A comprehensive review of treatments for postmenopausal osteoporosis

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Received: 15 October 2001 / Accepted: 18 July 2002
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Abstract The aim of this review is to assess the efficacy of treatments for postmenopausal osteoporosis in women with low bone mass or with an existing vertebral fracture. We searched the literature for studies (randomized, double-masked, placebo-controlled and prospective) that reported on drugs registered in Europe or North America. We included 41 reports on 12 agents. To assess the consistency among the studies for each drug, we plotted the percent change in bone mineral density (BMD) for the control group against the percent change in BMD for the treated group for lumbar spine and femoral neck. We used methods of cluster analysis to determine consistency among the studies. For each agent we summarized the relative risk for vertebral fracture (patients with new fracture) and for hip fractures. The duration of the studies ranged from 1 to 4.3 years. The proportion of patients who discontinued treatment ranged from 4% to 80%. Most of the studies reported on change in BMD. Twenty-six studies (10 drugs) provided data on new vertebral fractures and 12 (6 drugs) on hip fractures. Apart from fluoride effects on spine BMD, increases in BMD with bisphosphonates were greater than those seen with the remaining treatments. Generally, for each agent the changes in BMD (relative to placebo) were consistent among the studies. The exceptions were calcitriol and calcitonin for changes in BMD of the spine and of the femoral neck. Alendronate, calcitonin, risedronate and raloxifene caused significant reductions in the risk of vertebral fractures. Alendronate, risedronate or the combination of calcium plus vitamin D had a significant effect on the risk of hip fracture. Most therapies are effective in increasing BMD; some decrease the risk of vertebral fracture. For hip fracture, alendronate and risedronate reduce the risk in women with osteoporosis, and calcium and vitamin D reduce the risk in institutionalized patients.

Keywords Bone · Bone mineral density · Fracture · Prevention

Introduction

The incidence of osteoporotic fractures in postmenopausal women increases exponentially with age. As a consequence of the progressive aging of the population, the related problems are becoming major issues in many countries [1]. By causing prolonged handicap, fractures markedly alter the quality of life, and represent a major source of health costs [2]. The fracture burden is expected to worsen because, for instance, the number of hip fractures is expected to quadruple over the next 30 years, exceeding 6 million cases per year by 2050 [3]. By increasing the demand for health care, the treatment and consequences of osteoporotic fractures could compromise the economy and social equilibrium in many countries. Under these conditions, there is an unavoidable necessity to select optimal and most efficacious treatments aimed at preventing and/or treating osteoporosis, and diminishing thereby the incidence of osteoporotic fractures. There is a need not only to provide patients with the best possible therapy, but also to spend the available resources on well-proven efficacious treatments, in order to achieve the highest benefits/costs ratio. To solve this clinical problem, evidence-based medicine offers an objective and analytical approach, using the available evidence to guide patient management. Evidence-based medicine is the conscientious search for the best evidence available [4]. It is based on the establishment of a hierarchy in the level of evidence. Consistent results from a well-conducted meta-analysis based on well-conducted randomized controlled trials is
at the top of the hierarchy. Results from a well-conducted single randomized controlled trial are at the next highest level. However, the latter achieve a higher degree of certainty than observational studies. Finally, expert opinion represents the least convincing evidence [4].

An improved understanding of the pathophysiology of osteoporosis has led to the development of treatments with effects on bone mineral density (BMD), bone turnover and/or fracture [5,6]. The various agents available for the treatment of osteoporosis and the prevention of osteoporotic fractures do not equally meet the criteria of evidence-based medicine. The present review attempts a critical appraisal of the evidence and, in addition, an assessment of the levels of evidence attained by the studies of the various drugs or agents used in the treatment of osteoporosis and/or in the prevention of osteoporotic fractures. Thus, we searched the literature for randomized, double-masked, placebo-controlled studies on drugs with vertebral or hip fracture as a primary or secondary end-point.

**Statistical methods**

**Data collection**

We systematically searched the literature for randomized, double-masked, controlled and prospective trials, that reported on drugs for the treatment of osteoporosis in Europe or North America. To be eligible for analysis, the studies had to include patients with a low bone mass, as defined by a BMD T-score below or equal to –2.0, or with an existing morphometrically determined vertebral fracture. Based on these criteria, we included in the analysis 41 reports on 12 agents used in the treatment of osteoporosis: alendronate, alpha-calcidol, calcitonin, calcitriol, calcium alone, calcium and vitamin D, etidronate, fluoride, hormone replacement therapy, raloxifene, risedronate, and vitamin D alone. Only full articles published in peer-reviewed journals were analyzed. We excluded studies reported only in abstract form. A quality score (maximum 32) assessing various aspects of the presentation of the paper, such as a clear formulation of the hypothesis, the full description of statistical analysis and of dropouts, internal and external validity, was attributed to each report [7] (see Appendix).

**Bone mineral density**

For each study we plotted the percent change in BMD for the control group on the vertical axis and the percent change in BMD for the treated group on the horizontal axis. The size of the symbol used in the plot is proportional to the total number of patients who were evaluated at the end of the study. Symbols on the so-called line of equality indicate that the percent changes in BMD in the control group were the same as those in the treated group. Symbols below the line of equality indicate that percent changes in BMD in the treated group exceeded those in the controls. Symbols above the line indicate that the treated group had percent changes lower than those in the control group. If there was an increase in the treated group but a decrease in the controls, then the symbols are in the lower region on the right. Lastly, symbols in the lower left quadrant indicate a BMD decrease in both treated and control groups.

For each study we computed the distance of the symbol from the line of equality. This distance is proportional (by a factor equal to \(1/\sqrt{2}\)) to the difference between the change in BMD in the treated group and the change in BMD in the control group. To summarize the data from each agent we computed the mean distance of all the studies for a particular agent from the line of equality. The mean was weighted by the number of patients randomized into the study. To evaluate consistency of the data for each agent, we computed the weighted deviation from the line of equality and the weighted standard error of the mean.

**Fracture risk**

To summarize the relative risk for vertebral fractures and for hip fractures, we used the method of analysis for combining multiple contingency tables as proposed by Mantel and Haenszel [8]. For some agents there was only one study. In such cases we reported the published relative risk if the analysis was based on women with fracture as opposed to number of fractures. Indeed, to avoid deriving overestimates of the relative risk if the analysis was based on number of fractures, we computed the relative risk based on women with a new fracture (i.e., fracture incidence) rather than a risk based on events per person-year [9].

**Results**

With the exception of three studies [10–12], where the mean age was in the eighties, all studies having BMD, or vertebral fracture or hip fracture as an end-point, enrolled patients whose mean age was in the seventies (Table 1). Study duration ranged from 1 to 4.3 years. The number of patients included per study varied markedly from 34 (for calcitriol) [13] to more than 9000 (for risedronate) [14]. The dropout rate also varied markedly according to the study, from a low of 4% (for alendronate) [15] to a high of 80% (one study on fluoride) [16]. The mean age among studies in which morphometric vertebral fracture was an end-point ranged from 60 to 71 years (Table 2). The definition of a morphometric fracture differed among the trials. Most trials compared the heights (anterior, middle and posterior) of the vertebral bodies at baseline with the corresponding heights at selected time points during the study. The definition of an event (a fracture) among the different trials ranged from a reduction in vertebral body height of 15% to 20%. The total number of events (patients with at least one fracture) per study was as low as 10 (for alendronate, calcium or fluoride) [17–19] and as high as 358 (for raloxifene) [20] (Table 2). Among the studies on hip fracture incidence, only 2 [10,14] had hip fracture as a primary end-point. Specifically this means that sufficient patients, assuming a specific incidence rate in the placebo groups, were enrolled to detect a prespecified reduction in the risk of hip fracture. The remaining studies had hip fracture as a secondary end-point. This means that the number of patients enrolled could not guarantee the power needed to detect a prespecified difference. Four (for alendronate, calcium and vitamin D, raloxifene or risedronate) [10,14,20,21] had sufficient power to detect a difference (Table 3). The number of hip fracture events was 58 in the report on calcium and vitamin D in institutionalized elderly [10] and in the study with raloxifene [20]. It reached 232 in the study with risedronate [14]. The quality score ranged from 11 (for one study with fluoride) [22] to 28 (one study with alendronate) [15].