Yearly Zoledronic Acid in Postmenopausal Osteoporosis

TO THE EDITOR: In their report on the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial, Black et al. (May 3 issue) conclude that a once-yearly infusion of zoledronic acid reduces the risk of vertebral, hip, and other fractures. Although this is a well-designed and well-done study, we are concerned about the increase in atrial fibrillation in patients treated with zoledronic acid. Hypocalcemia as a cause was ruled out. There is no report of hypokalemia during the study. Another electrolyte imbalance, hypomagnesemia, is reported as a side effect of zoledronic acid and can cause cardiac arrhythmias. It would be interesting to know the incidence of hypomagnesemia during the HORIZON study, mainly among the patients with atrial fibrillation.

Forty-nine patients in the zoledronic-acid group had transient hypocalcemia at days 9 to 11 after the infusion. There are several case reports describing hypocalcemia during treatment with zoledronic acid, inducing a compensatory increase in parathyroid hormone. In the study by Black et al., however, we are not informed about the mean change in calcium and parathyroid hormone concentrations during treatment.

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TO THE EDITOR: Black et al. do not have a satisfactory explanation for their report of an increased incidence of serious atrial fibrillation in patients receiving zoledronic acid. Rapid atrial fibrillation, severe hypocalcemia, and a marked increase in the serum parathyroid hormone level were presenting features in a woman with hypovitaminosis D who had been treated with 60 mg of pamidronate 3 weeks before the episode, as reported in the Journal in 2003. Clinically, hypocalcemia may lower the ejection fraction, leading to myocardial dysfunction. The report by Black et al. contains little evidence that serum calcium was maintained at pretreatment levels after the administration of zoledronic acid, beyond the statement that the drug had “little or no effect” on levels 9 to 11 days after infusion.

We previously reported that zoledronic acid (at a dose of 4 mg) lowered serum calcium levels, usually into the lowest quartile of the reference range. This finding was evident from the second day (Fig. 1). Calcium levels remained suppressed...
and had only partly recovered 10 days later. Two thirds of our treated patients also had phosphate levels below the lower limit of the normal range within 10 days.

Reid et al. reported decreased calcium and phosphate levels in women with osteoporosis 1 month after infusion of zoledronic acid. Women who were treated with quarterly infusions (at a dose of 1 mg) had mean values of parathyroid hormone that were 30% higher than baseline values 3 months after their last infusion. Prolonged relative hypocalcemia and associated secondary hyperparathyroidism might underlie cardiac arrhythmogenesis, as seen in the secondary hyperparathyroidism of patients undergoing hemodialysis. Further studies are needed to document the duration of relative hypocalcemia and its likely preventable determinants — for instance, vitamin D insufficiency — before treatment.

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TO THE EDITOR: Black et al. report a significant increase in the risk of atrial fibrillation, classified as a serious adverse event, among patients treated with intravenous zoledronic acid. In a letter in the same issue of the Journal, Cummings et al. report a trend toward an increased risk of atrial fibrillation among patients treated with oral alendronate.

To determine whether there was a similar effect with oral risedronate, we evaluated the incidence of nonadjudicated adverse events of atrial fibrillation and cerebrovascular accident and of death from these events in placebo-controlled, phase 3 clinical trials of risedronate for the treatment of osteoporosis. These trials followed approximately 15,000 patients for up to 3 years (Table 1).

In the risedronate group, as compared with the placebo group, there was no significant difference in the incidence of atrial fibrillation (classified as an adverse event or a serious adverse event), cerebrovascular accident, or death associated with cardiovascular adverse events. The difference in the rate of death from cerebrovascular accident (P=0.003) was consistent with findings reported previously. These data do not support a causal association between atrial fibrillation and the use of risedronate.

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Dr. Camm reports receiving consulting fees from Procter & Gamble, Merck, and Novartis; and Dr. McClung, research grants and consulting fees from Amgen, Lilly, Merck, Novartis, Procter & Gamble, Roche, and Sanofi-Aventis and lecture fees from Lilly, Merck, and Sanofi-Aventis. No other potential conflict of interest relevant to this letter was reported.

To the Editor: The report by Black et al. adds an important new dimension to the management of postmenopausal osteoporosis. However, a number of trials have already shown the efficacy of bisphosphonates in preventing osteoporotic fractures. Since Black et al. have been in the forefront of research in this area, we are concerned about their choice of a placebo-controlled trial to show the usefulness of zoledronic acid in osteoporosis. In our view, only a lack of evidence regarding the effectiveness of a trial drug should justify conducting a placebo-controlled trial. We believe that the data available before the start of the study by Black et al., in 2002, should have led to a trial comparing oral (daily, weekly, or monthly) bisphosphonates with yearly parenteral zoledronic acid. Such a trial would have been more pertinent, both clinically and ethically.

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Table 1. Demographic Characteristics and Incidence of Atrial Fibrillation, Cerebrovascular Accident, and Death among Patients with Osteoporosis Receiving Risedronate.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=5048)</th>
<th>Risedronate 2.5 mg (N=4998)</th>
<th>Risedronate 5 mg (N=5020)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>73.4±9.2</td>
<td>73.6±9.1</td>
<td>73.5±9.3</td>
<td>0.44</td>
</tr>
<tr>
<td>Duration of drug exposure — mo</td>
<td>23.8±13.2</td>
<td>21.5±12.6</td>
<td>24.0±13.2</td>
<td>0.50</td>
</tr>
<tr>
<td>Atrial fibrillation — no. (%)</td>
<td>70 (1.4)</td>
<td>60 (1.2)</td>
<td>70 (1.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>24 (0.5)</td>
<td>24 (0.5)</td>
<td>29 (0.6)</td>
<td>0.49</td>
</tr>
<tr>
<td>Cerebrovascular accident — no. (%)</td>
<td>77 (1.5)</td>
<td>71 (1.4)</td>
<td>70 (1.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>24 (0.5)</td>
<td>15 (0.3)</td>
<td>7 (0.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Death associated with cardiovascular adverse event — no. (%)</td>
<td>96 (1.9)</td>
<td>83 (1.7)</td>
<td>80 (1.6)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Data are from the Vertebral Efficacy with Risedronate Therapy Trial, the Bone Mineral Density Trial, the Risedronate 5 mg Daily Prevention Trial, the Glucocorticosteroid-Induced Osteoporosis Prevention and Treatment Trials, and the Hip Intervention Program Trial.

† P values are reported only for the comparison between the group receiving 5 mg of risedronate and the placebo group, since 5 mg is the approved dose and the 2.5-mg dose was discontinued early in some trials.
zoledronic acid before having renal failure. In this group, six patients underwent dialysis. Two of these patients died, in addition to a third patient. Furthermore, five patients continued to have elevated serum creatinine levels after discontinuation of zoledronic acid.

The Food and Drug Administration continues to have concerns about the safety of zoledronic acid. In January 2005, the product labeling was updated to include medication dosing based on the baseline creatinine clearance.4

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**THE AUTHORS REPLY:** Poole et al. and de Nijs and Westgeest note the potential relationship between clinically important changes in electrolytes and the occurrence of cardiac arrhythmias. We also evaluated electrolyte changes in the HORIZON trial. There were significant differences between study groups in the change in serum calcium from the level before the first infusion of zoledronic acid to the level 9 to 11 days after the infusion, but the magnitude of the difference was relatively small (a reduction of 0.2±0.5 mg per deciliter in the zoledronic-acid group vs. an increase of 0.03±0.4 mg per deciliter in the placebo group). No difference was evident at 12 months, and no significant changes occurred with subsequent doses. In the zoledronic-acid group, the change in calcium levels after the first infusion did not differ between women with atrial fibrillation and those without atrial fibrillation. Over the 3 years of the study, mean serum calcium levels increased in both study groups, although the mean increase was slightly larger in the placebo group than in the zoledronic-acid group. The difference in the mean serum calcium level between study groups 9 to 11 days after the initial infusion (0.2 mg per deciliter) was less than that observed by Poole et al. at 10 days (0.6 mg per deciliter).1

In our study, a similar pattern was seen for phosphorous: 9 to 11 days after the initial infusion, there was a slightly larger decrease in the zoledronic-acid group than in the placebo group, but in the zoledronic-acid group, phosphorus levels did not differ between women with atrial fibrillation and those without atrial fibrillation. Magnesium and potassium levels did not differ between the two study groups and were similar in women with and those without atrial fibrillation.

As discussed in our article, episodes of atrial fibrillation did not cluster in time immediately after any infusion, when serum electrolytes are most affected. Taken together, these findings support our speculation that if the observed increase in atrial fibrillation was in fact related to the administration of zoledronic acid, it was probably not due to changes in serum electrolytes.

We welcome the data from Karam et al. on risendronate and look forward to the publication of data on other bisphosphonates to further elucidate this finding.

The investigators and industry sponsor of our trial incorporated ethical considerations regarding placebo controls, such as those raised by Najib and Aziz, into the study design. The protocol specified that patients had to be unable or unwilling to take oral bisphosphonates. All women were counseled regarding the risk of fracture and the availability of approved osteoporosis medications. One innovation of the trial was that women who were receiving nonbisphosphonate treatments for osteoporosis (including hormone therapy, raloxifene, and calcitonin) were included ("stratum 2"), and all patients were free to begin any of these treatments during the study while continuing to receive the study treatment. Furthermore, we monitored patients for excessive bone loss or multiple fractures, and women who met either criterion were again counseled about alternative treatment options. We agree that a trial with an active comparator would be of great clinical interest, but the numbers required for such a trial to demonstrate equivalence or superiority with respect to the risk of fracture are prohibitive (20,000 to 30,000 patients).

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THE EDITORIALIST REPLIES: In my editorial, the reference to Dr. Chang’s letter was not intended to support the absence of long-term adverse renal effects associated with zoledronic acid but, rather, to provide a context in which the long-term renal safety in the HORIZON study could be regarded as reassuring. As Dr. Chang points out, long-term adverse effects of zoledronic acid on renal function have been documented in a small number of patients and remain a potential concern.

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Antiretroviral Drugs and the Risk of Myocardial Infarction

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TO THE EDITOR: We agree with the Perspective article by Hughes and Williams (April 26 issue) that a more detailed presentation of data from the well-conducted Data Collection on Adverse Effects of Anti-HIV Drugs (DAD) Study Group collaboration may help to disentangle several variables that potentially affect the risk of myocardial infarction among persons infected with human immunodeficiency virus type 1 (HIV-1). First, data on the nadir CD4+ lymphocyte count, but not the recent CD4+ count, were presented in relation to the risk of myocardial infarction. Inflammation may trigger an acute myocardial infarction by activating prothrombotic mechanisms, and the patient’s immune status at the time of the myocardial infarction is most relevant in this regard. Moreover, inflammation increases markedly with the onset of clinical AIDS. Therefore, threshold models relating a low CD4+ count (i.e., <200 cells per cubic millimeter) with myocardial infarction may be more biologically plausible than linear models.

Second, what was the hazard ratio associated with the duration of nucleoside reverse-transcriptase inhibitor use? As with protease inhibitors, previous data have implicated constituents of the nucleoside reverse-transcriptase inhibitor class in metabolic abnormalities. Controlling for the use of nucleoside reverse-transcriptase inhibitors attenuated the hazard ratio relating the use of protease inhibitors with the risk of myocardial infarction; this suggests the presence of an association between the use of nucleoside reverse-trancriptase inhibitors and myocardial infarction.

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TO THE EDITOR: The DAD Study Group observed a relationship between exposure to protease inhibitors and myocardial infarction. No association was found between HIV-related factors, such as the nadir CD4+ lymphocyte count or the peak HIV-1 RNA level, and the risk of myocardial infarction. However, HIV-related factors might have been confounded with treatment effects. Patients with myocardial infarction had a lower rate of viral suppression, although more of them had received antiretroviral treatment. Therefore, the analysis should have been adjusted for a treatment effect on viral suppression. Can the lower rate of viral suppression among patients with myocardial infarction at least partly be explained by a higher rate of interruption of treatment with protease inhibitors?

In addition, we think it is not appropriate to incorporate high-density lipoprotein (HDL) cholesterol levels into the multivariate model only in a time-updated manner. HDL cholesterol levels