Upper Gastrointestinal Tract Safety Profile of Alendronate

The Fracture Intervention Trial

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Objectives: To determine whether alendronate sodium treatment is associated with upper gastrointestinal (GI) tract adverse experiences (AEs)—particularly those of the stomach, duodenum, or esophagus—in the Fracture Intervention Trial, and to assess the relationship between alendronate use and upper GI tract events among women at increased risk for these outcomes.

Design: Randomized, double-blind, placebo-controlled trial with a mean follow-up of 3.8 years. Women were initially randomized to receive alendronate sodium, 5 mg/d, or placebo. After 2 years, the alendronate sodium dose was increased to 10 mg/d.

Participants: A total of 6459 women aged 54 to 81 years recruited from 11 US clinical centers. All participants had low hip bone mineral density. Women with major upper GI tract disease (recent ulcers, upper GI tract bleeding, or use of daily medication for dyspepsia) were excluded. Regular nonsteroidal anti-inflammatory drug users were not excluded.

Measurements: Self-reported upper GI tract AEs were ascertained by interview every 3 months. Serious upper GI tract AEs were confirmed and classified by review of hospital records and endoscopy reports, if available. Upper GI tract AEs were further analyzed in 2 specified groups—gastroduodenal and esophageal—to examine events that might be related to upper GI tract mucosal irritation. Gastric and duodenal perforations, ulcers, and bleeding events were combined for analysis of these clinically important outcomes.

Results: The overall incidence of upper GI tract events was similar in the alendronate and placebo groups (47.5% vs 46.2%; relative risk [RR], 1.02; 95% confidence interval [CI], 0.95-1.10). The incidence of gastroduodenal perforations, ulcers, and bleeding events was 1.6% in the alendronate group and 1.9% in the placebo group (RR, 0.86; 95% CI, 0.59-1.24). The incidence of nonspecific upper GI tract conditions, such as abdominal pain, dyspepsia, nausea, and vomiting, was also similar in the 2 groups. Esophageal events occurred in 10.0% and 9.4% of patients in the alendronate and placebo groups, respectively (RR, 1.06; 95% CI, 0.91-1.24). Esophagitis not reported as reflux was more common in the alendronate group (0.7%) than in the placebo group (0.4%), but not significantly so (RR, 1.71; 95% CI, 0.90-3.39). Alendronate use was not associated with a significant increase in upper GI tract events among women at increased risk for these events (those aged ≥75 years with previous upper GI tract disease or using nonsteroidal anti-inflammatory drugs).

Conclusion: In these older women, upper GI tract complaints, particularly dyspepsia and abdominal pain, were common, but alendronate treatment was not associated with an increased incidence of upper GI tract events, even in high-risk subgroups.

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PARTICIPANTS AND METHODS

STUDY DESIGN AND PARTICIPANTS

A detailed description of the FIT design and methods has been previously published. The FIT comprised 2 arms: the vertebral fracture arm, a 3-year study of 2027 women with at least 1 vertebral fracture on baseline radiographs, and the clinical fracture arm, a 4.5-year study of 4432 women without vertebral fractures at baseline. With the exception of the presence or absence of a vertebral fracture at baseline, patients in the 2 study arms were enrolled on the basis of identical entry criteria, and this article includes combined data from the vertebral and clinical fracture arms. The primary purpose of combining safety results for these 2 studies was to maximize power to detect rare AEs.

We enrolled 6459 postmenopausal women aged 54 to 81 years with low femoral neck bone mineral density (≤0.68 g/cm²). Women were excluded from participating in the study if they had major medical problems that would be likely to preclude participation for 3 to 4 years. In addition, women were excluded if they had a history of major upper GI tract mucosal erosive disease, defined as significant upper GI tract bleeding within the past 5 years requiring hospitalization or transfusion; documented recurrent or recent ulcer disease (2 episodes in the preceding 3 years or 1 episode in the preceding 12 months); esophageal or gastric varices; or daily use of medication for dyspepsia. Women with past or current histories of other upper GI tract diseases (including hiatal hernia, esophageal reflux, esophagitis, and heartburn) were eligible for randomization. Six hundred sixty-one (1.4%) of those observed in controlled clinical trials. In a series of cases reported from postmarketing surveillance, De Groen et al.57 found that some cases of esophagitis and esophageal ulceration were temporally related to alendronate use; many of these occurred in individuals who did not follow the recommended dosing instructions or who continued using alendronate despite new or worsening esophageal symptoms.

Many women with osteoporosis are elderly, and age and previous GI tract problems are among the strongest risk factors for peptic ulcer disease and its complications (primarily perforation and bleeding).18-28 Furthermore, many older women take nonsteroidal anti-inflammatory drugs (NSAIDs) on a regular basis, and upper GI tract complications are 2 to 3 times more common among individuals using NSAIDs.18-23

The Fracture Intervention Trial (FIT) was a prospective, multicenter, double-blind, randomized, placebo-controlled trial designed to determine the effect of alendronate use on the frequency of fractures in postmenopausal women with low bone mass. The investigation was carried out as 2 parallel study arms in 2027 women with baseline vertebral fractures, and 4432 women without baseline fractures. There was no evidence of an overall increase in the incidence of upper GI tract AEs in either arm of the study12,28; however, detailed analyses of upper GI tract events in the 2 study arms combined have not been previously reported.

To further evaluate the relationship between alendronate treatment and upper GI tract AEs, particularly among high-risk women, we compared the incidence of upper GI tract events in placebo- and alendronate-treated women in the entire FIT study.

A total of 6459 women were randomized into the FIT (3236 to alendronate and 3223 to placebo treatment). The study population had a mean age of 69 years, and 97% identified themselves as white; potential confounding variables were equally distributed between the 2 treatment groups (Table 1). At the baseline visit, 472 women in the placebo group (14.6%) and 453 in the alendronate group (14.0%) reported a medical history of upper GI tract conditions that did not exclude study participation, such as peptic ulcers or reflux esophagitis; 54% of each group reported a history of any digestive system disorder.

Before and during the study, use of NSAIDs, aspirin, and gastroprotective agents (histamine-2-blockers, proton pump inhibitors, and sucralfate) was similar in the alendronate and placebo groups. Use of these medi-
of association with study therapy. Serious AEs were defined as those that were life threatening or disabling or that required hospitalization. The decision to hospitalize FIT participants was independent of the study and was at the discretion of each participant’s attending physician.

At the request of an independent data safety and monitoring board, hospital records and/or endoscopy reports (if available) were requested for all serious upper GI tract events. In addition, because of reports about potential esophageal toxic effects among alendronate-treated women, medical records were also requested for all nonserious esophageal AEs other than reflux esophagitis or acid re- gurgitation in participants still enrolled in the study. All requested medical records were reviewed by a physician at the University of California, San Francisco, coordinating center without knowledge of treatment assignment to maximize accuracy of the reported AE terms. Daily prescription and over-the-counter medication use was also documented every 3 months.

We analyzed upper GI tract events as a group and by specific symptoms and diagnoses according to the terms reported by the investigators. Furthermore, to define the location of any potential upper GI tract mucosal injury, events that could be associated with irritation of the esophagus, stomach, or duodenum were categorized as follows for additional evaluation: (1) Esophageal AEs: acid regurgitation, dysphagia, odynophagia, esophageal ulcer, esophageal stricture, esophagitis, Barrett esophagus, and esophagitis. Based on potentially differing pathophysiological conditions, esophagitis was further classified as reflux, erosive, or not otherwise specified. (2) Gastrointestinal AEs: gastritis; duodenitis; and any gastric, duodenal, or peptic (site not specified) perforations, ulcers, or bleeding or upper GI tract hemorrhage (site not specified). Perforations, ulcers, and bleeding events (PUBs) were further analyzed as a combined gastrointestinal end point.

**STATISTICAL METHODS**

All analyses are by intention to treat, ie, every randomized woman was analyzed by the treatment group to which she was assigned. All participants were followed up to study completion for safety and efficacy end points whenever possible regardless of whether they continued alendronate or placebo treatment. The time at risk for each patient was measured from the date of randomization to the earliest of the following: (1) date of the first event within each class of events, (2) date of death, or (3) last day of the study. Adverse experiences that occurred after discontinuation of the study medication are included in these analyses; however, an analysis of events occurring only while taking the study medication and up to 14 days after therapy discontinuation revealed no meaningful differences.

Follow-up differed between the 2 arms of the study: up to 3 years for the vertebral fracture arm and up to 4.5 years for the clinical fracture arm. Therefore, all analyses were controlled for study arm. Cumulative incidences for the events of interest were computed using life tables, and the log-rank test was used to evaluate differences in the cumulative incidence curves. A proportional hazards model was used to evaluate the relative risk (RR) of the alendronate vs placebo groups. In addition, the proportional hazards model was used to determine whether the treatment effect depended on age or history of upper GI tract disease. A time-dependent proportional hazards model was used to evaluate NSAID and aspirin use as a risk factor for the events of interest. All periods of NSAID and aspirin use and nonuse were measured up to (and not beyond) the time of an event.

During the trial 124 serious upper GI tract events occurred (18 esophageal events in 16 patients, 59 gastrointestinal events in 49 patients, and 47 other events), and objective documentation (hospital discharge summary, endoscopy report, or radiology report) was obtained for 115 of these events. Documentation was obtained and reviewed for all 18 serious esophageal events. Masked review of the supportive documentation from 115 serious upper GI tract events by a coordinating center physician (D.C.B.) resulted in reclassification of the original, investigator-reported diagnosis for 24 events. In most cases, reclassification simply resulted in greater specificity of a diagnosis. For example, if a participant reported a gastric ulcer to the investigator but central review of endoscopy reports revealed only evidence of gastritis, the AE term was reclassified as gastritis. Additional unreported diagnoses were added to the AE database if confirmed by objective evidence, but in no instance did review result in the complete removal of an upper GI tract event. Clinical records were obtained for 109 nonserious esophageal events reported during the clinical fracture arm of the FIT (excluding reflux esophagitis and acid regurgitation), and 24 of these events were reclassified after a masked review of the medical records.

**ALL UPPER GI TRACT EVENTS**

During mean follow-up of 3.8 years (2.9 and 4.25 years in the vertebral and clinical fracture arms, respectively), the proportion of women reporting 1 or more symptoms or clinical events referable to the upper GI tract was similar in the alendronate and placebo groups (47.5% vs 46.2%; RR, 1.02; 95% confidence interval [CI], 0.95-1.10) (**Figure 1** and **Table 2**). During the first 12 months of study when women took either 5 mg of alendronate or placebo, approximately 30% of both groups reported at least 1 upper GI tract AE, and by the end of the study nearly half of the women enrolled in the FIT had reported at least 1 upper GI tract AE.

The most common upper GI tract AE was dyspepsia, which occurred in 18.2% of women who received alendronate and 19.1% of those who received placebo (RR, 0.94; 95% CI, 0.84-1.05). Similarly, nonspecific...
upper GI tract complaints, such as nausea, vomiting, and abdominal pain, occurred at a similar incidence in the alendronate and placebo groups. No individual upper GI tract AE was significantly increased with alendronate treatment. Sixty-five women (2.0%) in the alendronate group and 59 (1.8%) in the placebo group reported a serious upper GI tract event that required hospitalization or was considered life threatening or disabling (RR, 1.02; 95% CI, 0.95-1.10; P = .46).

A total of 102 women (3.2%) receiving alendronate discontinued treatment because of an upper GI tract AE that required hospitalization or was considered life threatening or disabling, of a serious upper GI tract AE that required hospitalization or was considered life threatening or disabling.

**GASTRODUODENAL EVENTS**

The overall incidence of gastroduodenal events in the FIT was similar in the alendronate and placebo groups (Table 2). The incidence of clinically important gastric or duodenal upper GI tract complications such as PUBs was also similar in the alendronate and placebo groups (1.6% and 1.9%; RR, 0.86; 95% CI, 0.59-1.24) (Table 2 and Figure 2). There was no relationship between treatment group and the occurrence of gastritis or duodenitis.

A total of 15 women (0.5%) taking alendronate discontinued treatment because of a gastroduodenal AE compared with 16 women (0.5%) taking placebo (RR, 0.93; 95% CI, 0.46-1.89). Four women (0.1%) in the alendronate group discontinued study medication use because of a serious gastric or duodenal AE compared with 9 (0.3%) in the placebo group.
ESOPHAGEAL EVENTS

The overall incidence of esophageal events in the FIT was 10.0% in the alendronate group and 9.4% in the placebo group (RR, 1.06; 95% CI, 0.91-1.24) (Table 2 and Figure 2). The most common esophageal AE in the alendronate and placebo groups was acid regurgitation, reported in 6.6% and 6.1% of patients, respectively (RR, 1.09; 95% CI, 0.90-1.32). Reflux esophagitis was reported in 65 women (2.0%) receiving alendronate and 72 (2.2%) taking placebo (RR, 0.90; 95% CI, 0.64-1.25). Esophagitis not attributed to reflux was reported in 24 women (0.7%) taking alendronate and 14 (0.4%) taking placebo (RR, 1.71; 95% CI, 0.90-3.39). Esophageal ulcers were reported in 7 patients in the alendronate group and 6 in the placebo group (0.2% of both groups). No esophageal perforations or bleeding was reported. Serious esophageal AEs occurred in 11 women (0.3%) taking alendronate and 5 (0.2%) taking placebo (RR, 2.19; 95% CI, 0.80-6.95).

A total of 26 women (0.8%) taking alendronate and 9 (0.3%) taking placebo discontinued study medication because of an esophageal event (RR, 2.88; 95% CI, 1.40-6.52). Further review of these events revealed that they were primarily nonserious events reported as acid regurgitation or reflux esophagitis, and there was no clear pattern with regard to previous conditions, duration of treatment, or concurrent medication use. Only one woman taking alendronate and no women taking placebo permanently discontinued study medication because of a serious esophageal AE (reflux esophagitis that was an exacerbation of a preexisting condition and required hospitalization).

ALENDRONATE DOSE AND UPPER GI TRACT AE

To determine whether there was a relationship between dose of alendronate and incidence of upper GI tract AEs, we compared the relative incidence for alendronate vs placebo of upper GI tract events reported during the first 2 years of the trial (when patients were receiving alendronate sodium, 5 mg/d, or placebo) with that reported during years 3 through 4.5 (when patients were receiving alendronate sodium, 10 mg/d, or placebo). The proportion of women reporting any upper GI tract event was similar in the alendronate and placebo groups during treatment with 5 mg/d (37.3% vs 37.9%) and 10 mg/d (21.9% vs 20.3%). The proportions of women with serious upper GI tract events were also similar in the alendronate and placebo groups during treatment with 5 mg/d (1.2% vs 1.0%) and 10 mg/d (0.9% vs 0.8%).

UPPER GI TRACT EVENTS IN HIGH-RISK SUBGROUPS

As demonstrated in previous studies, age, previous upper GI tract disease, and NSAID use were independent risk factors for upper GI tract events in this study, particularly for gastroduodenal PUBs. The relationships between these risk factors and upper GI tract events among women treated with alendronate and placebo are shown in Figures 3, 4, and 5.

Age

Figure 3 shows the age-specific event rates for gastroduodenal PUBs and for esophageal AEs. The incidence
of PUBs, but not esophageal events, increased with age, but even in the oldest age group (women ≥75 years) there was no evidence of a disproportionate number of events in the alendronate group.

History of Upper GI Tract Disease

A history of at least 1 nonexclusionary upper GI tract disease before randomization was reported in 925 participants (453 in the alendronate group and 472 in the placebo group). Figure 4 shows the event rates for gastroduodenal PUBs and for esophageal AEs among women with and without a history of upper GI tract disease. Gastroduodenal PUBs and esophageal events occurred more commonly in women with previous upper GI tract disease, but even among women with previous disease there was no evidence of a disproportionate number of events in the alendronate group.

Use of NSAIDs

Approximately 88% of all FIT participants reported at least 1 day of NSAID or aspirin use during the study (88.4% in the alendronate group and 87.5% in the placebo group). Figure 5 shows the gastroduodenal PUB event rates per 1000 person-years at risk during periods of NSAID use and nonuse. Women could contribute years at risk to both periods. During the use period there were 79 PUB events (35 in the alendronate group and 44 in the placebo group), and during the nonuse period there were 35 PUB events (18 in the alendronate group and 17 in the placebo group) (Figure 5). As anticipated, event rates were higher during NSAID use compared with the nonuse period in both treatment groups. Sensitivity analyses that extended the NSAID use period 7 or 14 days beyond the actual dates of use were also performed (data not shown). In each case, there was no evidence that concurrent use of alendronate and NSAIDs resulted in an excess of gastroduodenal or esophageal events compared with concurrent use of NSAIDs and placebo. Similar analyses of esophageal events revealed no evidence of an excessive number of events among women taking alendronate and NSAIDs.

In this double-blind, randomized clinical trial involving more than 6400 postmenopausal women followed up for up to 4.5 years, we found that the incidence of upper GI tract events was similar in women receiving alendronate sodium, 5 to 10 mg/d, or placebo. Upper GI tract complaints were common among women enrolled in this trial independent of treatment with alendronate or placebo, and approximately 30% of all participants reported an upper GI tract AE within the first year of the study. The incidence of more worrisome upper GI tract events, namely, PUBs, was low and no greater in the alendronate group compared with the placebo group.

Although esophageal AEs were rare and the overall incidence was similar in the alendronate and placebo groups, we observed a nonsignificant increase in serious esophageal events in the alendronate-treated women (0.3%) compared with those taking placebo (0.2%). Women taking alendronate were more likely to discontinue treatment because of an esophageal event (0.8% vs 0.3%). Although the importance of these findings is not clear because of the small number of events (and consequently wide CIs), a true association cannot be ruled out. Furthermore, esophagitis not reported as reflux was reported more often among women taking alendronate (0.7%) compared with placebo (0.4%), and this relationship approached statistical significance. However, the more common reports of reflux esophagitis were slightly less frequent in the alendronate group (2.0%) relative to the placebo group (2.2%). Because the choice between these 2 terms as a diagnosis was not necessarily based on objective data or applied consistently by patients or clinicians (eg, some patients with endoscopy reports documenting reflux esophagitis were diagnosed as having esophagitis), this distinction must be viewed with caution. These results are consistent with previously reported postmarketing results suggesting that alendronate use might be infrequently associated with esophageal mucosal injury and underscore the importance of proper administration of alendronate and early recognition of new esophageal symptoms. Several recent articles have attempted to elucidate the possible mechanism of bisphosphonate-associated esophageal irritation.

Despite the findings from several controlled clinical trials demonstrating that alendronate treatment has a favorable tolerability profile, some clinicians believe that alendronate treatment is not tolerated in a substantial proportion of patients. Few objective clinical data support this belief; most of the published articles suggesting that alendronate use is associated with upper GI tract symptoms are case reports, uncontrolled studies in clinical practice, or small endoscopic studies that report lesions of unclear clinical significance. For example, one small endoscopic study of 8 women and 5 men given alendronate sodium, 40 mg/d (4 times the osteoporosis treatment dose), aspirin (1300 mg/d), or placebo for 4 days found that 40-mg/d alendronate sodium might be associated with asymptomatic gastric erosions at rates similar to those seen with aspirin therapy.
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In contrast, larger endoscopic studies are concordant with the results from the FIT and do not suggest that treatment doses of alendronate adversely affect the GI tract mucosa. In one such study,53 the endoscopic effect of 14 days of therapy with 5 or 10 mg of alendronate sodium on esophageal, gastric, and duodenal mucosa was examined in 79 postmenopausal women. In this blinded study,53 the proportion of participants taking alendronate who developed mucosal erosions was low and did not differ from placebo. Similarly, a study in 65 healthy volunteers found no evidence that use of alendronate sodium (10 or 40 mg) or etidronate disodium (400 mg) delayed healing of aspirin-induced gastric lesions relative to a no-treatment control group.53,54

Several explanations might account for the discordance between the results of large, masked studies, such as the FIT, and the impression that alendronate use is associated with a higher incidence of upper GI tract AEs. First, although the number was small (1.4% of those screened), women with active ulcers or symptoms requiring daily treatment were excluded from the FIT. Second, all women who were enrolled were counseled about the correct dosing instructions at regular intervals. Some events reported from clinical practice might reflect mucosal irritation caused by high local concentrations of alendronate in patients who do not follow dosing instructions properly or who have underlying upper GI tract disease that would have excluded them from the FIT.
Third, FIT women were treated with alendronate sodium, 5 mg/d, during the first 2 years of the study and were treated with 10 mg/d thereafter, whereas the approved dose for clinical use is 10 mg/d. However, the most likely contributing factor for the perception that alendronate frequently causes GI tract intolerance is that upper GI tract complaints are common among older women, regardless of treatment with alendronate or placebo. The high incidence of upper GI tract complaints observed in the FIT placebo group is similar to that observed in other observational studies.55

We also addressed the question of whether specific high-risk subpopulations could be identified in which alendronate use was associated with excess risk for upper GI tract complications. Our results are consistent with the known epidemiology of upper GI tract ulcer disease, ie, the incidence of gastroduodenal PUBs is increased among the elderly, patients with a history of upper GI tract disease, and patients taking NSAIDs. However, the effects of age, history of upper GI tract disease, and NSAID use were similar in the alendronate and placebo groups. Subgroup analysis of women with and without these risk factors did not suggest any subpopulation of women that was at increased risk of developing esophageal complications or gastroduodenal PUBs with alendronate use.

In summary, in this large, controlled trial in older women with low bone mass, we found that the incidence of upper GI tract AEs was similar in women receiving alendronate sodium, 5 to 10 mg/d, or placebo. The incidence of more severe gastric and duodenal events, such as bleeding and ulceration, was also similar even among women who were at increased risk of developing these complications. We found small increases in some esophageal AEs among women taking alendronate, but these relationships were not statistically significant, the events were rare, and the overall reporting of esophageal events was similar in the alendronate and placebo groups. These data are consistent with those obtained from other clinical trials of oral alendronate treatment groups. Subgroup analysis of women with and without these risk factors did not suggest any subpopulation of women that was at increased risk of developing esophageal complications or gastroduodenal PUBs with alendronate use.

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