± 6		-45 ± 6	-18 ± 9	(-35, -1)	0.04

^aChange from baseline. Means adjusted for baseline and study center.

^bP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.09, 0.02, and 0.12 for Pentasa, placebo, and Pentasa – placebo, respectively.

A P of value <0.05 is referred to as (statistically) significant.

Pooled analysis. A supplementary-pooled analysis, based on the individual patient data from the 3 trials together, also was performed. The pooled data were analyzed by using the same statistical method applied in the individual study reports. Thus, a model adjusting for baseline CDAI and study center was used; if a study center was involved in more than one trial, the corresponding patient data also were stratified by trial. The main purpose of the pooled analysis was to evaluate whether baseline disease severity (as indicated by the baseline CDAI) modified the treatment effect.

Results

Meta-Analysis: Intent-to-Treat Patients

Table 5 shows the meta-analysis results based on the trial-specific intent-to-treat endpoint analyses. The overall mean reduction of the CDAI from baseline to the final visit was -63 points in the Pentasa 4-g/day groups. Compared with placebo, the 4-g/day dose of Pentasa was associated with a statistically significant improvement in the CDAI from baseline to the final visit (P = 0.04). The

difference between Pentasa and placebo was -18 (95% confidence interval: -35 to -1) CDAI points. However, there was a tendency of heterogeneity across the trials; in particular, the trial-specific placebo effects on the CDAI differed significantly (Figure 1, Table 5).

Meta-Analysis: Protocol Correct Patients

When the meta-analysis was restricted to protocol correct patients, the overall mean reduction in the Pentasa groups were -83 CDAI points (Table 5). Also, the difference in CDAI change between Pentasa and placebo became somewhat more pronounced, for example, -25 CDAI points (95% confidence interval: -46 to -3 points; P = 0.02). Again, the placebo effect on the CDAI clearly differed among the trials, contrary to the Pentasa groups in which the trial-specific mean reductions became more consistent (Figure 2, Table 6).

Pooled Analysis: Intent-to-Treat Patients

The pooled intent-to-treat endpoint analysis implied a mean reduction (adjusted for study center and baseline CDAI) of -67 CDAI points. The treatment

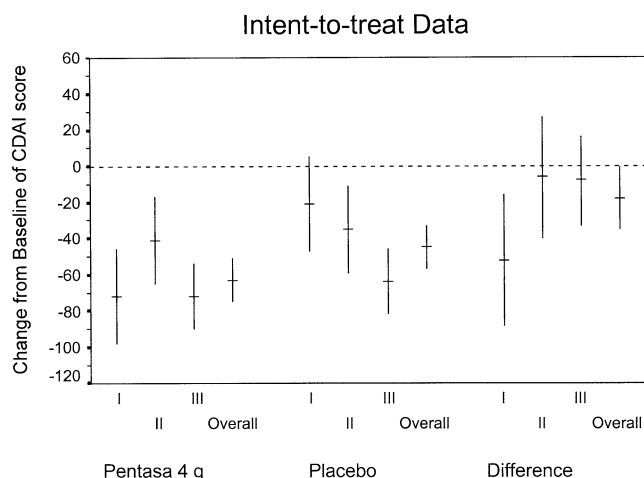


Figure 1. Trial-specific (referred to as I, II, and III, respectively) and overall mean reductions of the CDAI, with 95% confidence intervals, obtained from the intent-to-treat endpoint analyses.

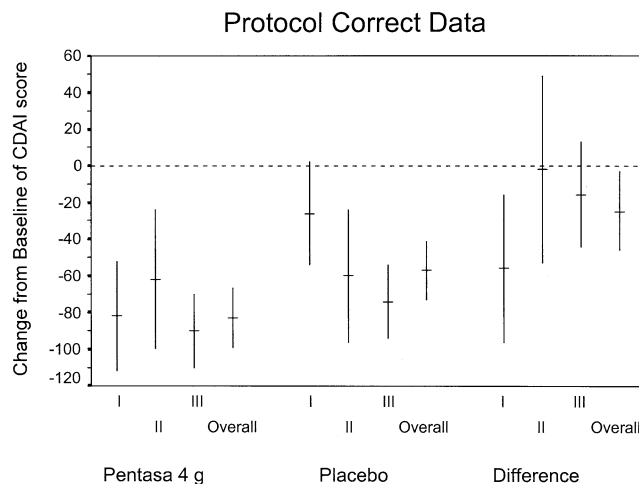


Figure 2. Trial-specific (referred to as I, II, and III, respectively) and overall mean reductions of the CDAI, with 95% confidence intervals, obtained from the protocol correct endpoint analyses.

Table 6. Summary of Protocol Correct Endpoint Analysis of the CDAI Score, With Corresponding Meta-Analysis Results

Trial	Pentasa 4 g ^a		Placebo ^a		Pentasa 4 g – placebo ^a		
	N	Mean ± SE	N	Mean ± SE	Mean ± SE	95% confidence interval	P value
Crohn's I	54	-82 ± 15	59	-26 ± 14	-56 ± 20	(-96, -16)	0.006
Crohn's II	41	-62 ± 19	43	-60 ± 18	-2 ± 26	(-53, 49)	0.9
Crohn's III	120	-90 ± 10	115	-74 ± 10	-16 ± 15	(-44, 13)	0.3
Overall effect ^b		-83 ± 8		-57 ± 8	-25 ± 11	(-46, -3)	0.02

^aChange from baseline. Means adjusted for baseline and study center.

^bP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.4, 0.02, and 0.18 for Pentasa, placebo, and Pentasa – placebo, respectively.

effect estimate (i.e., difference in CDAI change between Pentasa and placebo) was -25 points (95% confidence interval: -44 to -6 points; $P = 0.01$). The baseline CDAI was a significant predictor of response ($P < 0.001$); patients with higher CDAI had greater reduction in CDAI after treatment. However, there was no evidence that the baseline CDAI modified the treatment effect ($P = 0.9$). The model included (statistically significant, $P = 0.02$) interactions by treatment centers.

Subgroup Meta-Analyses: Intent-to-Treat Patients

Table 7 gives the results of the subgroup analysis according to response to prior steroid use. The overall difference between Pentasa and placebo was only significant among patients who had experienced remission or

benefit ($P = 0.002$). However, the trial-specific patterns differed somewhat. The subgroup analysis according to response to prior sulfasalazine use did not reveal any significant overall differences between Pentasa and placebo (Table 8), although there were the trial-specific inconsistencies (e.g., in Crohn's III, information on response to steroid/sulfasalazine use was restricted to prior 365 days).

The subgroup meta-analysis with respect to duration of disease implied a significantly stronger overall effect of Pentasa 4 g/day compared with placebo for patients who had Crohn's disease for less than 7–8 years, but not in patients with longer disease duration (Table 9). The trial-specific mean reductions of the CDAI were more consistent for patients with disease duration less than 7–8 years in the Pentasa and placebo groups, respectively.

Table 7. Summary of Subgroup Analysis of the CDAI Score (Response to Prior Steroid Use),^a With Corresponding Meta-Analysis Results: Endpoint Analysis; Intent-to-Treat Datasets

Trial	Pentasa 4 g ^b		Placebo ^b		Pentasa 4 g – placebo ^b		
	N	Mean ± SE	N	Mean ± SE	Mean ± SE	95% confidence interval	P value
Remission or benefit							
Crohn's I	45	-73 ± 17	42	6 ± 18	-79 ± 25	(-128, -30)	0.001
Crohn's II	34	-32 ± 19	41	-28 ± 17	-4 ± 26	(-54, 46)	0.9
Crohn's III	38	-78 ± 18	42	-27 ± 17	-51 ± 25	(-100, -2)	0.04
Overall effect ^c		-62 ± 10		-17 ± 10	-46 ± 14	(-74, -17)	0.002
None							
Crohn's I	5	-32 ± 51	8	-11 ± 41	-21 ± 65	(-149, 107)	0.7
Crohn's II	4	-144 ± 54	3	-24 ± 61	-120 ± 82	(-280, 40)	0.14
Crohn's III	4	42 ± 56	4	-152 ± 56	194 ± 79	(39, 349)	0.01
Overall effect ^d		-46 ± 31		-52 ± 29	15 ± 43	(-69, 100)	0.7
Not applicable or unknown							
Crohn's I	25	-78 ± 23	30	-49 ± 21	-29 ± 31	(-90, 32)	0.4
Crohn's II	37	-37 ± 18	31	-43 ± 19	6 ± 26	(-45, 57)	0.8
Crohn's III	112	-75 ± 11	110	-75 ± 11	0 ± 16	(-31, 31)	1.0
Overall effect ^e		-67 ± 9		-64 ± 9	-3 ± 12	(-27, 21)	0.8

^aIn Crohn's III, response to steroid use was restricted to prior 365 days.

^bChange from baseline. Means adjusted for baseline and study center.

^cP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.16, 0.3, and 0.10 for Pentasa, placebo, and Pentasa – placebo, respectively.

^dP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.05, 0.11, and 0.02 for Pentasa, placebo, and Pentasa – placebo, respectively.

^eP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.17, 0.26, and 0.7 for Pentasa, placebo, and Pentasa – placebo, respectively.

Table 8. Summary of Subgroup Analysis of the CDAI Score (Response to Prior Sulfasalazine Use),^a With Corresponding Meta-Analysis Results: Endpoint Analysis; Intent-to-Treat Datasets

Trial	Pentasa 4 g ^b		Placebo ^b		Pentasa 4 g – placebo ^b		
	N	Mean ± SE	N	Mean ± SE	Mean ± SE	95% confidence interval	P value
Remission or benefit							
Crohn's I	29	-118 ± 21	24	-41 ± 23	-77 ± 31	(-138, -16)	0.01
Crohn's II	23	-50 ± 22	27	-36 ± 20	-14 ± 30	(-72, 44)	0.6
Crohn's III	26	-39 ± 22	29	-51 ± 22	12 ± 31	(-49, 73)	0.7
Overall effect ^c		-71 ± 13		-42 ± 12	-26 ± 18	(-61, 9)	0.14
None							
Crohn's I	14	-22 ± 30	29	18 ± 21	-40 ± 37	(-112, 32)	0.28
Crohn's II	17	2 ± 26	16	-63 ± 26	65 ± 37	(-7, 137)	0.08
Crohn's III	12	-21 ± 33	7	-78 ± 43	57 ± 54	(-49, 163)	0.29
Overall effect ^d		-12 ± 23		-22 ± 15	21 ± 23	(-25, 67)	0.4
Not applicable or unknown							
Crohn's I	32	-55 ± 20	27	-33 ± 22	-22 ± 30	(-80, 36)	0.5
Crohn's II	35	-57 ± 18	32	-20 ± 19	-37 ± 26	(-88, 14)	0.16
Crohn's III	116	-84 ± 11	120	-66 ± 10	-18 ± 15	(-47, 11)	0.23
Overall effect ^e		-73 ± 9		-53 ± 8	-23 ± 12	(-46, 1)	0.06

^aIn Crohn's III, response to sulfasalazine use was restricted to prior 365 days.

^bChange from baseline. Means adjusted for baseline and study center.

^cP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.02, 0.9, and 0.11 for Pentasa, placebo, and Pentasa – placebo, respectively.

^dP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.8, 0.02, and 0.10 for Pentasa, placebo, and Pentasa – placebo, respectively.

^eP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.27, 0.06, and 0.8 for Pentasa, placebo, and Pentasa – placebo, respectively.

The subgroup analysis according to duration of current episode indicated a significant overall response difference between Pentasa and placebo for patients with acute disease (i.e., with an episode of <28 days), but not for patients with longer duration of current exacerbation (Table 10). However, the trial-specific patterns differed markedly for patients with acute disease because of different placebo effects.

The subgroup analysis with respect to sex did not reveal any consistent patterns; sex seemed to act as an effect modifier only in Crohn's I (Table 11).

Discussion

The results of the current meta-analysis support the initial publication regarding a dose-ranging study of

Table 9. Summary of Subgroup Analysis of the CDAI Score (Duration of Disease), With Corresponding Meta-Analysis Results: Endpoint Analysis; Intent-to-Treat Datasets

Trial	Pentasa 4 g ^a		Placebo ^a		Pentasa 4 g – placebo ^a		
	N	Mean ± SE	N	Mean ± SE	Mean ± SE	95% confidence interval	P value
<7 or 8 yr^b							
Crohn's I	38	-74 ± 19	39	-19 ± 19	-55 ± 27	(-108, -2)	0.04
Crohn's II	37	-53 ± 18	35	-24 ± 18	-29 ± 26	(-79, 21)	0.25
Crohn's III	73	-87 ± 14	79	-50 ± 13	-37 ± 19	(-74, 0)	0.05
Overall effect ^c		-74 ± 10		-36 ± 9	-39 ± 13	(-65, -13)	<0.001
≥7 or 8 yr^b							
Crohn's I	36	-67 ± 19	41	-14 ± 18	-53 ± 26	(-104, -2)	0.04
Crohn's II	38	-29 ± 17	40	-44 ± 17	15 ± 24	(-32, 62)	0.5
Crohn's III	81	-60 ± 13	77	-79 ± 13	19 ± 18	(-17, 55)	0.3
Overall effect ^d		-53 ± 9		-53 ± 9	1 ± 13	(-24, 26)	1.0

^aChange from baseline. Means adjusted for baseline and study center.

^bSubgroups defined in Crohn's I: <8 and ≥8 yr; subgroups defined in Crohn's II and III: <7 and ≥7 yr.

^cP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.3, 0.3, and 0.8 for Pentasa, placebo, and Pentasa – placebo, respectively.

^dP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.24, 0.01, and 0.06 for Pentasa, placebo, and Pentasa – placebo, respectively.

Table 10. Summary of Subgroup Analysis of the CDAI Score (Duration of Episode), With Corresponding Meta-Analysis Results: Endpoint Analysis; Intent-to-Treat Datasets

Trial	Pentasa 4 g ^a		Placebo ^a		Pentasa 4 g – placebo ^a		
	N	Mean ± SE	N	Mean ± SE	Mean ± SE	95% confidence interval	P value
Acute (<28 days)							
Crohn's I	19	-75 ± 27	22	-15 ± 25	-60 ± 37	(-132, 12)	0.10
Crohn's II	24	-95 ± 21	23	4 ± 22	-99 ± 30	(-159, -39)	0.001
Crohn's III	47	-76 ± 17	47	-77 ± 17	1 ± 24	(-46, 48)	1.0
Overall effect ^b		-82 ± 12		-40 ± 12	-42 ± 17	(-75, -9)	0.01
Chronic (≥28 days)							
Crohn's I	56	-70 ± 16	58	-17 ± 15	-53 ± 22	(-96, -10)	0.02
Crohn's II	51	-16 ± 15	52	-52 ± 15	36 ± 21	(-6, 78)	0.09
Crohn's III	104	-70 ± 11	102	-58 ± 11	-12 ± 16	(-43, 19)	0.4
Overall effect ^c		-56 ± 8		-46 ± 8	-10 ± 11	(-31, 12)	0.4

^aChange from baseline. Means adjusted for baseline and study center.

^bP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.8, 0.008, and 0.03 for Pentasa, placebo, and Pentasa – placebo, respectively.

^cP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.009, 0.08, and 0.01 for Pentasa, placebo, and Pentasa – placebo, respectively.

Pentasa for the treatment of mild to moderately active Crohn's disease.³ The 2 subsequent trials (Crohn's II, III) were not published in their entirety, however, Pentasa had comparable efficacy with the Crohn's I trial,^{6,7,10} although the efficacy of Pentasa in the Crohn's II trial was lower than in Crohn's I, and the placebo response in Crohn's I was somewhat lower than the responses observed in the other 2 trials. Overall, there was a substantial mean reduction of the CDAI from baseline to the final visit in the Pentasa 4-g/day groups (-63 and -83 points based on the intent-to-treat and protocol correct meta-analyses, respectively, and -67 points based on the pooled analysis of intent-to-treat data). Compared with placebo, the 4-g/day dose of Pentasa was associated with a statistically significant improvement in the CDAI from

baseline to the final visit ($P = 0.04$ and 0.02 based on the intent-to-treat and protocol correct meta-analyses, respectively, and $P = 0.01$ based on the pooled analysis of intent-to-treat data). The placebo effect on the CDAI differed significantly among the trials; in particular, Crohn's II and III showed pronounced placebo effects. In contrast, the Pentasa groups' trial-specific mean reductions were consistent.

It is well recognized that Crohn's disease encompasses a heterogeneous spectrum of clinical patterns^{13,14} that could account for differences in response to therapy and placebo.^{15,16} In the subgroup meta-analyses the overall difference between Pentasa and placebo was most evident among patients with positive response to prior steroid use (remission or benefit), disease duration less than 7–8

Table 11. Summary of Subgroup Analysis of the CDAI Score (Sex), With Corresponding Meta-Analysis Results: Endpoint Analysis; Intent-to-Treat Datasets

Trial	Pentasa 4 g ^a		Placebo ^a		Pentasa 4 g – placebo ^a		
	N	Mean ± SE	N	Mean ± SE	Mean ± SE	95% confidence interval	P value
Men							
Crohn's I	20	-18 ± 25	33	-42 ± 19	24 ± 31	(-38, 86)	0.4
Crohn's II	26	-48 ± 21	29	-45 ± 20	-3 ± 29	(-60, 54)	0.9
Crohn's III	61	-79 ± 15	58	-62 ± 15	-17 ± 21	(-59, 25)	0.4
Overall effect ^b		-59 ± 11		-52 ± 10	-4 ± 15	(-33, 26)	0.19
Women							
Crohn's I	55	-92 ± 16	47	0 ± 17	-92 ± 23	(-138, -46)	<0.001
Crohn's II	49	-37 ± 16	46	-29 ± 16	-8 ± 23	(-52, 36)	0.7
Crohn's III	93	-67 ± 12	98	-64 ± 12	-3 ± 17	(-36, 30)	0.9
Overall effect ^c		-66 ± 8		-39 ± 8	-27 ± 12	(-50, -4)	0.02

^aChange from baseline. Means adjusted for baseline and study center.

^bP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.09, 0.7, and 0.6 for Pentasa, placebo, and Pentasa – placebo, respectively.

^cP values obtained from tests for homogeneity of the effect (mean) across the trials⁸: 0.05, 0.007, and 0.005 for Pentasa, placebo, and Pentasa – placebo, respectively.

years, or duration of current episode less than 28 days; however, the trial-specific differences were significantly inconsistent for the latter subgroup. Prior analyses also have shown that cigarette smoking is a negative factor pertaining to response.¹⁷

In the statistical analyses performed for the individual study reports⁶⁻⁹ the CDAI was treated as a continuous response even though it is an ordinal response. The treatment effect thereby could be defined as the difference between the treatment-specific efficacy responses; implicitly, a CDAI reduction of, for example, 50 points is regarded as twice as effective as a 25-point reduction. Furthermore, we point out that the efficacy response variables were based on the CDAI change from baseline to the final visit, without considering the time between these 2 assessments. However, because observations that were made at a patient's last clinic visit were used as that patient's final visit evaluation, the treatment effect may well be underestimated. Indeed, a Kaplan-Meier analysis of the data from Crohn's I was performed to compare time with remission after study initiation among the treatment groups,³ and the results showed a highly significantly shorter time to remission for patients taking Pentasa 4 g/day than for patients taking placebo.

Mesalamine is available throughout the world in a variety of different formulations.¹⁸ The original parent compound from which mesalamine was derived, sulfasalazine, has been beneficial in subgroups of patients with mild to moderately active Crohn's disease in whom the colon is involved.^{19,20} The recognition that the mesalamine (5-aminosalicylic acid) moiety carries therapeutic benefits^{18,19} has led to the use of mesalamine formulations in a variety of settings in Crohn's disease including mild to moderately active disease and maintenance therapy for quiescent disease.^{21,22} It is as yet unclear whether any specific formulation has shown site specificity for Crohn's disease. The reasons for this lack of clarity may include the relatively small numbers of patients in each trial, and in each subgroup by regional involvement, and the variations between the doses and other trial methodologies.¹⁵ Nevertheless, the relative response to Pentasa was similar to recent comparative trials between Pentasa and ciprofloxacin²³ and controlled-ileal release budesonide.²⁴ The current meta-analysis consists of the largest number of patients with Crohn's disease studied with a single formulation evaluated with consistent trial methodology. Even within this trial there was considerable heterogeneity between patients and outcomes. The use of meta-analysis has, recently, been called into question when several smaller trials led to contrasting results with larger trials.²⁵ Although the

total number of patients treated with 4 g/day of Pentasa in this analysis (304 vs. 311 with placebo) was large considering the relative prevalence of Crohn's disease, a larger trial with a homogeneous group of patients (e.g., newly diagnosed) would be desirable to finally position the value of mesalamine in mild to moderately active Crohn's disease.

In summary, the meta-analysis of 3 large, double-blind, randomized studies in the treatment of active Crohn's disease confirms that Pentasa 4 g/day is superior to placebo in reducing the CDAI. Subgroup analyses in this study do not provide sufficiently clear answers that could inform clinicians which group should preferentially receive this medication. In addition, the clinical significance of the mean -18 point difference on the CDAI is not clear because, in individual trials, a 70- to 100-point decrease generally is required to establish clinical efficacy. Extrapolation of CDAI changes has not been compared in other meta-analyses for alternative agents. Given the data supporting the efficacy of other medications in the treatment of Crohn's disease,^{1,22} it is useful for the prescriber to have a clearer understanding of the improvement that can be expected if patients with active Crohn's disease are treated with Pentasa 4 g/day.

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