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Review article

Medical treatment of severe osteoporosis including new concept of advanced severe osteoporosis

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Abstract

Osteoporosis is a metabolic bone disease characterized by decreased bone strength, leading to an increased risk of fracture. The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) of 2.5 standard deviations below that of a young adults (T-score of −2.5 or lower). Severe osteoporosis is differentiated from osteoporosis by the presence of one or more fragility fractures in addition to this T-score. However, the current WHO definition may be insufficient to reflect the diverse spectrum of osteoporosis or severe osteoporosis, which can encompass various number and severity of prevalent fractures. To overcome these shortcomings of the WHO definition of osteoporosis, we propose a concept of 'advanced severe osteoporosis', which is defined by the presence of proximal femur fragility fracture or two or more fragility fractures in addition to BMD T-score of −2.5 or less. Based on the previous clinical trials and *post-hoc* analyses, we recommend selective estrogen receptor modulators, bisphosphonates, receptor activator of nuclear factor kappa-B ligand (RANKL) monoclonal antibody, and parathyroid hormone for the medical treatment of severe osteoporosis. In cases of advanced severe osteoporosis or osteoporosis that does not respond to previous anti-osteoporotic treatments, we also recommend parathyroid hormone, bisphosphonates, and RANKL monoclonal antibody. In conclusion, we need more precise assessment of osteoporosis and further stratification of the disease by number of prevalent fractures in addition to BMD. More aggressive managements should be provided for those with advanced severe osteoporosis.

Keywords: Advanced severe osteoporosis; Fragility fractures; Medical treatment; Severe osteoporosis

1. Introduction

Osteoporosis is a metabolic bone disease characterized by decreased bone strength, leading to an increased risk of fracture. Recently, osteoporosis has become one of the most common public health problems with a progressive increase in the elderly population. Medical-related expenses are expected to rapidly rise around the world [1]. Osteoporosis related fractures can cause significant morbidity and disability, reducing the quality of life, and can even lead to death in severe cases. If hip fracture occurs, 20–30% of patients die within one year [2,3]. Furthermore, 40% of patients are unable to walk independently, and 60% have difficulty with at least one essential activity of daily living one year after hip fracture [3].

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The incidences of fragility fracture vary globally. It was previously reported that about 40% of white women and 13% of white men in the United States have at least one fragility fracture after 50 years of age [3]. A recent report based on the Health Insurance Review and Assessment Service (HIRA) in Korea documented residual lifetime probability of osteoporosis-related fractures is 59.5% and 23.8 for Korean women and men, respectively [4]. Asia is expected to be seriously affected by osteoporosis-related fractures in the near future with its rapidly aging population. It is estimated that 50% of all osteoporotic fractures will occur in Asia by 2050 [5]. Based on the Korea National Health and Nutrition Examination Survey (KNHANES), the prevalence of osteoporosis in adults aged 50 years or older was 35.5% in women and 7.5% in men [6]. However, the estimated diagnosis rate of osteoporosis is only 26.2% (women 29.9%, men 5.8%) and the treatment rate is as low as 12.8% (women 14.4%, men 4.0%) in Korea [6]. Despite its devastating effect on public health, osteoporosis is still being under-diagnosed and under-treated in modern societies.

The World Health Organization (WHO) defines osteoporosis as a bone mineral density (BMD) of 2.5 standard deviations below that of a young adults (T-score of −2.5 or lower) [7]. Severe osteoporosis is differentiated from osteoporosis by the presence of one or more fragility fractures in addition to BMD T-score below −2.5 [7]. The presence of fragility fractures has a clinically significant implication for subsequent fractures. Patients with a vertebral fracture are at about 3−5-fold higher risk for another vertebral fracture within the following year than those without fracture [8,9]. Therefore, it is clinically more important to treat those with prevalent fractures with medications that have clear evidence of fracture reduction in such patients. Based on the results of previous clinical trials, we chose four classes of pharmacological agents that have clear evidences of anti-fracture efficacy in such patients and summarized the effects of those medications (Table 1). These pharmacological agents include selective estrogen receptor modulators (SERMs), bisphosphonates, receptor activator of nuclear factor kappa-B ligand (RANKL) monoclonal antibody, and parathyroid hormone. In this topic review, we also discuss the limitations of the current WHO definition of severe osteoporosis and proposed a concept of 'advanced severe osteoporosis' to provide a more accurate assessment of the disease and allow more proactive managements.

2. SERMs

2.1. Raloxifene

The Multiple Outcomes of Raloxifene (MORE) trial studied the effects of raloxifene in 7705 postmenopausal women with osteoporosis. Raloxifene decreased the cumulative risk of new vertebral fractures, increased BMD, and decreased biochemical markers of bone turnover in the 36-month treatment period [10]. *Post hoc* analyses studied the effects of placebo, raloxifene 60 mg/day and raloxifene 120 mg/day on new fracture risk in women with the most severe prevalent vertebral fractures ($n = 614$) among the MORE population. The presence and severity of prevalent vertebral fractures were determined from visual semiquantitative (SQ) analysis of spinal radiographs taken at baseline. In patients with severe baseline vertebral fractures (SQ 3), raloxifene 60 mg/day decreased the risks of new vertebral [Relative Risk (RR) 0.74, 95% Confidence Interval (CI) 0.54−0.99; $P = 0.048$] and nonvertebral (clavicle, humerus, wrist, pelvis, hip, and leg) fractures [Relative Hazard (RH) 0.53, 95% CI 0.29−0.99; $P = 0.046$] at 3 years [11]. The MORE study had a 12-month blinded extension phase to further assess the cumulative effects of raloxifene on the incidence of fractures, changes in BMD and bone turnover ($n = 6828$). After 4 years, the cumulative relative risks for new vertebral fractures were reduced in the total study population with both raloxifene doses (60 mg/day, 120 mg/day). For women with prevalent vertebral fractures, the RR for new vertebral fractures was 0.66 (95% CI 0.55−0.81) with raloxifene 60 mg/day and 0.54 (95% CI 0.44−0.66) with raloxifene 120 mg/day. There was no evidence that raloxifene treatment lowered the risk for nonvertebral fractures in the total study population [12]. The Continuing Outcomes Relevant to Evista (CORE) trial assessed the effects of raloxifene on breast cancer and nonvertebral fracture for 4 additional years beyond the 4-year MORE osteoporosis treatment trial. Raloxifene therapy had no effect on nonvertebral fracture risk after 8 years. However, the risk for new nonvertebral fractures was significantly decreased in women with prevalent vertebral fractures at the baseline of MORE [Hazard Ratio (HR) 0.78, 95% CI 0.63−0.96] [13]. Raloxifene therapy significantly decreased the risk of subsequent vertebral and nonvertebral fractures at 3 years in the small subgroup of women with severe vertebral fractures at baseline. Furthermore, nonvertebral fracture risk reduction might be maintained in some high-risk subgroups by exploratory analyses after 8 years of raloxifene.

2.2. Bazedoxifene

In a 3-year, randomized, double-blind, placebo- and active-controlled study, healthy postmenopausal women with osteoporosis ($n = 6847$, 55−85 years of age) were treated with bazedoxifene 20 or 40 mg/day, raloxifene 60 mg/day, or placebo [14]. Among subjects with prevalent fracture, bazedoxifene 20 and 40 mg and raloxifene 60 mg significantly reduced the risk of new vertebral fractures relative to placebo by 45% (HR 0.55, 95% CI 0.32−0.94), 38% (HR 0.62, 95% CI 0.37−1.05), and 43% (HR 0.57, 95% CI 0.34−0.97), respectively. In a *post hoc* analysis of a subgroup of women at higher fracture risk (femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe vertebral fracture or multiple mild vertebral fractures; $n = 1772$), bazedoxifene 20 mg produced a 50% and 44% reduction in nonvertebral fracture risk relative to placebo ($P = 0.02$) and raloxifene 60 mg ($P = 0.05$), respectively. Bazedoxifene treatment of postmenopausal women with osteoporosis significantly reduced the risk of vertebral fracture in the total subjects as well as subjects with pre-existing