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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