

## A COMPARISON OF OMEPRAZOLE WITH RANITIDINE FOR ULCERS ASSOCIATED WITH NONSTEROIDAL ANTIINFLAMMATORY DRUGS

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### ABSTRACT

**Background** Suppressing acid secretion is thought to reduce the risk of ulcers associated with regular use of nonsteroidal antiinflammatory drugs (NSAIDs), but the best means of accomplishing this is uncertain.

**Methods** We studied 541 patients who required continuous treatment with NSAIDs and who had ulcers or more than 10 erosions in either the stomach or duodenum. Patients were randomly assigned to double-blind treatment with omeprazole, 20 mg or 40 mg orally per day, or ranitidine, 150 mg orally twice a day, for four or eight weeks, depending on when treatment was successful (defined as the resolution of ulcer and the presence of fewer than five erosions in the stomach and fewer than five erosions in the duodenum, and not more than mild dyspepsia). We randomly assigned 432 patients in whom treatment was successful to maintenance treatment with either 20 mg of omeprazole per day or 150 mg of ranitidine twice a day for six months.

**Results** At eight weeks, treatment was successful in 80 percent (140 of 174) of the patients in the group given 20 mg of omeprazole per day, 79 percent (148 of 187) of those given 40 mg of omeprazole per day, and 63 percent (110 of 174) of those given ranitidine ( $P < 0.001$  for the comparison with 20 mg of omeprazole and  $P = 0.001$  for the comparison with 40 mg of omeprazole). The rates of healing of all types of lesions were higher with omeprazole than with ranitidine. During maintenance therapy, the estimated proportion of patients in remission at the end of six months was 72 percent in the omeprazole group and 59 percent in the ranitidine group. The rates of adverse events were similar between groups during both phases. Both medications were well tolerated.

**Conclusions** In patients who use NSAIDs regularly, omeprazole healed and prevented ulcers more effectively than did ranitidine. (N Engl J Med 1998;338:719-26.)

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**N**ONSTEROIDAL antiinflammatory drugs (NSAIDs) are commonly used to treat pain and inflammation.<sup>1</sup> Their use is frequently limited by gastrointestinal side effects, ranging from dyspeptic symptoms to life-threatening bleeding or perforation of gastroduodenal ulcers,<sup>2-4</sup> especially in the elderly.<sup>4</sup>

NSAIDs are thought to cause mucosal injury by several mechanisms.<sup>5</sup> Some have a direct toxic action

on the gastric mucosa that is exacerbated by acidity, since acidity promotes the absorption of NSAIDs in their non-ionized form.<sup>6</sup> They also impair prostaglandin-dependent mucosal protective mechanisms. When the surface cells have been damaged by either of these mechanisms, a second wave of injury mediated by luminal acid often occurs and generates deeper ulcerative lesions.<sup>7</sup> Prior approaches to preventing the side effects of NSAIDs have included treatment with histamine H<sub>2</sub>-receptor antagonists to inhibit acid secretion and the administration of prostaglandin analogues to replace the depleted endogenous prostaglandins. However, H<sub>2</sub>-receptor antagonists are not very effective for healing or preventing NSAID-associated gastric ulcers during continued therapy with NSAIDs, although they speed healing<sup>8</sup> and help prevent duodenal ulcers.<sup>8-10</sup> The use of prostaglandin analogues such as misoprostol is limited by gastrointestinal side effects such as diarrhea and abdominal cramps.<sup>11</sup>

In short-term studies, the proton-pump inhibitor omeprazole prevented aspirin-induced gastric mucosal damage and lesions.<sup>12,13</sup> Omeprazole heals ulcers effectively and is equally efficacious for gastric or duodenal ulcers in the presence or absence of NSAID treatment.<sup>14,15</sup> We compared the efficacy of omeprazole and ranitidine in patients with gastroduodenal ulcers and erosions associated with continuous NSAID therapy.

### METHODS

#### Study Design and Recruitment

The study, conducted between August 1992 and April 1995, was an international double-blind, randomized evaluation of

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omeprazole and ranitidine for healing and preventing gastroduodenal lesions in patients receiving long-term treatment with NSAIDs. The study was conducted in 73 centers in 15 countries, in accordance with the principles of good clinical practice<sup>16</sup> and the Declaration of Helsinki (Tokyo amendments).

The study had two phases: a healing phase and a maintenance phase.

### Healing Phase

Patients of either sex, 18 to 85 years of age, who had any condition requiring continuous therapy with NSAIDs above specified therapeutic doses (no maximal dose), and not more than 10 mg of prednisolone or its equivalent per day, were recruited. The minimal (and mean) daily oral doses of the commonly used NSAIDs were as follows: 50 mg (113 mg) of diclofenac, 50 mg (111 mg) of indomethacin, and 500 mg (775 mg) of naproxen. The patients underwent endoscopy, and those found to have any or all of the following were invited to enter the study: ulcers that were 3 mm or more in diameter, more than 10 erosions in the stomach, and more than 10 erosions in the duodenum. Erosions were assessed with the modified Lanza scale.<sup>9,10</sup> Major exclusion criteria were neck instability that would compromise endoscopy, concurrent erosive or ulcerative esophagitis, pyloric stenosis, major active gastrointestinal bleeding, or disorders that might modify the absorption of study drugs.

All patients provided written informed consent. They were randomly assigned (in blocks of three per site) to receive oral double-blind treatment with 20 mg of omeprazole (Losec, Astra Hässle, Mölndal, Sweden) per day, 40 mg of omeprazole per day, or 150 mg of ranitidine (Zantac, Glaxo Wellcome, Research Triangle Park, N.C.) twice daily for four or eight weeks, depending on when treatment was successful. Treatment success was defined in advance as the disappearance of ulcer and the presence of fewer than five erosions in the stomach, fewer than five erosions in the duodenum, and not more than mild dyspeptic symptoms. Patients in whom treatment remained unsuccessful after eight weeks received 40 mg of omeprazole per day for a further four or eight weeks. The patients visited the clinic monthly and continued to take NSAIDs throughout the study.

### Maintenance Phase

Patients in whom treatment was successful in the healing phase were eligible for the maintenance phase if they used therapeutic doses of NSAIDs at least five days per week, had no concurrent erosive or ulcerative reflux esophagitis, and had no abnormalities in the laboratory tests regarded as clinically important by the investigator. The patients were randomly assigned (in blocks of two per site) to treatment with either 20 mg of omeprazole per day or 150 mg of ranitidine twice daily for six months. They were evaluated after one, three, and six months and if they had troublesome dyspeptic symptoms or adverse events. Treatment failure, specified in advance, during the maintenance phase was defined as a finding of any of the following: gastric or duodenal ulcer, more than 10 erosions in the stomach, more than 10 erosions in the duodenum, moderate or severe symptoms of dyspepsia, or adverse events resulting in the discontinuation of treatment. When a patient withdrew from the study, both randomized treatment and assessment of its effectiveness ceased.

### Clinical and Laboratory Assessments

At all visits, the esophagus, stomach, and duodenum were examined endoscopically for erosions or ulcers and biopsy specimens were obtained from gastric ulcers to rule out malignant conditions. Antral-biopsy specimens were obtained at the beginning of the healing phase to evaluate the patients' *Helicobacter pylori* status with the urease enzyme test (CLO test, Delta West, Bentley, Australia). Patients infected with *H. pylori* were not treated for the infection, because there was no evidence that this benefited them<sup>17,18</sup> and because *H. pylori*-stimulated mucosal synthe-

sis of prostaglandin has been suggested to be beneficial for NSAID-associated ulcers.<sup>19</sup>

Patients were asked standardized questions about their overall upper gastrointestinal symptoms and dyspeptic symptoms (epigastric or abdominal pain, heartburn, nausea, vomiting, upper abdominal bloating, and empty feeling in stomach) during the preceding seven days. Their overall symptoms and individual symptoms were graded as absent, mild (easily tolerated), moderate (interfering with normal activities), or severe (incapacitating; leaving the patient unable to perform normal activities). Safety assessments were based on the reported symptoms, adverse events, and the results of standard blood screening. We assessed compliance by measuring the amount of medication that was returned.

### Statistical Analysis

We compared the rates of successful treatment in all patients who received at least one dose of medication using a Mantel-Haenszel life-table test combining data at four and eight weeks. We also calculated the rates of healing of gastric ulcer, duodenal ulcer, and erosions separately and compared the rates between treatment groups using the Mantel-Haenszel test. A logistic-regression analysis of prognostic factors that may have influenced the success of treatment at four weeks included treatment, site and type of lesion, ulcer size, *H. pylori* status at entry, blood group, type of arthritic disease, smoking status, age, and sex. Upper gastrointestinal symptoms were analyzed by Wilcoxon's test, with stratification according to severity at enrollment.

The length of time to treatment failure in the maintenance phase was compared between treatment groups with remission curves estimated by Kaplan-Meier life-table analysis and the log-rank test. To evaluate possible prognostic factors, a Cox regression model was used with the duration of remission as the dependent variable.

The study was designed to have a power of at least 80 percent for two-sided tests at the 1.7 percent level of significance in the healing phase (with the Bonferroni adjustment for the three pairwise comparisons) and at the 5 percent level in the maintenance phase. The primary efficacy analysis used an intention-to-treat approach that included all patients meeting major entry criteria who had taken at least one dose of medication. The safety analysis included all patients who received at least one dose of medication and for whom there were safety data, regardless of whether they met the entry criteria for the trial. For these reasons there were small differences in the numbers of patients included in the efficacy and safety analyses. No interim analyses were conducted. For cases in which data censoring arising from the use of the life-table approach to data analysis prevented valid statistical comparisons, P values are not presented.

## RESULTS

### Characteristics of the Patients

#### Healing Phase

Of 541 patients randomly assigned to treatment, 535 were included in the efficacy analysis according to treatment actually received (174 received 20 mg of omeprazole per day, 187 received 40 mg of omeprazole per day, and 174 received 150 mg of ranitidine twice daily). Three patients who received no trial drug, one patient who did not receive an NSAID, one whose NSAID dosage was below the required threshold, and one in whom inflammation was not verifiable were not evaluated. Demographic characteristics, endoscopic findings, *H. pylori* status, and the various underlying arthritic diseases requir-

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS INCLUDED IN THE EFFICACY ANALYSIS.

CHARACTERISTIC	HEALING PHASE			MAINTENANCE PHASE	
	OMEPRAZOLE, 20 mg/DAY (N = 174)	OMEPRAZOLE, 40 mg/DAY (N = 187)	RANITIDINE, 150 mg TWICE DAILY (N = 174)	OMEPRAZOLE, 20 mg/DAY (N = 210)	RANITIDINE, 150 mg TWICE DAILY (N = 215)
Sex (M/F)	49/125	73/114	53/121	64/146	66/149
Age (yr)					
Mean	56	57	57	56	56
Range	25–80	26–80	20–82	31–78	20–80
Mean weight (kg)					
Men	80	79	74	76	78
Women	70	68	68	71	68
Mean height (cm)					
Men	173	172	172	173	172
Women	161	160	160	161	161
no. of patients					
Previous gastrointestinal disease					
Dyspeptic symptoms	139	157	144	177	176
Peptic ulcer	51	53	60	53	68
Bleeding	17	17	19	16	15
Current gastrointestinal disease					
Duodenal ulcer with or without erosions	36	42	42	41	56
Gastric ulcer with or without erosions	70	67	70	81	74
Duodenal ulcer and gastric ulcer with or without erosions	7	5	5	3	10
Erosions only	61	73	57	85	75
Maximal ulcer diameter (all sites)					
<5 mm	18	20	17	25	17
5–9 mm	53	55	70	60	81
≥10 mm	42	39	30	40	42
<i>Helicobacter pylori</i> status					
Positive	83	91	72	104	100
Negative	77	76	86	85	96
Unknown	14	20	16	21	19
Disease requiring NSAIDs					
Rheumatoid arthritis	79	74	81	99	88
Osteoarthritis	59	69	54	67	71
Psoriatic arthritis	10	13	7	16	11
Ankylosing spondylitis	8	8	8	11	12
Others	11	14	14	11	18
Combinations	7	9	10	6	15

ing treatment with NSAIDs were similar at base line among the three groups (Table 1). The most commonly used NSAIDs in the group as a whole were diclofenac (29 percent of patients), indomethacin (23 percent), and naproxen (16 percent). Most patients had rheumatoid arthritis or osteoarthritis.

#### Maintenance Phase

At the end of the healing phase, 432 patients were enrolled in the maintenance phase after randomization, of whom 425 patients were included in the efficacy analysis according to treatment received. Seven patients could not be evaluated: six because they declined to continue in the study, and one because

of noncompliance with the NSAID regimen. The patients had similar base-line characteristics (Table 1) and were well balanced with respect to treatment received during the healing phase (data not shown).

#### Clinical Efficacy

##### Healing Phase

At eight weeks, treatment was successful in 80 percent (140 of 174) of the patients in the group given 20 mg of omeprazole, 79 percent (148 of 187) of those given 40 mg of omeprazole, and 63 percent (110 of 174) of those given ranitidine ( $P < 0.001$  for the comparison with 20 mg of omeprazole).

razole and  $P=0.001$  for the comparison with 40 mg of omeprazole). The success rates were similar when all 541 patients were analyzed according to the treatment assigned.

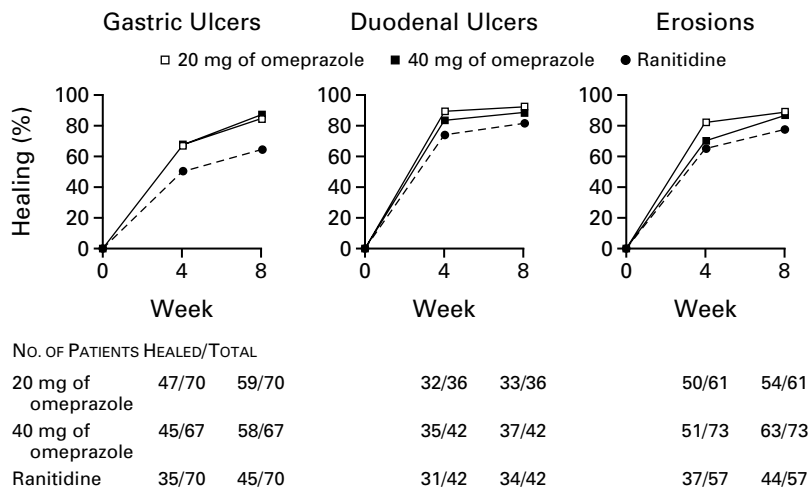
The rates of healing of all types of lesions were higher in patients treated with 20 mg or 40 mg of omeprazole than in those treated with ranitidine (Fig. 1). The rates of gastric-ulcer healing during the eight-week period were significantly higher with 20 mg of omeprazole (84 percent,  $P<0.001$ ) and 40 mg of omeprazole (87 percent,  $P<0.001$ ) than with ranitidine (64 percent). When the data were analyzed to include patients with concurrent duodenal ulcers initially, the respective values were 81 percent (62 of 77 patients), 86 percent (62 of 72), and 64 percent (48 of 75). The rates of healing of duodenal ulcers were also higher with 20 mg of omeprazole (92 percent,  $P=0.03$ ) and 40 mg of omeprazole (88 percent,  $P=0.17$ ) than with ranitidine (81 percent). When the data were analyzed to include patients with concurrent gastric ulcers initially, the respective values were 93 percent (40 of 43), 87 percent (41 of 47), and 79 percent (37 of 47). The rates of healing of erosions were also higher with 20 mg of omeprazole (89 percent,  $P=0.008$ ) and 40 mg of omeprazole (86 percent,  $P=0.19$ ) than with ranitidine (77 percent). There were no significant differences between the two doses of omeprazole for the three types of lesions. The number of patients in whom treatment was not successful after eight weeks as judged by the persistence of moderate-to-severe symptoms was low: none in the group given 20 mg of omeprazole, one in the group given 40 mg of omeprazole, and two in the ranitidine group. The major reasons for treatment failure were therefore lack of healing of ulcers or erosions.

Most patients obtained relief from upper gastrointestinal symptoms within the first four weeks of either treatment. However, the percentage of patients with improvement of overall symptoms at four weeks was significantly greater in the group given 20 mg of omeprazole than in the group given ranitidine ( $P=0.04$  by Wilcoxon's test). Only 6 percent of those treated with 20 mg of omeprazole had moderate-to-severe symptoms at four weeks, as compared with 52 percent at base line, whereas 12 percent of those treated with ranitidine had such symptoms, as compared with 50 percent at base line. By eight weeks, most patients had mild symptoms or were free of symptoms, and the differences between the groups were not significant.

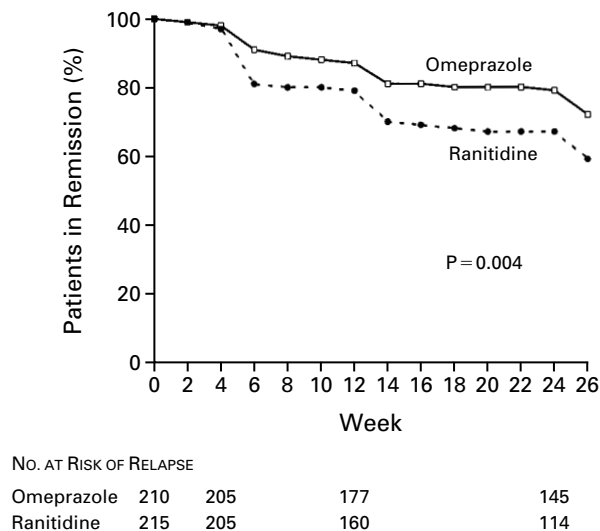
#### Maintenance Phase

During the maintenance phase, patients treated with 20 mg of omeprazole were in remission (defined as the absence of a relapse of lesions, dyspeptic symptoms, and adverse events leading to the discontinuation of treatment) significantly longer than those treated with ranitidine ( $P=0.004$  by the log-rank test). The estimated proportion of patients in remission at the end of six months was 72 percent in the omeprazole group and 59 percent in the ranitidine group (Fig. 2).

All categories of relapse were more common with ranitidine than with omeprazole. Gastric ulcers recurred in 5.2 percent of the patients treated with omeprazole (11 of 210), as compared with 16.3 percent (35 of 215) of those treated with ranitidine. The respective proportions with a recurrence of duodenal ulcers were 0.5 percent (1 of 210 patients) and 4.2 percent (9 of 215) and with erosions only, 5.7 percent (12 of 210) and 7.0 percent (15 of 215).



**Figure 1.** Cumulative Rates of Healing of Gastric Ulcers, Duodenal Ulcers, and Erosions at Four and Eight Weeks during Treatment with 20 mg of Omeprazole Daily, 40 mg of Omeprazole Daily, or 150 mg of Ranitidine Twice Daily.



**Figure 2.** Estimated Rates of Remission among Patients Treated with 20 mg of Omeprazole Daily or 150 mg of Ranitidine Twice Daily for up to 26 Weeks.  $P = 0.004$  by the log-rank test for the difference between groups.

## Prognostic Factors

### Healing Phase

The factors associated with a significantly greater likelihood of successful treatment in the healing phase were treatment with 20 mg of omeprazole ( $P = 0.04$  for the comparison with ranitidine), the presence of duodenal ulcers or erosions (both  $P < 0.001$  for the comparison with gastric ulcers), female sex ( $P = 0.04$  for the comparison with male sex), and *H. pylori*-positive status ( $P = 0.05$  for the comparison with negative status). At eight weeks the respective rates of successful treatment among *H. pylori*-positive patients and *H. pylori*-negative patients were 83 percent (69 of 83 patients) and 75 percent (58 of 77) in the group given 20 mg of omeprazole, 82 percent (75 of 91) and 71 percent (54 of 76) in the group given 40 mg of omeprazole, and 72 percent (52 of 72) and 55 percent (47 of 86) in the ranitidine group.

### Maintenance Phase

In the maintenance phase, treatment with 20 mg of omeprazole and a positive test for *H. pylori* were both associated with a significantly greater likelihood of remaining in remission. The estimated proportions of *H. pylori*-positive patients and *H. pylori*-negative patients who remained in remission at six months were 79 percent and 60 percent, respectively, in the group given 20 mg of omeprazole and 66 percent and 53 percent, respectively, in the ranitidine group. An analysis that included only patients

with ulcers showed that those with smaller ulcers at the initial endoscopy had a significantly higher probability of successful treatment in the healing phase ( $P = 0.003$ ) and of continued remission during the maintenance phase ( $P = 0.008$ ) than those with larger ulcers. For this analysis, ulcer size was used as a continuous variable.

## Safety

Unfavorable changes in any laboratory variable regarded by the investigator as clinically relevant were classified as adverse events. Data on 533 patients in the healing phase were available for the evaluation of adverse events. The overall rates were high: 30 percent in the group given 20 mg of omeprazole, 38 percent in the group given 40 mg of omeprazole, and 40 percent in the ranitidine group. In part this may reflect the fact that most of the patients had chronic arthritis.

Data on 426 patients in the maintenance phase were available for the evaluation of adverse events. The mean duration of exposure to the study drug was longer in the omeprazole group than the ranitidine group (151 days vs. 131 days). The frequencies of adverse events were similar in the omeprazole group (64 percent) and the ranitidine group (58 percent), despite the longer duration of exposure to the study drug in the omeprazole group. The six most common adverse events in each phase of the study are summarized in Table 2, along with the proportions of patients who discontinued the study because of adverse events or for other reasons. A bleeding duodenal ulcer developed in one patient after 10 days of maintenance treatment with omeprazole. The patient was hospitalized and treated with 20 mg of omeprazole twice daily orally and 2 units of blood, and the bleeding stopped.

## DISCUSSION

When peptic ulcers develop in patients taking NSAIDs, the preferred approach is to stop the NSAID when possible.<sup>20</sup> Ulcers heal slowly during treatment with  $H_2$ -receptor antagonists when NSAIDs are continued and more quickly when they are stopped.<sup>8,14,21</sup> However, stopping the NSAID therapy may exacerbate the underlying arthritis. We compared the abilities of omeprazole and ranitidine to heal and prevent NSAID-associated gastroduodenal lesions in patients receiving continuous NSAID therapy. Because we studied patients with lesions at base line, who are at higher risk for ulceration than patients without lesions,<sup>22</sup> our study is relevant to clinical situations in which ulcer prophylaxis would be considered. Omeprazole has also been shown to be effective in placebo-controlled trials in preventing ulcers in patients who are taking NSAIDs but who are at lower risk for ulceration.<sup>23,24</sup>

The main end point for the healing phase was suc-

**TABLE 2.** INCIDENCE OF MODERATE-TO-SEVERE ADVERSE EVENTS IN ALL PATIENTS AND REASONS FOR DISCONTINUATION OF TREATMENT AND FOLLOW-UP IN PATIENTS INCLUDED IN THE EFFICACY ANALYSIS.

VARIABLE	HEALING PHASE			
	OMEPRAZOLE, 20 mg/DAY (N = 173)	OMEPRAZOLE, 40 mg/DAY (N = 185)	RANITIDINE, 150 mg TWICE DAILY (N = 175)	OPEN-LABEL OMEPRAZOLE, 40 mg/DAY* (N = 81)
Mean duration of exposure to drug (days)	36	37	40	41
Most common adverse events (% of patients)				
Diarrhea	1.7	1.6	4.0	2.5
Arthritis	2.3	0.5	3.4	2.5
Headache	0.6	1.1	2.3	3.7
Nausea	0.6	1.6	1.7	2.5
Constipation	0.6	0.5	2.3	1.2
Flatulence	0.6	0.5	2.3	1.2
Discontinuation of treatment (% of patients)	10.2	10.1	14.1	3.9
Adverse event or lack of efficacy	2.8	3.2	8.5	1.1
Other reasons†	7.4	6.9	5.6	2.8
	MAINTENANCE PHASE			
	OMEPRAZOLE, 20 mg/DAY (N = 210)		RANITIDINE, 150 mg TWICE DAILY (N = 215)	
Mean duration of exposure to drug (days)	151		131	
Most common adverse events (% of patients)				
Arthritis	2.4		3.2	
Rheumatoid arthritis	4.3		1.4	
Vomiting	2.9		2.3	
Abdominal pain	2.9		1.9	
Diarrhea	3.3		1.4	
Respiratory tract infection	2.4		2.3	
Discontinuation of treatment (% of patients)	14.5		13.3	
Adverse event	6.1		3.2	
Other reasons‡	8.4		10.1	

\*All other drugs were given in a double-blind manner.

†The main other reason was unwillingness to continue in the study (four patients in the group given 20 mg of omeprazole, four in the group given 40 mg of omeprazole, six in the ranitidine group, and three given open-label omeprazole).

‡The main other reason was unwillingness to continue in the study (seven patients in the omeprazole group and seven in the ranitidine group).

cessful treatment, defined as complete healing of ulcers, the disappearance of erosions or a marked reduction in the number of erosions, and the presence of no more than minimal symptoms of dyspepsia. Treatment failure in the maintenance phase was defined as reappearance of these features or the discontinuation of treatment due to adverse events. We chose these end points before the study began because we believed that patients would consider success in all these areas to be the most desirable outcome. These goals were more demanding than those in most previous studies,<sup>8-11,14,15,22-25</sup> especially since the primary assessment was based on all patients treated. Nevertheless, treatment was successful in 80 percent of the patients given 20 mg of omeprazole daily for eight weeks in the healing phase, and this treatment was clearly superior to 150 mg of ranitidine twice daily. The rates of healing of gastric ulcers, duodenal ulcers, and erosions were all better with either 20 mg or 40 mg of omeprazole than with ranitidine. Use of the higher dose of omeprazole provided no obvious advantage overall (rate of successful treatment, 79 percent).

Our study was not designed to investigate complications of ulcers, since very large numbers of patients would be required to yield significant results. A bleeding duodenal ulcer developed in one patient after 10 days of maintenance treatment with omeprazole. In the whole program, including the study reported by Hawkey et al.<sup>26</sup> in the next article in this issue as well as an assessment of prophylaxis among patients who were initially free of ulcers,<sup>24</sup> only 1 of 654 patients who were taking 20 mg of omeprazole and 2 of 331 patients who were taking placebo had such complications.

In previous studies, the use of standard doses of H<sub>2</sub>-receptor antagonists has been disappointing with respect to preventing NSAID-associated ulcers. A 400-mg dose of cimetidine each night for 10 months was ineffective.<sup>25</sup> Two large placebo-controlled trials of ranitidine showed a substantial reduction in the incidence of duodenal ulcers during NSAID treatment, but no effect on gastric ulcers.<sup>9,10</sup> This is a problem, since most ulcers that develop during NSAID treatment are gastric,<sup>27-29</sup> as we also found. A large, prospective evaluation showed that therapy with H<sub>2</sub>-receptor antagonists does not reduce the risk of ulcer complications in NSAID users.<sup>30</sup> Findings such as these led to the conclusion that NSAID-associated gastric ulcers are not caused by acid.<sup>31</sup> However, our findings challenge this view. The rate of continued remission was significantly higher with omeprazole than with ranitidine, presumably because of the greater inhibition of acid induced by omeprazole.<sup>32</sup> In keeping with the view that acid suppression is required to prevent NSAID-associated gastric damage, Taha et al. recently showed that high-dose famotidine (40 mg twice daily) gave better

protection against NSAID-associated gastric ulcer than the standard dose (20 mg twice daily) or placebo.<sup>28</sup> Although our study did not include a placebo group, three other recent trials showed substantial reduction in the incidence of NSAID-associated gastroduodenal ulcer in patients treated with 20 mg of omeprazole as compared with placebo for three or six months.<sup>23,24,26</sup>

The analysis of prognostic factors showed that treatment was more likely to be successful in patients with smaller ulcers at the initial endoscopy. This was no surprise, since ulcer size has often been noted to affect the healing rate, with larger ulcers healing more slowly,<sup>33</sup> but we did not expect those with larger ulcers initially to be more likely to relapse during the maintenance phase. This finding should be added to the list of risk factors that may be clinically useful when one is deciding whether to recommend preventive therapy in patients who are receiving NSAIDs.

There is disagreement whether *H. pylori* infection increases the risks associated with NSAIDs.<sup>34,35</sup> Although it would seem logical to remove all potentially ulcerogenic factors, when the study started we were aware of data showing that *H. pylori* could abrogate NSAID-associated reductions in gastric mucosal synthesis of prostaglandins<sup>19</sup> and that *H. pylori* status did not influence the risk of NSAID-associated bleeding ulcers.<sup>17,18</sup> We therefore decided not to eradicate *H. pylori*. We found higher rates of success in *H. pylori*-positive patients than in those who were negative for *H. pylori* during both phases of the study regardless of treatment assignment. We studied a selected group of patients, and proving that *H. pylori* infection is beneficial to NSAID users would require a formal randomized study.

In conclusion, in patients taking NSAIDs daily, we found that treatment with 20 mg of omeprazole daily is superior to ranitidine with respect to healing and preventing gastroduodenal ulcers and erosions, as well as controlling dyspeptic symptoms.

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## APPENDIX

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