

TO THE EDITOR

I appreciate the opportunity to comment on the article by Ettinger et al concerning clinic visits and hospitalizations for acid-related upper gastrointestinal (GI) disorders (ARD) in women using alendronate for osteoporosis.¹ The study was sponsored by Novartis, which manufactures a competing treatment for osteoporosis (intranasal salmon calcitonin). Importantly, the article does not consider the very high potential for reporting biases caused by increased awareness of the potential for upper GI adverse events with alendronate and by an increased number of medical encounters. These factors would increase the rate of identification of ARD in the early months of alendronate treatment, independent of any actual adverse effect of the drug, and thus bring into question the conclusions of this report.

Increased awareness by physicians and patients with respect to potential upper GI effects of alendronate may well have resulted in a temporary, but significant increase in the detection and treatment of ARD. The study relates to a time period during which Merck enhanced its educational campaign to improve compliance with dosing instructions and notified physicians and pharmacists of the potential for rare cases of esophagitis.² These activities were likely to have intensified specific cautioning of patients by the health plan physicians with respect to the potential for ARD symptoms, and questioning as to their occurrence on treatment. Increased questioning in itself would have led to increased diagnosis of ARD, because the prevalence of ARD is very high in the population at large. For example, approximately half of the general population in the United States experience heartburn or acid regurgitation.³ In contrast, the prevalence of these disorders in the Kaiser health plan is reported in the article to be only 2.8%, suggesting a very substantial degree of underdiagnosis or underreporting.

For the purpose of this study, an ARD diagnosis was not necessarily the sole or primary reason for an outpatient visit or hospital admission. It seems likely that most women receiving a prescription for a new medication would have a scheduled follow-up visit within 3 to 6 months of initiation of treatment. In addition, the frequency of outpatient visits and hospitalization tends to be increased in this population due to osteoporosis and related fractures. Medical encounters, therefore, were almost certainly substantially more common in the group that received alendronate relative to the overall population of women over 50 years of age, and thus the opportunity for physicians to inquire about and identify upper GI symptoms in alendronate users would be much greater than in the overall population.

Taken together, these two factors would clearly be expected to result in a substantial increase in the identification of ARD diagnoses, especially during the early months of therapy. This is exactly what was observed, with rate of 26.6 per 100 patient-years during the initial 3 months of therapy, dropping to approximately 15.9 events per 100 patient-years at 9 months and only 3.8 events per 100 patient-years at 1 year of therapy. When considered relative to the overall rate for the reference population, (ie, all female plan participants over 50 years of age) of 17.6 per 100 patient-years, the findings can hardly be interpreted as unambiguous evidence of a drug-related effect. In view of these considerations, the lack of an appropriately matched control group, such as osteoporotic women taking other medications for osteoporosis, is a major limitation. Thus, the authors' conclusion that "our current study suggests that ARD events recur among alendronate users, making it difficult or impossible for patients to comply with this treatment" is not supported by the evidence presented in this article.

Alendronate has clearly and consistently been demonstrated to prevent fractures at the spine and hip and is the only medicine that has been demonstrated to have such marked antifracture benefits in randomized controlled double blind studies.^{4,5} To date, alendronate has been used by more than 3 million patients worldwide and has an overall favorable safety profile. The unsupported conclusions from this report may well cause patients taking alendronate or their physicians to become unnecessarily alarmed, and may result in patients discontinuing or failing to initiate treatment with alendronate, thus not benefitting from the substantial antifracture benefit of this medicine.

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AUTHOR'S REPLY

Dr. Yates offers alternative reasons for our finding a 60% higher incidence of acid-related upper gastrointestinal (GI) disorders (ARD) among 812 women using alendronate 10mg compared the approximately 360,000 age- and gender-matched Kaiser Foundation Health Plan members.¹ He suggests that increased patient awareness of alendronate's propensity to irritate the upper GI tract could have increased doctor office visits for such problems. He further hypothesizes that physicians caring for women receiving alendronate might have arranged additional office visits to follow-up treatment in the first 3-6 months, and at these visits there would have been an increased opportunity for physicians to query and for patients to register ARD symptoms.

We believe that these are not tenable explanations for the substantial increase in ARD that were recorded in the early months of alendronate treatment. We did not find evidence of additional office visits in the early months of alendronate use. Women using alendronate had, on average 4 medical encounters in the 6 months prior to starting alendronate, and 4 encounters in the 6 months after starting. These visit rates are nearly identical to rates for women the same age in our health plan. If surveillance and reporting bias were responsible for our finding an increase in ARD events, this effect should have occurred across all age ranges. However, we found no increase in ARD among younger women, but an increasing risk with increasing age above 70 years. We suggest that the apparent decrease in ARD events with time was more likely due to susceptible women developing intolerable GI symptoms and their discontinuation of treatment. The 33% of women in this cohort who reported new GI problems ascribed to alendronate² were underrepresented among users who continued beyond a few months. Thus, there was a weaning out of women prone to alendronate-associated ARD symptoms, particularly those over 70 years of age, those on nonsteroidal anti-inflammatory drugs, and those using H₂ blockers.

Dr. Yates identifies the difficulty of providing a proper control group for alendronate users. We discuss this problem at length in our paper. If osteoporosis is associated with an increased risk of ARD, then underrepresentation of osteoporotic women in the control group would result in this group having a lower rate of ARD compared to women receiving alendronate. At this time, no proof exists that osteoporosis is associated with ARD, and the findings of our study argue against this hypothesis. Because the majority of older women have osteoporosis, older controls would tend to be more like alendronate users, and this would lead to

much smaller bias among older women than younger. Our findings are quite the opposite. When we compared alendronate users to nonusers, the incidence rate ratios were greatest among older women. We suspect the higher ARD rates are actually conservative, since prescribing bias could have resulted in healthier alendronate users due to physicians' awareness of alendronate's potential GI toxicity and their reticence to prescribe it for a women at high risk for developing ARD.

We have recently completed a Merck-sponsored, multi-HMO study that compared incidence rates of hospitalization for peptic ulceration and/or bleeding between women using alendronate and nonusers; random controls were chosen in a fashion similar to the method we used in our paper. However, in this new study, the risk of ARD will be adjusted for chronic disease score and concomitant medications.

We share Dr. Yates' enthusiasm for alendronate's potential value as an osteoporosis treatment. The challenge we face as clinicians is to make its long-term use more acceptable to women who most need it. Managed care organizations need to find ways to enhance efficacy and reduce costs associated with the additional resources required to deal with alendronate's treatment-related problems. In my practice, many women intolerant of 10mg daily alendronate do not have intolerance when they take 10mg every other day. Studies of 5mg alendronate show quite acceptable skeletal effects³ and using 10mg every other day halves the cost of using the drug. Merck is currently studying the efficacy and tolerability of alendronate given just once or twice a week. By providing a longer drug-free interval, there would be more time for superficial upper GI erosions to heal. We believe that the first step in remedying a problem is to acknowledge that one exists.

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