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Mesalamine Did Not Prevent Recurrent Diverticulitis in Phase 3 Controlled Trials

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See editorial on page 733.

BACKGROUND & AIMS: No therapy has been proven to prevent the recurrence of diverticulitis. Mesalamine has shown efficacy in preventing relapse in inflammatory bowel disease, and there is preliminary evidence that it might be effective for diverticular disease. We investigated the efficacy of mesalamine in preventing recurrence of diverticulitis in 2 identical but separate phase 3, randomized, double-blind, placebo-controlled, multicenter trials (identical confirmatory trials were conducted for regulatory reasons). **METHODS:** We evaluated the efficacy and safety of multimatrix mesalamine vs placebo in the prevention of recurrent diverticulitis in 590 (PREVENT1) and 592 (PREVENT2) adult patients with $\geq$1 episodes of acute diverticulitis in the previous 24 months that resolved without surgery. Patients received mesalamine (1.2 g, 2.4 g, or 4.8 g) or placebo once daily for 104 weeks. The primary end point was the proportion of recurrence-free patients at week 104. Diverticulitis recurrence was defined as surgical intervention at any time for diverticular disease or presence of computed tomography scan results demonstrating bowel wall thickening (>5 mm) and/or fat stranding consistent with diverticulitis. For a portion of the study, recurrence also required the presence of abdominal pain and an increase in white blood cells. **RESULTS:** Mesalamine did not reduce the rate of diverticulitis recurrence at week 104. Among patients in PREVENT1, 53%−63% did not have disease recurrence, compared with 65% of those given placebo. Among patients in PREVENT2, 59%−69% of patients did not have disease recurrence, compared with 68% of those given placebo. Mesalamine did not reduce time to recurrence, and the proportions of patients requiring surgery were comparable among treatment groups. No new adverse events were identified with mesalamine administration. **CONCLUSIONS:** Mesalamine was not superior to placebo in preventing recurrent diverticulitis. Mesalamine is not recommended for this indication. ClinicalTrials.gov ID: NCT00545740 and NCT00545103.

Keywords: Colon Inflammation; Anti-Inflammatory; Clinical Trial; Diverticula.

The prevalence of diverticulosis increases with age, affecting about half to two thirds of individuals older than 80 years.[1,2] The most common complication of diverticular disease is diverticulitis, an acute inflammatory process in which diverticula are associated with pericolonic inflammation, affecting 10% to 25% of patients with diverticulosis, with recent estimates as low as 4%.[1–3] Current guidelines recommend treating mild acute diverticulitis with broad-spectrum oral antibiotics. More severe diverticulitis might require hospitalization, intravenous antibiotics, bowel rest, percutaneous drainage, or surgery.[4,5] One quarter to one third of patients who experience an initial attack of diverticulitis will experience recurrent episodes.[4,6] An elective surgical resection of the affected segment might be needed for patients with repeated or severe episodes.[4,7] Because recurrent episodes of diverticulitis are common, unpredictable, and can occur without warning, a pharmacologic treatment to prevent recurrent diverticulitis would be valuable.

Mesalamine reduces inflammation in patients with inflammatory bowel disease[8,9] and has been suggested to reduce chronic mucosal inflammation associated with diverticular disease,[10,11] a process that can contribute to the inflammation of diverticulitis.[12,13] A subset of patients with diverticulosis can develop segmental colitis associated with diverticula.[12,14] Although the relationship between segmental colitis associated with diverticula and overt episodes of clinical diverticulitis remains unclear, treatment of the inflammatory processes associated with both disease states could potentially be beneficial. Mesalamine is thought to reduce inflammation through multiple mechanisms, including influencing prostaglandin production and activating the peroxisome proliferator-activated-γ receptor.[10,11] In several studies investigating the efficacy of either mesalamine, probiotics, or balsalazide for the prevention of recurrent diverticulitis, only mesalamine resulted in significantly fewer recurrences.[13,15–17] Limited evidence suggests that long-term mesalamine therapy can reduce the likelihood of recurrence of diverticulitis.[18–23]

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Abbreviations used in this paper: AE, adverse event; CT, computed tomography; HRQOL, health-related quality of life; HUI2, Health Utilities Index Version Mark 2; QD, once daily; TEAE, treatment-emergent adverse event.

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We conducted 2 phase 3, multicenter, global, randomized, double-blind, dose–response, placebo-controlled studies (PREVENT1 and PREVENT2) with identical trial designs to evaluate whether multimatrix mesalamine prevents recurrent acute diverticulitis.

Methods

Patients

Eligible patients were 18 years of age or older with ≥1 documented episodes of acute diverticulitis in the previous 24 months that resolved without colonic resection, and without signs or symptoms of diverticulitis within 6 weeks of enrollment. In both PREVENT1 and PREVENT2, a report confirming an earlier episode of diverticulitis was required and could include computed tomography (CT; n = 469 and 372, respectively), magnetic resonance imaging (n = 0 and 2), ultrasound (n = 11 and 35), colonoscopy (n = 87 and 144), sigmoidoscopy (n = 18 and 21), and barium enema (n = 5 and 7). These numbers are based on how the most recent episode of diverticulitis was documented and might not have been the report(s) used to enroll patients in the study; patients could have >1 qualifying report. Endoscopic confirmation of ≥3 diverticula was required, and white blood cell count and polymorphonuclear leukocyte levels had to be within normal reference ranges at enrollment. Pregnant patients were excluded. Additional exclusion criteria included previous colorectal surgery, including surgical intervention for diverticular disease (with the exceptions of hemorrhoidectomy, colonic removal of polyps, and appendectomy); no complicated diverticulitis (no perforation or fistulization present on CT); right-sided diverticulosis only; active peptic ulcer disease; and history or current presence of inflammatory bowel disease. Patients with active irritable bowel syndrome, gastrointestinal bleeding, endometriosis or dysmenorrhea (≤6 months before baseline), or current or historical use of biologic drugs (ie, anti–tumor necrosis factor agents), immunomodulators, or systemic/rectal steroids (≤6 weeks before baseline) were also excluded.

Study Design

Two identical phase 3, multicenter, randomized, double-blind, dose–response, placebo-controlled studies were conducted globally to evaluate the efficacy and safety of 3 dosages of mesalamine vs placebo in the prevention of recurrence of diverticulitis during a period of 104 weeks. A screening visit occurred up to 21 days before randomization. Eligible patients were randomly assigned in a 1:1:1:1 ratio to receive: mesalamine 1.2 g once daily (QD) plus 3 matching placebo tablets per day, mesalamine 2.4 g QD (two 1.2-g tablets) plus 2 matching placebo tablets per day, mesalamine 4.8 g QD (four 1.2-g tablets), or placebo QD (4 tablets). The intervention assigned to each patient was determined by a computer-generated fixed-block randomization schedule. Randomization was stratified by country and by number of previous episodes of diverticulitis (1 or >1). Patients were to remain in the study for up to 104 weeks. Patients who prematurely discontinued the study intervention without protocol-defined recurrence were asked to participate in monthly telephone follow-up.

The primary end point was the proportion of patients who were diverticulitis recurrence free at 104 weeks. Secondary end points included time to recurrence of diverticulitis and the proportion of patients requiring surgical intervention. Tertiary end points included assessments of health-related quality of life (HRQOL) using the EQ-5D and Health Utilities Index Version Mark 2 (HUI2) questionnaires. Initially, diverticulitis recurrence was defined as either surgical intervention for diverticular disease or the presence of all of the following: bowel wall thickening (>5 mm) and/or fat stranding consistent with acute diverticulitis on CT of the abdomen/pelvis, elevated white blood cell count, and abdominal pain. However, after discussions with key experts in the field, it was agreed that the defining factor in diagnosing diverticulitis recurrence was a positive CT scan. Therefore, the protocol was amended in May 2008 (6 months after study initiation) so that a positive CT scan alone would be considered as a recurrence of diverticulitis. In March 2011 (12 months before study completion), the original primary end-point definition of diverticulitis recurrence (CT scan plus abdominal pain plus 15% white blood cell count increase) was reinstated for regulatory reasons. However, for the majority of the study, diverticulitis recurrence was defined as CT recurrence only.

Study Evaluations

Patients had 14 visits to the study center during 104 weeks, with periodic physical examination and laboratory monitoring, and were routinely queried about abdominal symptoms. At each visit, a symptom-driven examination was performed, presence or absence of abdominal pain consistent with diverticulitis was assessed, and vital signs (including weight) were recorded. Hematology and chemistry samples were also obtained. All patients who presented with clinical signs and symptoms of a suspected recurrent episode of acute diverticulitis were administered a full abdominal CT scan (within 24 hours) and laboratory assessment. Episodes of diverticulitis were classified as uncomplicated or complicated (presence of peritoneal abscess, diverticular stricture, fistula, or obstruction). The EQ-5D and HUI2 questionnaires were completed by patients at baseline and weeks 16, 52, 78, and 104. The EQ-5D questionnaire measures current HRQOL in 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The HUI2 questionnaire measures health status and generic HRQOL during the past week on the following 7 dimensions of health: sensation, cognition, mobility, self-care, emotion, pain, and fertility.

Study protocols were approved by appropriate independent ethics committees and Institutional Review Boards before study initiation (ClinicalTrials.gov ID: NCT00545740 and NCT00545103). Patients signed informed consent forms before any study procedures being conducted.

Statistical Analyses

The study population included randomized patients who took ≥1 dosages of study drug. Comparisons between study arms were conducted using Cochran-Mantel-Haenszel tests, stratified by number of previous diverticulitis episodes before study entry (1 or >1).

The sample size calculations assumed a 75% recurrence-free rate in the placebo arm and a 90% recurrence-free rate

in the mesalamine 4.8-g/d arm.[24,25] With these assumptions, 146 patients per study arm (584 patients total in each study) would provide 90% power to reject the null hypothesis of no difference in the primary end point between placebo and mesalamine 4.8 g/d at the 2-sided $\alpha = .05$ significance level.

All patients who discontinued the study intervention were encouraged to continue in the study via monthly telephone calls through week 104. Those who subsequently experienced signs and symptoms of recurrent diverticulitis were asked to return to the study site for follow-up testing to confirm recurrence. Patients who completely withdrew from the study (ie, no follow-up) before week 104 without a protocol-defined recurrence of diverticulitis were considered dropouts and assumed to be treatment failures for the intention-to-treat primary analysis. The type I error from performing 3 primary comparisons (each dosage level of mesalamine vs placebo) was minimized using a closed-test step-down method. In this iterative method, mesalamine 4.8 g/d vs placebo was evaluated first; only if that comparison was significant ($\alpha \leq .05$) would the next highest dosage be compared vs placebo.

Additional sensitivity analyses were performed using different methods for handling dropouts. These analyses included examination of the full analysis set, imputing the proportion of patients without recurrence based on study completers in the placebo arm, as an estimate of the proportion of patients without recurrence for all patients with missing data; study completers only, excluding any patients who withdrew from the study before week 104 without recurrence of diverticulitis; and intervention completers only, excluding any patients who discontinued the study intervention before week 104 without recurrence of diverticulitis. The difference between study completers and intervention completers was that study completers also included patients who stopped the study intervention but remained in the study via monthly follow-up calls.

Subgroup analyses were also conducted, comparing recurrence rates by geographic region, number of previous episodes of diverticulitis, time since the most recent recurrence, age group, baseline body mass index, race, and sex. Patients in PREVENT1 were recruited from the United States (n = 277), South America (Argentina [n = 15] and Colombia [n = 74]), Europe (France [n = 23], Spain [n = 8], Sweden [n = 38], and the United Kingdom [n = 13]), India (n = 13), Israel (n = 95), and Australia (n = 19)/New Zealand (n = 15). Patients in PREVENT2 were recruited from the United States (n = 351), South Africa (n = 60), Eastern Europe (Romania [n = 42] and Hungary [n = 14]), Western Europe (Finland [n = 18], Germany [n = 21], Italy [n = 9], and the Netherlands [n = 18]), Canada (n = 19), and Brazil (n = 40).

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities, version 14.1, and treatment-emergent AEs (TEAEs) were summarized by system organ class.

All authors had access to the study data, and reviewed and approved the final manuscript.

Results

Patient Characteristics

Demographic and baseline characteristics, as well as diverticular disease history, were well balanced across study arms (Table 1). In both studies, >79% of patients had body mass index scores in the overweight (25.0 kg/m^2 to <30.0 kg/m^2) or obese (≥30.0 kg/m^2) ranges. Across both studies, 5 patients without an earlier documented episode of diverticulitis were enrolled; these patients were retained in the intention-to-treat analysis.

A CONSORT (Consolidated Standards of Reporting Trials) diagram of patient outcomes is presented in Figure 1. In PREVENT1 (November 2007 through March 2012), of 776 patients screened, 590 were randomized. Of these, 515 (87.3%) completed the study to end-point evaluation, including 355 (60.2%) patients who completed the study to week 104 (completing study intervention or telephone follow-up), 150 (25.4%) who had recurrent diverticulitis, and 10 (1.7%) who had surgery due to diverticular disease. Due to the protocol amendment regarding the definition of recurrence, most of the 150 patients with protocol-defined recurrent diverticulitis were diagnosed with a positive CT only. The proportion of patients who completed the study intervention varied across study arms (range, 36.4% [n = 55/151; mesalamine 4.8 g/d] to 52.3% [n = 78/149; placebo]). Common reasons for discontinuation of the study intervention included lack of efficacy (46.8% [n = 152/325]), consent withdrawal (20.3% [n = 66/325]), and AEs (17.2% [n = 56/325]). In PREVENT2 (December 2007 through November 2011), 592 of 730 screened patients were randomized. A total of 536 (90.5%) patients completed the study to end-point evaluation, including 379 (64.0%) patients who completed the study to week 104, 150 (25.3%) who had recurrent diverticulitis, and 7 (1.2%) who had surgery due to diverticular disease. The proportion of patients who completed the study intervention was similar across study arms (range, 47.3% [n = 70/148; mesalamine 2.4 g/d] to 52.1% [n = 76/146; placebo]). Common reasons for premature discontinuation of the study intervention in PREVENT2 were lack of efficacy (50.5% [n = 151/299]), consent withdrawal (18.7% [n = 56/299]), and AEs (17.1% [n = 51/299]).

Efficacy

Primary and secondary efficacy end-point results, including sensitivity analyses from both studies, are summarized in Table 2. In both studies, none of the 3 dosages of mesalamine (1.2, 2.4, or 4.8 g/d) demonstrated a positive effect on the proportion of diverticulitis recurrence-free patients at week 104 compared with placebo. In PREVENT1, the difference in the proportion of patients without recurrence was lower for mesalamine 4.8 g/d compared with placebo (52.7% vs 64.6%; $P = .047$). In PREVENT2, there were no significant differences in diverticulitis recurrence-free rates at week 104 between any dosage of mesalamine and placebo. However, all 3 sensitivity analyses (imputation of recurrence rate from the placebo arm for patients with missing data, study completers only, and intervention completers only) revealed significantly fewer recurrence-free patients on mesalamine 1.2 g/d compared with placebo. In addition, in the intervention completers' analysis, significantly fewer patients on

Table 1. Demographic and Baseline Characteristics

Characteristic	PREVENT1					PREVENT2				
		Mesalamine dosage					Mesalamine dosage			
	Placebo (n = 147)	1.2 g/d (n = 143)	2.4 g/d (n = 143)	4.8 g/d (n = 150)	Overall (N = 583)	Placebo (n = 142)	1.2 g/d (n = 148)	2.4 g/d (n = 147)	4.8 g/d (n = 149)	Overall (N = 586)
Age, *y*, mean (SD)	57.1 (10.42)	55.1 (11.11)	54.5 (11.96)	54.5 (11.93)	55.3 (11.39)	55.7 (11.15)	57.8 (10.88)	54.2 (10.10)	56.7 (11.76)	56.1 (11.04)
Sex, n (%)										
Male	76 (51.7)	79 (55.2)	74 (51.7)	79 (52.7)	308 (52.8)	70 (49.3)	65 (43.9)	76 (51.7)	61 (40.9)	272 (46.4)
Female	71 (48.3)	64 (44.8)	69 (48.3)	71 (47.3)	275 (47.2)	72 (50.7)	83 (56.1)	71 (48.3)	88 (59.1)	314 (53.6)
BMI category, n (%)										
Underweight: <18.5	4 (2.7)	2 (1.4)	0 (0)	0 (0)	6 (1.0)	0 (0)	1 (0.7)	0 (0)	0 (0)	1 (0.2)
Normal: 18.5 to <25.0	28 (19.0)	25 (17.5)	26 (18.2)	28 (18.7)	107 (18.4)	26 (18.3)	31 (20.9)	25 (17.0)	24 (16.1)	106 (18.1)
Overweight: 25.0 to <30.0	54 (36.7)	56 (39.2)	64 (44.8)	62 (41.3)	236 (40.5)	54 (38.0)	70 (47.3)	54 (36.7)	56 (37.6)	234 (39.9)
Obese: ≥30.0	60 (40.8)	56 (39.2)	52 (36.4)	59 (39.3)	227 (38.9)	62 (43.7)	46 (31.1)	67 (45.6)	68 (45.6)	243 (41.5)
Missing	1 (0.7)	4 (2.8)	1 (0.7)	1 (0.7)	7 (1.2)	0 (0)	0 (0)	1 (0.7)	1 (0.7)	2 (0.3)
Race, n (%)										
Caucasian	122 (83.0)	113 (79.0)	119 (83.2)	123 (82.0)	477 (81.8)	134 (94.4)	139 (93.9)	137 (93.2)	141 (94.6)	551 (94.0)
Asian	4 (2.7)	4 (2.8)	3 (2.1)	3 (2.0)	14 (2.4)	0 (0)	0 (0)	1 (0.7)	1 (0.7)	2 (0.3)
Black/African American	2 (1.4)	5 (3.5)	2 (1.4)	4 (2.7)	13 (2.2)	5 (3.5)	5 (3.4)	5 (3.4)	7 (4.7)	22 (3.8)
Other[a]	19 (12.9)	21 (14.7)	19 (13.3)	20 (13.3)	79 (13.6)	3 (2.1)	4 (2.7)	4 (2.7)	0 (0)	11 (1.9)
Ethnicity, n (%)										
Hispanic or Latino	30 (20.4)	37 (25.9)	37 (25.9)	32 (21.3)	136 (23.3)	27 (19.0)	20 (13.5)	27 (18.4)	23 (15.4)	97 (16.6)
Not Hispanic or Latino	117 (79.6)	106 (74.1)	106 (74.1)	118 (78.7)	447 (76.7)	115 (81.0)	128 (86.5)	120 (81.6)	126 (84.6)	489 (83.4)
Duration since first episode of diverticulitis, *wk*										
Median (range)	21.9 (0–701)	23.1 (1–622)	21.1 (3–592)	31.0 (3–842)	24.1 (0–842)	35.3 (3–785)	27.8 (0–814)	38.1 (1–529)	33.1 (2–967)	34.0 (0–967)
Documented episodes of diverticulitis, n (%)										
0	0 (0)	0 (0)	2 (1.4)	0 (0)	2 (0.3)	1 (0.7)	0 (0)	0 (0)	2 (1.3)	3 (0.5)
1	89 (60.5)	80 (55.9)	86 (60.1)	84 (56.0)	339 (58.1)	87 (61.3)	95 (64.2)	83 (56.5)	85 (57.0)	350 (59.7)
2	34 (23.1)	42 (29.4)	32 (22.4)	40 (26.7)	148 (25.4)	32 (22.5)	30 (20.3)	37 (25.2)	34 (22.8)	133 (22.7)
3	13 (8.8)	11 (7.7)	10 (7.0)	16 (10.7)	50 (8.6)	12 (8.5)	12 (8.1)	16 (10.9)	13 (8.7)	53 (9.0)
4–5	7 (4.8)	8 (5.6)	11 (7.7)	6 (4.0)	32 (5.5)	7 (4.9)	8 (5.4)	6 (4.1)	13 (8.7)	34 (5.8)
6–10	4 (2.7)	2 (1.4)	2 (1.4)	4 (2.7)	12 (2.1)	3 (2.1)	3 (2.0)	4 (2.7)	1 (0.7)	11 (1.9)
≥11	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.7)	1 (0.7)	2 (0.3)
Diverticulitis hospitalizations, n (%)										
0	60 (40.8)	57 (39.9)	52 (36.4)	60 (40.0)	229 (39.3)	86 (60.6)	87 (58.8)	78 (53.1)	86 (57.7)	337 (57.5)
1	74 (50.3)	70 (49.0)	76 (53.1)	75 (50.0)	295 (50.6)	42 (29.6)	51 (34.5)	51 (34.7)	49 (32.9)	193 (32.9)
2–3	12 (8.2)	15 (10.5)	10 (7.0)	15 (10.0)	52 (8.9)	13 (9.2)	9 (6.1)	17 (11.6)	11 (7.4)	50 (8.5)
4–5	1 (0.7)	1 (0.7)	3 (2.1)	0 (0)	5 (0.9)	0 (0)	1 (0.7)	1 (0.7)	0 (0)	2 (0.3)
Missing	0 (0)	0 (0)	2 (1.4)	0 (0)	2 (0.3)	1 (0.7)	0 (0)	0 (0)	3 (2.0)	4 (0.7)
Duration since most recent episode of diverticulitis, *wk*										
Median (range)	14.7 (0–94)	12.0 (1–419)	12.9 (1–93)	13.6 (1–114)	13.0 (0–419)	17.9 (2–100)	16.5 (0–101)	18.3 (1–122)	13.9 (2–93)	16.5 (0–122)

BMI, body mass index.

[a]Includes Hispanic, multiracial, mixed race, Armenian, New Zealand Maori, Middle Eastern, Caucasian plus Asian, Caucasian plus African American, and Hispanic plus white.

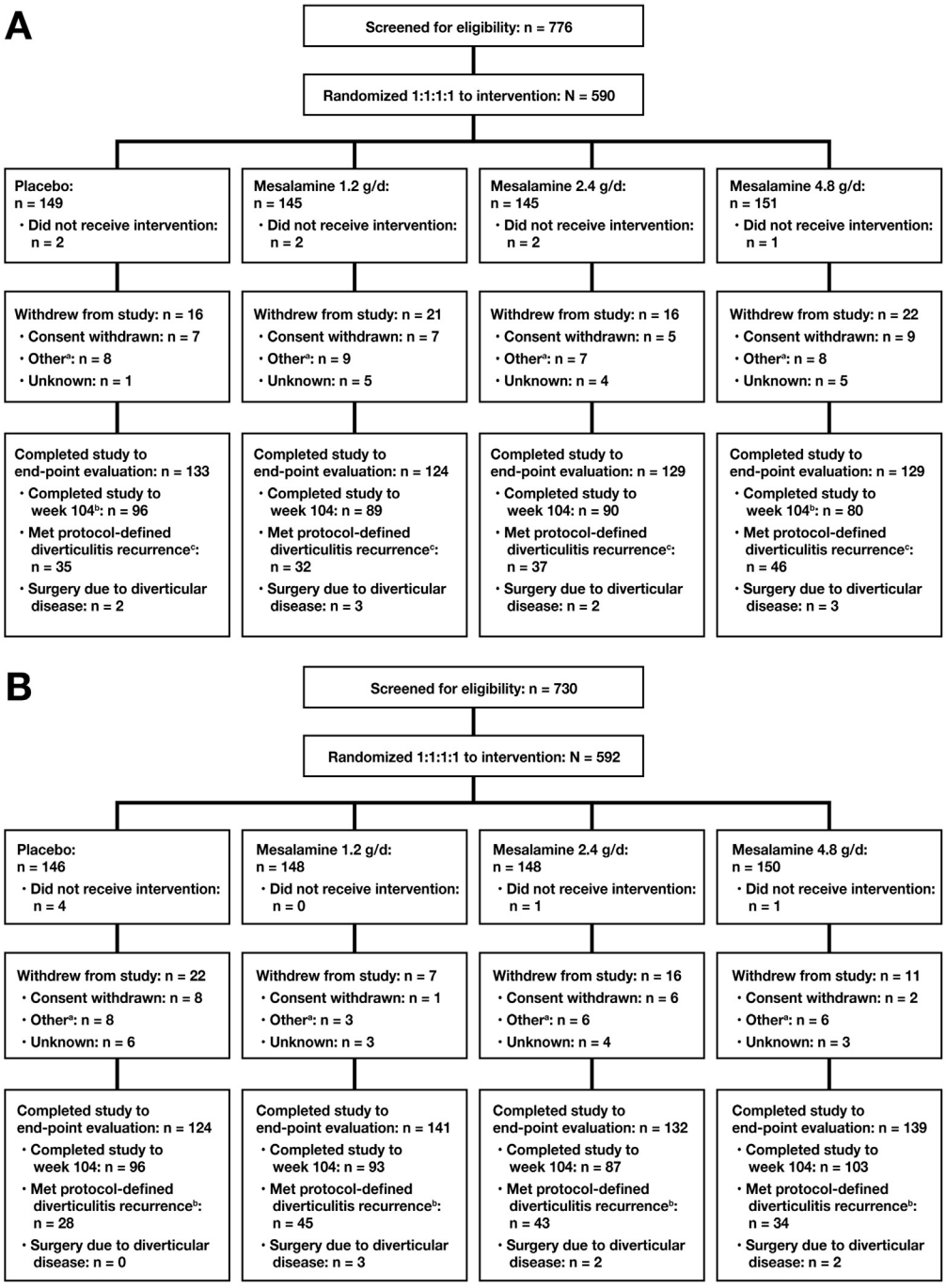

Figure 1. Patient disposition in (*A*) PREVENT1 and (*B*) PREVENT2. (*A*) PREVENT1 [a]"Other" reasons included lost to follow-up, contact not made, suspected recurrence of diverticulitis, study terminated at site, confirmed episode of diverticulitis, serious adverse event, noncompliance, patient's husband did not want her to participate, and investigator's decision. [b]Two patients who completed the study via telephone follow-up had a recurrence that met the primary end point. [c]For the majority of the study, diverticulitis recurrence was defined as a positive CT scan only. (*B*) PREVENT2. [a]"Other" reasons included lost to follow-up, recurrence of diverticulitis, AE or serious AE, and protocol violation (no disease under study). [b]For the majority of the study, diverticulitis recurrence was defined as a positive CT scan only.

mesalamine 2.4 g/d were recurrence-free compared with placebo. Sensitivity analyses confirmed the primary efficacy results in both studies, showing no positive effect of mesalamine in the reduction of diverticulitis at week 104. There were no meaningful trends in any subgroup analyses on the primary end point.

Secondary end points also showed no therapeutic benefit of mesalamine on diverticulitis recurrence. Mesalamine did not positively affect the time to recurrence (Figure 2). In PREVENT2, the time to recurrence was significantly shorter for mesalamine 1.2 and 2.4 g/d than for placebo ($P = .013$ and $P = .044$, respectively). The presence of abdominal pain was similar across study arms (PREVENT1: 11.7% [n = 51/436] for mesalamine vs 10.9% [n = 16/147] for placebo; PREVENT2: 11.9% [n = 53/444] for mesalamine vs 8.5% [n = 12/142] for placebo). In both studies, the proportion of patients requiring surgery for diverticular disease was low and generally comparable across study arms (range, 2.0%−3.3% [PREVENT1]; 1.4%−4.7% [PREVENT2]).

With regard to tertiary HRQOL end points, a majority of patients reported "no problems" for all 5 measured domains

Table 2. Summary of Efficacy Results: Patients Without Recurrence of Diverticulitis

Parameter	PREVENT1				PREVENT2			
		Mesalamine dosage				Mesalamine dosage		
	Placebo	1.2 g/d	2.4 g/d	4.8 g/d	Placebo	1.2 g/d	2.4 g/d	4.8 g/d
Diverticulitis recurrence-free rate[a]								
Full analysis set, n	147	143	143	150	142	148	147	149
Patients without recurrence, n (%)	95 (64.6)	89 (62.2)	90 (62.9)	79 (52.7)	96 (67.6)	93 (62.8)	87 (59.2)	103 (69.1)
Difference from placebo, %	NA	−2.4	−1.7	−12.0	NA	−4.8	−8.4	1.5
95% CI for the difference	NA	−14.2 to 9.4	13.4 to 10.1	−23.7 to −0.2	NA	−16.4 to 6.9	−20.2 to 3.3	−9.9 to 12.9
P value[b]	NA	.780	.741	.047	NA	.368	.159	.778
Sensitivity analyses								
Using imputation of placebo arm recurrence rate for study withdrawals,[c] n	147	143	143	150	142	148	147	149
Patients without recurrence, n (%)	116 (78.9)	118 (82.5)	113 (79.0)	114 (76.0)	126 (88.7)	118 (79.7)	122 (83.0)	128 (85.9)
Difference from placebo, %	NA	3.6	0.1	−2.9	NA	−9.0	−5.7	−2.8
95% CI for the difference	NA	−6.2 to 13.4	−10.0 to 10.2	−13.1 to 7.3	NA	−18.0 to 0	−14.4 to 2.9	−11.1 to 5.5
P value[b]	NA	.328	.984	.668	NA	.032	.164	.488
Study completers only,[d] n	120	110	115	109	108	120	110	123
Patients without recurrence, n (%)	95 (79.2)	89 (80.9)	90 (78.3)	79 (72.5)	96 (88.9)	93 (77.5)	87 (79.1)	103 (83.7)
Difference from placebo, %	NA	1.7	−0.9	−6.7	NA	−11.4	−9.8	−5.1
95% CI for the difference	NA	−9.5 to 12.9	−12.2 to 10.4	−18.7 to 5.3	NA	−21.8 to −0.1	−20.4 to 0.8	−14.8 to 4.5
P value[b]	NA	.584	.885	.383	NA	.019	.053	.295
Intervention completers only,[e] n	99	85	85	80	86	95	92	91
Patients without recurrence, n (%)	77 (77.8)	70 (82.4)	62 (72.9)	55 (68.8)	76 (88.4)	73 (76.8)	70 (76.1)	74 (81.3)
Difference from placebo, %	NA	4.6	−4.8	−9.0	NA	−11.5	−12.3	−7.1
95% CI for the difference	NA	−0.8 to 17.2	−18.4 to 8.8	−23.2 to 5.1	NA	−23.5 to 0.4	−24.4 to 0.1	−18.7 to 4.6
P value[b]	NA	.362	.485	.239	NA	.048	.035	.202

CI, confidence interval; NA, not applicable.
[a]Primary efficacy end point was the proportion of patients without recurrence of diverticulitis at week 104 (withdrawals considered as recurrences).
[b]The proportion of patients without recurrence of diverticulitis at week 104 or those who were recurrence free of diverticulitis up to week 104 was compared among each of the 3 mesalamine groups and placebo using a Cochran-Mantel-Haenszel test stratified by number of previous episodes of diverticulitis (≥1).
[c]Examination of the full analysis set imputing the proportion of patients in the study completers population as an estimate of the proportion of patients without recurrence for all patients with missing data at week 104.
[d]Excluding any patients who withdrew from the study before week 104 without meeting the primary end point of recurrence.
[e]Excluding any patients who discontinued study drug prior to week 104 without meeting the primary end point of recurrence.

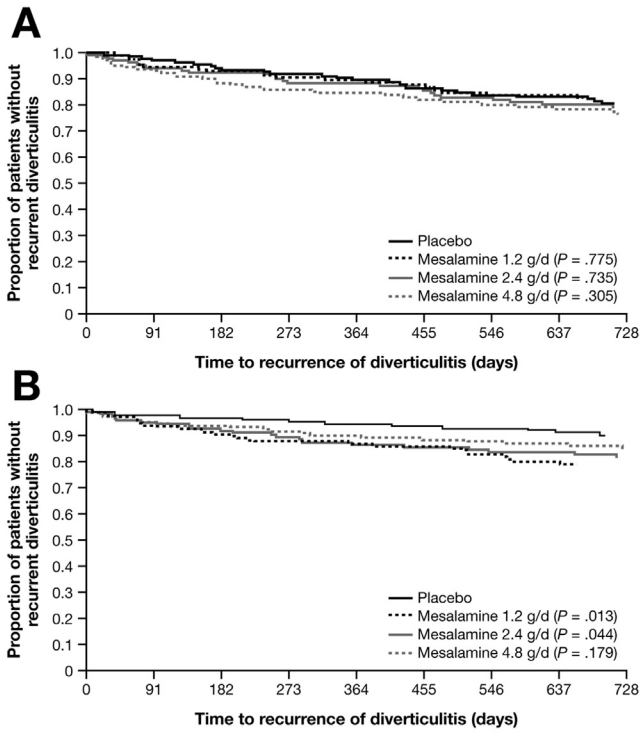

Figure 2. Kaplan-Meier analysis of the time to recurrence of diverticulitis in (*A*) PREVENT1 and (*B*) PREVENT2.

of the EQ-5D at baseline and week 104/early withdrawal. Overall, the EQ-5D results revealed no patterns or trends across study arms for both PREVENT1 and PREVENT2. Similarly, for the HUI2 questionnaire, no differences in results were observed across study arms at baseline or week 104 for both PREVENT1 and PREVENT2.

Safety

Safety results were similar across study arms in both PREVENT1 and PREVENT2 (Table 3). In PREVENT1, 72.5% of patients treated with mesalamine and 76.2% of patients who received placebo had ≥1 TEAEs; most were mild or moderate in severity.

The frequency of serious TEAEs in PREVENT1 was generally low and comparable across study arms (11.2% across patients receiving mesalamine and 10.9% receiving placebo). Most serious TEAEs occurred in 1 patient each; serious TEAEs occurring in >1 patient included angina pectoris (n = 4), acute myocardial infarction (n = 3), abdominal pain (n = 3), coronary artery insufficiency (n = 2), urinary tract infection (n = 2), gastroenteritis (n = 2), sepsis (n = 2), pneumonia (n = 2), road traffic accident (n = 2), uterine cancer (n = 2), and chronic obstructive pulmonary disease (n = 2). Three patients in the mesalamine 4.8-g/d group had serious TEAEs (pancreatic pseudocyst, acute pancreatitis, and pyrexia) considered related to study drug.

In PREVENT2, 74.1% of patients on mesalamine and 73.9% on placebo had ≥1 TEAEs. Serious TEAEs were reported in 8.1% (mesalamine) and 10.6% (placebo) of patients. Serious TEAEs occurring in >1 patient included pneumonia (n = 4), angina pectoris (n = 3), atrial fibrillation (n = 2), abdominal pain (n = 2), chest pain (n = 2), cerebrovascular accident (n = 2), and dyspnea (n = 2). One patient on mesalamine 4.8 g/d had a drug-related serious TEAE of agranulocytosis, which resolved on discontinuation of mesalamine and management with filgrastim. There was 1 death in this study due to cirrhosis-associated hepatic and multi-organ failure. The investigator considered all the patients' events as unrelated to study drug.

The proportions of patients who experienced TEAEs leading to discontinuation of the study intervention were comparable across study arms, with gastrointestinal disorders being the most common. Additionally, types and frequencies of TEAEs by maximum severity were similar among study arms, with no apparent trends by mesalamine dosage.

Discussion

Although several studies have suggested that mesalamine can be effective for prevention of diverticulitis recurrence,[13,18–23] the evidence from previous studies has been limited.[16,26] The PREVENT1 and PREVENT2 studies are the first large-scale, placebo-controlled, double-blind, randomized, controlled trials conducted to evaluate the efficacy of mesalamine for the prevention of recurrent diverticulitis. The studies provide consistent and strong evidence that none of the 3 dosages of mesalamine studied (1.2, 2.4, or 4.8 g/d) had a positive effect on the reduction of protocol-defined recurrence of diverticulitis compared with placebo. In PREVENT1, significantly fewer patients on mesalamine 4.8 g/d were recurrence-free compared with those on placebo (52.7% vs 64.6%); however, this difference was primarily attributable to the higher withdrawal rate in the mesalamine 4.8-g/d group (47.0% vs 35.6% for placebo), as patients who withdrew for any reason were considered to be treatment failures. Performing the analysis on the subset of patients who completed the study intervention to week 104 revealed no difference in recurrence-free rates between mesalamine 4.8 g/d and placebo. Results from the PREVENT2 sensitivity analyses showed improvement in recurrence-free rates with placebo compared with mesalamine at 1.2 g/d and 2.4 g/d. These PREVENT2 sensitivity results are in contrast to the primary analyses, which did not show any difference between groups when dropouts were considered failures. Regardless, it is clear that mesalamine provided no positive effect in prevention of diverticulitis. In addition, no consistent patterns or trends in HRQOL ratings were observed with mesalamine administration.

In the randomized populations in PREVENT1 and PREVENT2, 87.3% and 90.5% of patients, respectively, completed the study to evaluation and/or follow-up at week 104. In the full analysis set during the 2-year period, across all study arms, the diverticulitis recurrence-free rate ranged in PREVENT1 from 52.7% (mesalamine 4.8 g/d) to 64.6% (placebo), and in PREVENT2 from 59.2% (mesalamine 2.4 g/d) to 69.1% (mesalamine 4.8 g/d). Early patient withdrawals, ranging from 10.7% (placebo) to 14.6% (mesalamine 4.8 g/d) in PREVENT1 and 4.7% (mesalamine

Table 3. Treatment-Emergent Adverse Events (≥5% in Any Group)

	PREVENT1					PREVENT2				
		Mesalamine dosage					Mesalamine dosage			
TEAEs	Placebo (n = 147)	1.2 g/d (n = 143)	2.4 g/d (n = 143)	4.8 g/d (n = 150)	Overall (N = 436)	Placebo (n = 142)	1.2 g/d (n = 148)	2.4 g/d (n = 147)	4.8 g/d (n = 149)	Overall (N = 444)
≥1 TEAE	112 (76.2)	109 (76.2)	106 (74.1)	101 (67.3)	316 (72.5)	105 (73.9)	108 (73.0)	111 (75.5)	110 (73.8)	329 (74.1)
Abdominal pain	16 (10.9)	17 (11.9)	16 (11.2)	18 (12.0)	51 (11.7)	12 (8.5)	19 (12.8)	19 (12.9)	15 (10.1)	53 (11.9)
Diarrhea	12 (8.2)	13 (9.1)	12 (8.4)	12 (8.0)	37 (8.5)	12 (8.5)	15 (10.1)	15 (10.2)	18 (12.1)	48 (10.8)
Urinary tract infection	17 (11.6)	14 (9.8)	12 (8.4)	8 (5.3)	34 (7.8)	7 (4.9)	11 (7.4)	14 (9.5)	10 (6.7)	35 (7.9)
Headache	10 (6.8)	13 (9.1)	6 (4.2)	14 (9.3)	33 (7.6)	13 (9.2)	14 (9.5)	10 (6.8)	14 (9.4)	38 (8.6)
Nasopharyngitis	13 (8.8)	6 (4.2)	15 (10.5)	7 (4.7)	28 (6.4)	9 (6.3)	5 (3.4)	10 (6.8)	8 (5.4)	23 (5.2)
Upper respiratory tract infection	14 (9.5)	9 (6.3)	3 (2.1)	10 (6.7)	22 (5.0)	5 (3.5)	6 (4.1)	6 (4.1)	6 (4.0)	18 (4.l)
Back pain	12 (8.2)	8 (5.6)	5 (3.5)	8 (5.3)	21 (4.8)	12 (8.5)	10 (6.8)	11 (7.5)	11 (7.4)	32 (7.2)
Sinusitis	8 (5.4)	9 (6.3)	7 (4.9)	5 (3.3)	21 (4.8)	11 (7.7)	12 (8.1)	8 (5.4)	10 (6.7)	30 (6.8)
Influenza	3 (2.0)	5 (3.5)	11 (7.7)	4 (2.7)	20 (4.6)	11 (7.7)	11 (7.4)	8 (5.4)	9 (6.0)	28 (6.3)
Hypertension	1 (0.7)	5 (3.5)	8 (5.6)	6 (4.0)	19 (4.4)	8 (5.6)	6 (4.1)	8 (5.4)	2 (1.3)	16 (3.6)
Bronchitis	3 (2.0)	7 (4.9)	8 (5.6)	3 (2.0)	18 (4.1)	7 (4.9)	8 (5.4)	7 (4.8)	9 (6.0)	24 (5.4)
Dyspepsia	2 (1.4)	7 (4.9)	7 (4.9)	4 (2.7)	18 (4.1)	6 (4.2)	5 (3.4)	11 (7.5)	6 (4.0)	22 (5.0)
Nausea	5 (3.4)	10 (7.0)	1 (0.7)	6 (4.0)	17 (3.9)	11 (7.7)	5 (3.4)	8 (5.4)	10 (6.7)	23 (5.2)
Flatulence	4 (2.7)	9 (6.3)	5 (3.5)	3 (2.0)	17 (3.9)	5 (3.5)	4 (2.7)	7 (4.8)	4 (2.7)	15 (3.4)
Arthralgia	13 (8.8)	7 (4.9)	5 (3.5)	4 (2.7)	16 (3.7)	7 (4.9)	5 (3.4)	3 (2.0)	7 (4.7)	15 (3.4)
Constipation	8 (5.4)	7 (4.9)	3 (2.1)	5 (3.3)	15 (3.4)	12 (8.5)	9 (6.1)	6 (4.1)	6 (4.0)	21 (4.7)
Lower abdominal pain	7 (4.8)	7 (4.9)	3 (2.1)	2 (1.3)	12 (2.8)	7 (4.9)	5 (3.4)	2 (1.4)	10 (6.7)	17 (3.8)
Cough	3 (2.0)	1 (0.7)	3 (2.1)	1 (0.7)	5 (1.1)	2 (1.4)	9 (6.1)	3 (2.0)	4 (2.7)	16 (3.6)

NOTE. Values are n (%).
TEAE, treatment-emergent adverse event.

1.2 g/d) to 15.1% (placebo) in PREVENT2, were considered as recurrences. However, of the total number of treatment failures (study dropouts plus those with recurrence), the majority (63.8% and 70.4% of patients in PREVENT1 and PREVENT2, respectively) met the protocol definition of diverticulitis recurrence. In the sensitivity analysis examining study completers, diverticulitis recurrence-free rates ranged from 72.5% (mesalamine 4.8 g/d) to 80.9% (mesalamine 1.2 g/d) in PREVENT1 and from 77.5% (mesalamine 1.2 g/d) to 88.9% (placebo) in PREVENT2.

The robust results of these 2 large randomized studies suggest that mesalamine is not effective and should not be used for the prevention of recurrent diverticulitis. The low rates of surgery (<5% across all cohorts) observed in both PREVENT1 and PREVENT2 suggest that conservative management of recurrent diverticulitis is the norm, even in patients with a history of diverticulitis.[27] The rate of complicated diverticulitis was low (PREVENT 1, n = 9; PREVENT 2, n = 11), which contributed to the low observed rate of surgical treatment. The quest for therapy to prevent recurrent diverticulitis remains, and alternative options should continue to be explored. Although a few randomized studies have examined the effect of a high-fiber diet or fiber supplement in patients with diverticular disease, inconsistent findings have been reported with regard to overall improvement in disease symptoms.[28,29]

The rates of recurrence observed in the current studies are broadly consistent with the natural history of acute diverticulitis. Binda et al[30] found that most patients medically treated for diverticulitis (>60%) were asymptomatic for at least 9 years after an initial acute episode of diverticulitis, and about 1 in 5 patients had chronic persistent symptoms at 12 years of follow-up (mean actuarial follow-up, 10.7 years).[30] The rate of recurrence (defined as requiring hospital admission) for patients receiving medical therapy was 17.2% (recurrence-free rate of 82.8%), with a cumulative risk of emergency surgery of 8.3%. In our study, the recurrence-free rate after 2 years of follow-up was 60.5% across all study arms in PREVENT1 and 64.7% in PREVENT2; the surgical rate up to week 104 was 2.7% in PREVENT1 and 2.7% in PREVENT2. However, the rates of recurrence in the current studies included those who dropped out and did not include a requirement of hospitalization. In addition, patient follow-up ended at 2 years, limiting the utility of the data for studying the long-term natural history of diverticulitis.

Parente et al[31] also recently examined mesalamine for the prevention of diverticulitis recurrence. In this study, 96 patients with a history of uncomplicated diverticulitis were administered either mesalamine 800 mg twice daily for 10 days/month or placebo for 24 months. At month 24, 13% on mesalamine and 28% on placebo had experienced a recurrence; this difference was not significant. Patients on mesalamine did demonstrate significant improvement on a physical condition and quality of life questionnaire.[31] Stollman et al[32] also examined the efficacy of mesalamine 2400 mg QD in reducing gastrointestinal symptoms in patients with a history of diverticulitis. A total of 117 patients were assigned to receive placebo, mesalamine, or mesalamine plus probiotic for 12 weeks, and were followed for another 9 months. At predetermined visits across the year, gastrointestinal symptoms were consistently lower in the mesalamine groups, although these differences were not significant. At 1 year, there was no difference between groups on rate of diverticulitis recurrence (31% placebo; 28.1% mesalamine; 37% mesalamine plus probiotic). Time to recurrence was longer for the mesalamine groups, but not significantly different from standard of care.[32] Unlike the results from Parente and Stollman, the current PREVENT studies did not reveal any trend toward improvement in quality of life (data not shown) or diverticulitis symptoms with mesalamine compared with placebo. Despite the modest improvements demonstrated by Parente and Stollman with mesalamine administration, neither study showed significant improvements in prevention of diverticulitis.

Although obesity has been shown to be a risk factor for diverticulitis and diverticular bleeding,[33] subgroup analyses of the predominately overweight participants in the PREVENT studies showed no correlation of body mass index to diverticulitis recurrence. Subgroup analyses by geographic region also showed no meaningful trends in the overall results. Patients from diverse geographic regions were included. Although the prevalence of diverticular disease is high in the United States, Europe, and Australia, it is much lower in urbanized Asian areas and is almost unknown in rural Africa or Asia.[34]

Mesalamine did not prevent recurrence of diverticulitis compared with placebo; results were robust, with no therapeutic effect of mesalamine evident using diverticulitis recurrence and across all sensitivity analyses performed to account for dropouts. All dosages of mesalamine were well tolerated. In conclusion, mesalamine is not effective in preventing recurrent diverticulitis.

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