Early Effects of Raloxifene on Clinical Vertebral Fractures at 12 Months in Postmenopausal Women With Osteoporosis

Michael Maricic, MD; Jonathan D. Adachi, MD; Somnath Sarkar, PhD; Wentao Wu, MS; Mayme Wong, PhD; Kristine D. Harper, MD

Background: Raloxifene hydrochloride therapy reduces the risk for vertebral fractures at 3 years, but the effects on clinical vertebral fractures in the first year are not known.

Methods: The Multiple Outcomes of Raloxifene Evaluation (MORE) Trial enrolled 7705 women with osteoporosis, defined by prevalent vertebral fractures and/or a bone mineral density (BMD) T score at or below −2.5, who were treated with placebo or raloxifene at a dosage of 60 or 120 mg/d for 3 years. New clinical vertebral fractures were defined as incident vertebral fractures associated with signs and symptoms suggestive of vertebral fractures, such as back pain, and were diagnosed by means of postbaseline adjudicated spinal radiographs. Scheduled spinal radiographs were obtained at baseline and at 2 and 3 years. In addition, unscheduled spinal radiographs were obtained in women who reported signs or symptoms suggestive of vertebral fracture, and these radiographs subsequently underwent adjudication. If an adjudicated fracture was identified, this was also considered a clinical fracture.

Results: At 1 year, raloxifene, 60 mg/d, decreased the risk for new clinical vertebral fractures by 68% (95% confidence interval [CI], 20%-87%) compared with placebo in the overall study population, and by 66% (95% CI, 23%-89%) in women with prevalent vertebral fractures, who are at greater risk for subsequent fracture. The risk for clinical vertebral fractures in the raloxifene, 60 mg/d, group was decreased by 46% (95% CI, 14%-66%) at 2 years and by 41% (95% CI, 17%-59%) at 3 years. The cumulative incidence of new clinical vertebral fractures was lower in the group receiving raloxifene, 60 mg/d, compared with placebo (P<.001). We found no significant differences in the risk reductions for clinical vertebral fractures between the raloxifene groups at 1, 2, or 3 years.

Conclusion: The early risk reduction for new clinical vertebral fractures with 1 year of raloxifene treatment was similar to that reported with other antiresorptive agents.

Arch Intern Med. 2002;162:1140-1143

Although vertebral fractures are estimated to occur in approximately 25% of postmenopausal women, less than one third of all vertebral fractures come to clinical attention. Women who experience back pain due to a new vertebral fracture have functional limitations and experience more days of limited activity and bed rest. Vertebral fractures are also associated with increased mortality. Since women who have a vertebral fracture are at greater risk for future fractures, any new fracture should be avoided.

Several antiresorptive therapies that are currently available for osteoporosis prevention and treatment significantly reduced the risk for new vertebral fractures in clinical trials lasting 3 to 5 years. Raloxifene hydrochloride, a selective estrogen receptor modulator, reduced the risk for new vertebral fractures in the randomized, placebo-controlled, double-blind Multiple Outcomes of Raloxifene Evaluation (MORE) Trial in postmenopausal women with osteoporosis. Other antiresorptive agents, including the bisphosphonates alendronate sodium and risedronate sodium and salmon calcitonin nasal spray, also decreased the risk for new vertebral fractures in postmenopausal women.

Risedronate reduced the risks of new vertebral fractures, assessed in scheduled spinal radiographs obtained at 1 year, by 61% and 65% in the multinational and North American studies, respectively. Alendronate significantly decreased the risk for new clinical vertebral fractures reported at 1 year by 59% in women with osteoporosis defined by prevalent vertebral fractures, or by femoral neck BMD T scores below 2.5 SDs compared with the mean peak BMD value in young adults. It is not known whether antiresorptive agents other than bisphos-
PATIENTS AND METHODS

The MORE Trial enrolled 7705 postmenopausal women with osteoporosis, defined by a lumbar spine or femoral neck BMD T score of at least -2.5 and/or radiographically apparent prevalent vertebral fractures. Approximately one third of the women in the MORE Trial had at least 1 prevalent vertebral fracture. The inclusion and exclusion criteria are described in detail elsewhere.7 Women were randomized to treatment with raloxifene hydrochloride at 60 or 120 mg/d or an identical-appearing placebo. All women received daily supplements of calcium (500 mg) and cholecalciferol (400-600 IU). The 3-year skeletal efficacy results were reported previously.7

Radiologists who were masked to treatment group assignment but not temporal sequence of the radiographs assessed vertebral fractures in the spinal radiographs at a central laboratory, as described elsewhere.7 For the present analysis, women were grouped according to the presence or absence of an adjudicated vertebral fracture at baseline. An adjudicated fracture was confirmed by means of at least 2 of 3 determinations, consisting of 2 independent semiquantitative assessments and 1 quantitative morphometric measurement. The semiquantitative assessment criteria were used to define the fracture severity in each vertebra as 0, 1, 2, or 3, corresponding to no fracture or a mild, moderate, or severe fracture, respectively, depending on the degree of vertebral height loss from baseline.14 Normal vertebrae (grade 0) had minimal deformity, with less than 20% reduction in the anterior, middle, and posterior vertebral height. Mild vertebral deformities (grade 1) corresponded to a 20% to 25% reduction in vertebral height. Moderate (grade 2) and severe (grade 3) vertebral fractures had decreases in vertebral height of 25% to 40% and more than 40%, respectively. Vertebral fractures were also identified using quantitative morphometric criteria, consisting of a decrease in anterior, middle, and posterior vertebral height of at least 20% and at least 4 mm. In clinical trials of osteoporosis therapies, the standard method used to define incident vertebral fractures from radiographs consists of a combination of semiquantitative and quantitative morphometric assessment criteria. Incident vertebral fractures were described as new fractures in vertebrae that were not fractured at baseline.

Clinical vertebral fractures, which result in clinically observed symptoms, are a subgroup of all incident vertebral fractures identified using the above assessment criteria in radiographs, since most vertebral fractures are asymptomatic.15 In this analysis, new clinical vertebral fractures were defined as new fractures associated with signs or symptoms suggestive of vertebral fracture, such as back pain, reported at any postbaseline visit, and that were subsequently corroborated with radiographs and adjudicated. Scheduled spinal radiographs were performed at 2 and 3 years. Other efficacy end points of the MORE Trial were assessed at interim 6-month clinic visits. Additional unscheduled radiographs were obtained at these interim visits when patients reported symptoms of vertebral fracture, and if a new adjudicated fracture was identified, these were also considered to be clinical fractures. The primary analysis was the proportion of women with at least 1 new (incident) vertebral fracture, with further analysis performed for new clinical fractures.

We analyzed the incidence of new clinical vertebral fractures by the Pearson χ² test when the number of events in all treatment groups was at least 10, or by Fisher exact test when the number of events in the treatment groups ranged from 5 to 9. Statistical inference was not performed when fewer than 5 events occurred. The cumulative incidence of new clinical vertebral fractures observed in the placebo group and the group receiving raloxifene, 60 mg/d, for 3 years was plotted, and statistical significance was assessed by the log-rank test. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated using large sample procedures (Mantel-Haenszel CI).

RESULTS

The baseline characteristics of the women in the MORE Trial cohort were previously reported in detail by Ettinger et al.,7 and are summarized briefly in Table 1. Mean age was 66.5 years. They had been postmenopausal for a mean of 18.7 years and had a mean body mass index of 25.2. A prevalent vertebral fracture was present in 37.3% of the women enrolled. We found no statistically significant differences between therapy groups in the baseline characteristics.

Table 2 shows the number of women in each group who had at least 1 new clinical vertebral fracture during years 1, 2, and 3 in the study. In the first year, 19 women in the placebo group and 6 women in the group receiving raloxifene, 60 mg/d, had at least 1 new clinical vertebral fracture, resulting in a statistically significant 68% reduction in the RR of a new clinical vertebral fracture (Figure 1). Among women who had a prevalent vertebral fracture, the 60-mg/d dosage of raloxifene significantly decreased the RR for a new clinical vertebral fracture by 66% at 1 year (Figure 1). Among women with no prevalent vertebral fracture, 2 women (0.1%) in the placebo group and none in the 60-mg/d raloxifene group had a new clinical fracture at 1 year.

The cumulative incidence of new clinical vertebral fractures in the 60-mg/d raloxifene group was lower (P<.001) than in the placebo group (Figure 2). Like incident vertebral fractures, the cumulative RRs for new clinical vertebral fractures were 0.54 (95% CI, 0.34-0.86) at year 2, and 0.59 (95% CI, 0.41-0.83) at year 3.

For the group receiving raloxifene 120 mg/d, the RR were 0.21 (95% CI, 0.07-0.62) at year 1, 0.35 (95% CI, 0.20-0.59) at year 2, and 0.48 (95% CI, 0.33-0.70) at year 3. The decreased risks for clinical vertebral fractures were not significantly different between the 2 raloxifene groups at 1, 2, or 3 years.

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Raloxifene at a dosage of 60 mg/d reduced the risk for new clinical vertebral fractures by 68% in the first year in postmenopausal women with osteoporosis, and by 66% in women with prevalent vertebral fractures. The cumulative incidence of new clinical vertebral fractures was significantly lower in this group, compared with the placebo group. Significant RR reductions for new clinical vertebral fractures were also observed at 2 and 3 years. The decreased RRs were similar for the raloxifene dosages of 60 and 120 mg/d.

The risk reductions for new clinical vertebral fractures were also observed at 3 years with alendronate and risedronate. Only the risedronate trials included scheduled spinal radiographs for all women at 1 year, irrespective of clinical symptoms, and the observed risk reductions would be a closer estimate of the true efficacy of the drug for vertebral fracture.

Because of the small number of events, our study had inadequate statistical power to determine whether the risk reduction for clinical vertebral fractures was different for each individual year of the study. Data from the MORE Trial suggest that symptomatic vertebral fractures are usually associated with moderate or severe vertebral compression, and in the MORE Trial, significant reductions in moderate and severe vertebral compression fractures are observed through 3 and 4 years (Ethel Siris, MD, JDA, Ying Lu, PhD, Thomas Fuerst, PhD, Gerald Crans, PhD, MW, KDH, Harry Genant, MD, unpublished data, November 1999). The primary limitation to the use of self-report of clinically apparent vertebral fractures is that approximately two thirds of vertebral fractures do not produce clinical symptoms and would not be reported. Therefore, the 68% risk reduction for new clinical vertebral fractures may underestimate the actual 1-year efficacy of raloxifene for vertebral fractures. Unlike the risedronate

**Table 1. Baseline Characteristics of 7705 Postmenopausal Women With Osteoporosis**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo Group (n = 2576)</th>
<th>Raloxifene† Groups</th>
<th>Overall P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>60 mg/d (n = 2557)</td>
<td>120 mg/d (n = 2572)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>66.6 ± 7.1</td>
<td>66.5 ± 7.0</td>
<td>66.3 ± 7.1</td>
</tr>
<tr>
<td>No. of years since menopause</td>
<td>18.9 ± 8.5</td>
<td>18.8 ± 8.5</td>
<td>18.5 ± 8.3</td>
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<tr>
<td>Body mass index§</td>
<td>25.2 ± 4.0</td>
<td>25.2 ± 4.0</td>
<td>25.2 ± 4.0</td>
</tr>
<tr>
<td>Women with ≥1 prevalent vertebral fracture, %</td>
<td>36.4</td>
<td>38.1</td>
<td>37.5</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated.
†Raloxifene hydrochloride.
‡Indicates difference among all therapy groups.
§Calculated as weight in kilograms divided by the square of height in meters.

**Table 2. Incidence of New Clinical Vertebral Fractures in Postmenopausal Women With Osteoporosis Treated With Placebo or Raloxifene for 3 Years**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Placebo Group (n = 2292)</th>
<th>60 mg/d (n = 2259)</th>
<th>120 mg/d (n = 2277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19 (0.8)</td>
<td>6 (0.3)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td>2</td>
<td>33 (1.4)</td>
<td>22 (1.0)</td>
<td>14 (0.6)</td>
</tr>
<tr>
<td>3</td>
<td>29 (1.3)</td>
<td>19 (0.8)</td>
<td>21 (0.9)</td>
</tr>
<tr>
<td>0-3</td>
<td>81 (3.5)</td>
<td>47 (2.1)</td>
<td>39 (1.7)</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) of women. Baseline and follow-up radiographs were available for 6828 women (88.6%) of the 7705 enrolled in the study.
†Raloxifene hydrochloride.

**Figure 1.** Raloxifene hydrochloride, 60 mg/d, decreased the risk for new clinical vertebral fractures in the Multiple Outcomes of Raloxifene Evaluation (MORE) Trial. A, Decreased fracture risk in the total study population, consisting of women with and without prevalent vertebral fractures. Among women who had a baseline radiograph, 37.4% had prevalent vertebral fractures. RR indicates relative risk; CI, confidence interval. B, Raloxifene, 60 mg/d, also decreased the risk for new clinical vertebral fractures in those women with prevalent fractures, who are at greater risk for subsequent fractures.

**Figure 2.** The cumulative incidence of new clinical vertebral fractures in the groups receiving placebo and raloxifene hydrochloride, 60 mg/d. The difference between the groups was statistically significant, as determined by means of the log-rank test (P < .001).
study, the MORE Trial did not prospectively assess vertebral fractures by means of scheduled spinal radiographs at 1 year.

Antiresorptive agents primarily act by inhibiting bone resorption to transiently decrease the bone remodeling space. Whether these early transient changes may accumulate to sufficiently support bone strength is unknown, but the early onset of the effect and the significant reductions in the risk for new vertebral fractures with raloxifene, alendronate, and risedronate suggest that this may be possible.

Women with prevalent vertebral fractures experienced a significantly decreased incidence of new clinical vertebral fractures after 1 year of raloxifene therapy. We found insufficient numbers of clinical vertebral fracture events in women without prevalent vertebral fractures at this time to draw similar conclusions. The present study demonstrates that the skeletal effect of raloxifene occurs with a rapid onset at 1 year, similar to that observed with other antiresorptive agents.

Accepted for publication September 27, 2001.
Eli Lilly and Company, Indianapolis, Ind, provided funding for this study.

This study was presented in part as a poster at the 64th Annual Meeting of the American College of Rheumatology, Philadelphia, Pa, October 31, 2000.

We thank Michele Hill for editorial assistance.

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REFERENCES