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Osteoporosis and Sarcopenia 2 (2016) 13–19

http://www.elsevier.com/locate/afos

Review article

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

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Received 14 January 2016; revised 5 February 2016; accepted 12 February 2016
Available online 16 March 2016

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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Peer review under responsibility of The Korean Society of Osteoporosis.

http://dx.doi.org/10.1016/j.afos.2016.02.003

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

Table 1
Risk reduction of vertebral or nonvertebral fractures among patients with prevalent fractures

Pharmacologic agent	Study	Patients with prevalent fractures (overall population or subgroup)	Fracture risk		Reference
			Vertebral	Nonvertebral	
SERM					
Raloxifene	MORE	Severe vertebral fractures[a] (subgroup)	RR 0.74	RH 0.53	11
		Prevalent vertebral fractures (subgroup)	RR 0.66/RR 0.54[b]		12
	CORE	Prevalent vertebral fractures (subgroup)		HR 0.78	13
Bazedoxifene	Phase 3 trial	Prevalent vertebral fractures (subgroup)	HR 0.55/HR 0.62[c]		14
		≥1 moderate or severe vertebral fracture or multiple mild vertebral fractures and/or FN T-score ≤ −3.0 (subgroup)		HR 0.5	14
Bisphosphonates					
Alendronate	FIT	≥1 vertebral fracture (overall population)	RR 0.53/RH 0.45[d]	RH 0.72/RH 0.49[g]	15
Risedronate	VERT-NA	≥1 vertebral fracture (overall population)	RR 0.59	RR 0.6	16
	VERT-MN	≥2 vertebral fractures (overall population)	RR 0.51	RR 0.67	17
Ibandronate	BONE	1−4 prevalent vertebral fractures (overall population)	RR 0.38	RR 0.31	18
		1−4 prevalent vertebral fractures and FN T-score < −3.0 (subgroup)			18
Zoledronate	HORIZON-PFT	Prevalent vertebral fractures (63% of overall population)	RR 0.30	HR 0.75/HR 0.59[h]	20
	HORIZON-RFT	Hip fracture (overall population)	HR 0.54[e]	HR 0.73/HR 0.70[i]	22
RANKL monoclonal antibody					
Denosumab	FREEDOM	≥2 vertebral fractures of any degree of deformity or ≥1 vertebral fracture of moderate or severe deformity (subgroup)	RR 0.45		24
Parathyroid hormone					
Teriparatide	FPT	≥1 moderate vertebral fracture or ≥2 mild atraumatic vertebral fractures (overall population)	RR 0.35/RR 0.31[f]	RR 0.47/RR 0.46[j]	26

BONE: the oral ibandronate osteoporosis vertebral fracture trial in North America and Europe, CORE: the continuing outcomes relevant to Evista, FIT: the fracture intervention trial, FN: femur neck, FREEDOM: the fracture reduction evaluation of denosumab in osteoporosis every 6 months, FPT: the fracture prevention trial, HORIZON-PFT: the health outcomes and reduced incidence with zoledronic acid once yearly-pivotal fracture trial, HORIZON-RFT: the health outcomes and reduced incidence with zoledronic acid once yearly-recurrent fracture trial, HR: hazard ratio, MORE: the multiple outcomes of raloxifene evaluation, RANKL: receptor activator of nuclear factor kappa-B ligand, RH: relative hazard, RR: relative risk, SERM: selective estrogen receptor modulator, VERT-NA: the vertebral efficacy with risedronate therapy-North America, VERT-MN: the vertebral efficacy with risedronate therapy-multinational.

[a] Vertebral fracture severity assessed by the visual semiquantitative method.
[b] RR 0.66 for raloxifene 60 mg and RR 0.54 for raloxifene 120 mg.
[c] HR 0.55 for bazedoxifene 20 mg and HR 0.62 for bazedoxifene 40 mg.
[d] RR 0.53 for morphometric vertebral fracture and RH 0.45 for clinical vertebral fracture.
[e] HR 0.54 for clinical vertebral fracture.
[f] RR 0.35 for teriparatide 20 μg and RR 0.31 for teriparatide 40 μg.
[g] RH 0.72 for any clinical fracture including clinical vertebral fracture and RH 0.49 for hip fracture.
[h] HR 0.75 for nonvertebral fracture and HR 0.59 for hip fracture.
[i] HR 0.73 for nonvertebral fracture and HR 0.70 for hip fracture.
[j] RR 0.47 for teriparatide 20 μg and RR 0.46 for teriparatide 40 μg.

fracture. Bazedoxifene treatment also showed a significant reduction in the incidence of nonvertebral fractures in subjects at higher risk for fracture.

3. Bisphosphonates

3.1. Alendronate

In the randomized Fracture Intervention Trial (FIT) of effect of alendronate on risk of fracture in women with existing vertebral fracture [15], 2027 women aged 55−81 years with low femoral neck BMD and existing vertebral fracture were randomly assigned placebo or alendronate and followed up for 3 years. Mean age was 71 years. New vertebral fractures (morphometric and clinical), the primary endpoint, were assessed. Eight percent of women in the alendronate group had one or more new morphometric vertebral fractures compared with 15% in placebo group (RR 0.53, 95% CI 0.41−0.61). Also, alendronate significantly reduced clinical vertebral fracture risk compared with in the placebo group after 3-year follow up period (RH 0.45, 95% CI 0.27−0.72). The risk of any clinical fracture was lower in the alendronate than in the placebo group (RH 0.72, 95% CI 0.58−0.90). The risk of hip fracture and wrist fracture for alendronate vs. placebo was 0.49 (95% CI 0.23−0.99) and 0.52 (95% CI 0.31−0.87), respectively. Therefore, alendronate substantially reduces the risk of vertebral fractures, as well as hip fractures in postmenopausal women with prevalent vertebral fractures.

3.2. Risedronate

A representative randomized clinical trial of risedronate in postmenopausal women with vertebral fracture (VERT-NA) was reported in 1999 [16]. This clinical trial included 2,458 postmenopausal women younger than 85 years with at least 1 vertebral fracture. Subjects were randomly assigned to receive risedronate or placebo for 3 years and the mean age of the subjects was 69 years. Risedronate significantly decreased the risk of new vertebral fracture compared with placebo over 3 years (RR 0.59, 95% CI 0.43−0.82). A significant reduction of 65% in vertebral fracture risk was seen in the first year of treatment (95% CI 0.38−0.81). Also, risedronate reduced the cumulative incidence of non-vertebral fractures by 39% over 3 years (95% CI 0.06−0.61). Reginster et al. [17] reported the effects of risedronate on vertebral fracture in 1,226 postmenopausal women with two or more prevalent vertebral fracture in Europe and Australia (VERT-MN) for 3 years. Risedronate reduced the risk of new vertebral fractures by 61% within the first year and 49% over 3 years compared with control. However, non-vertebral fracture risk reduction was 33% compared with control over 3 years ($P = 0.06$).

3.3. Ibandronate

In terms of ibandronate effects on severe osteoporosis, the oral ibandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE) study has been the representative multicenter trial for oral ibandronate, which included 2946 postmenopausal women for 3 years [18]. The mean age of the subjects was 69 years, and 93−94% had at least one prevalent fracture and 42−44% were with at least two prevalent fractures. The protective effect on new vertebral fracture was remarked from year 2 and 62% significant risk reduction at year 3. However, nonvertebral fracture risk reduction was 69% only in the high risk group whose femoral neck BMD T-score was lower than −3.0. The Dosing IntraVenous Administration (DIVA) study compared intravenous (IV) ibandronate vs. oral regimen for one year in the United States and Europe [19]. The mean age of the 1395 postmenopausal women was 65.5 years and 41.8−43.7% had a prevalent fracture. IV ibandronate increased BMD of all sites compared with oral ibandronate, but no difference of clinical vertebral fracture risk was found in one year. Thus, oral and IV ibandronate reduce vertebral fracture risk in severe osteoporosis with prevalent fracture, but the risk reduction of nonvertebral fracture has been reported only in high risk group with femoral neck BMD T-score less than −3.0. Some caution is needed when applying ibandronate for severe osteoporosis, since the drug is indicated only for postmenopausal women and the risk reduction of nonvertebral or wrist fracture has limited outcome.

3.4. Zoledronate

Among various bisphosphonates, zoledronic acid has long been used and shown to be effective for hypercalcemia from cancers or bone metastasis. For osteoporosis and fracture prevention, the Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly-Pivotal Fracture Trial (HORIZON-PFT) is the representative trial with yearly injection of zoledronic acid in 3,889 postmenopausal women for 3 years held in the USA, Europe, and Asia [20]. The mean age of the subjects was 73 years and 63−79% had prevalent vertebral fracture. The morphometric vertebral fracture risk was reduced by 70%, nonvertebral fracture risk by 25%, and hip fracture risk by 41%. The prolonged effect of zoledronic acid was compared in the HORIZON-PFT extension study, which compared a 3-year extension of zoledronic acid or change to placebo after conventional therapy [21]. The subjects over 50% had a femoral BMD T-score less than −2.5 and 60% of subjects had at least one prevalent vertebral fracture. The morphometric vertebral fracture risk was reduced by 49% in the 6-year extension group but no difference was evident in the risk of nonvertebral or hip fracture. No significant differences in long-term side effects were reported. The HORIZON Recurrent Fracture Trial reported a 35% reduction of recurrent fracture, 46% of clinical vertebral fracture, and 27% of nonvertebral fracture in 2,127 men and women with recent repair for low-trauma hip fracture [22]. Moreover, mortality was significantly reduced by 28% in the 3-year trial. Thus, yearly injection of 5 mg zoledronic acid is effective in reducing clinical and morphometric vertebral, nonvertebral, and hip

fracture risk, and also reduces recurrent fractures and mortality in high risk groups of both men and postmenopausal women with severe osteoporosis.

4. RANKL monoclonal antibody

4.1. Denosumab

Fracture prevention with denosumab in postmenopausal women with osteoporosis was demonstrated in the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Trial [23]. FREEDOM was a 3-year, randomized, double-blind, placebo-controlled, phase 3 trial that enrolled 7868 postmenopausal women with osteoporosis. The subcutaneous administration of 60 mg of denosumab every 6 months for 36 months significantly reduced the risk of new radiographic vertebral fracture by 68% (RR 0.32, 95% CI 0.26–0.41; $P < 0.001$). Denosumab reduced the risk of hip fracture by 40% (HR 0.60, 95% CI 0.37–0.97; $P = 0.04$) and also reduced the risk of nonvertebral fracture by 20% (HR 0.80, 95% CI 0.67–0.95; $P = 0.01$). A *post hoc* analysis of FREEDOM trial evaluated fracture incidence in women with higher-risk for vertebral or hip fractures [24]. As compared with placebo, treatment with denosumab reduced the incidence of new vertebral fractures by 55% among women with multiple prevalent vertebral fractures and/or moderate or severe vertebral deformity (16.6% placebo vs. 7.5% denosumab; $P < 0.001$). Denosumab also reduced the risk of new vertebral fractures by 60% in those with multiple and/or moderate or severe vertebral deformities in addition to a femoral neck BMD T-score of −2.5 or less (20.1% placebo vs. 8.1% denosumab; $P = 0.001$). Denosumab treatment also significantly reduced the risk of hip fractures in subjects aged 75 years or older by 62% (2.3% placebo vs. 0.9% denosumab; $P < 0.01$) or with a baseline femoral neck BMD T-score of −2.5 or less by 47% (2.8% placebo vs. 1.4% denosumab; $P = 0.02$). The anti-fracture efficacies in higher-risk subgroup over 3 years were consistent with those reported for the overall FREEDOM population. These analyses demonstrated that denosumab reduces the risk of both new vertebral and hip fractures, regardless of the underlying risk and that the higher absolute fracture risk observed in the higher-risk subgroups is associated with greater absolute risk reduction with denosumab treatment.

5. Parathyroid hormone

5.1. Teriparatide

Teriparatide is an anabolic agent composed of the first 34 amino acids of recombinant human parathyroid hormone. Teriparatide stimulates bone formation by osteoblasts and subsequently bone resorption by osteoclasts, and has anabolic effects on bone with an anabolic window [25]. Because of this unique anabolic action, teriparatide showed superior efficacy in treating osteoporosis and preventing fractures. In the Fracture Prevention Trial, daily subcutaneous injection of teriparatide for 18 months in postmenopausal women with prior vertebral fractures increased BMDs by 9.7% and 2.8% at the lumbar spine and femur neck, respectively [26]. Moreover, teriparatide treatment reduced the risks of vertebral and non-vertebral fracture by 65% and 53%, respectively, in the postmenopausal women [26]. Teriparatide showed superior efficacy on increasing BMD at lumbar spine compared to alendronate (10.3% vs. 5.5% in areal BMD and 19.0% vs. 3.8% in volumetric BMD, $P < 0.05$ respectively) [25]. Although prior treatment with anti-resorptive agents modestly blunted the anabolic efficacy of teriparatide, teriparatide administration was effective in increasing BMD in postmenopausal women with previous anti-resorptive agents use [27,28]. Teriparatide has also been effective in male osteoporosis. Daily 20 μg subcutaneous injection of teriparatide significantly increased BMDs by 13.5% at lumbar spine and by 2.9% at femur neck in one study [29]. Teriparatide treatment provided efficacy in increasing BMD and reducing fractures in glucocorticoid induced osteoporosis with better outcomes in decreasing vertebral fractures and no differences in non-vertebral fractures compared to the alendronate group [30]. However, the combination therapy of teriparatide with anti-resorptive agents is not recommended because there has been no evidence of synergistic effects between those two drugs [31,32]. The common side effects in using teriparatide are mild gastrointestinal symptoms, especially nausea, and headache. The total exposure period is limited to 24 months, and switch to anti-resorptive agents is recommended to extend the anabolic effects of prior teriparatide [33].

6. Discussion

The clinical significance associated with osteoporosis is the occurrence of fragility fractures at various sites and the goal of osteoporosis management is prevention of fractures and ultimately reduction in morbidity and mortality. Therefore, it is clinically important to identify those who are at higher risk of fractures and more likely to benefit from osteoporosis management. In 1994, the WHO published the current definition of osteopenia and osteoporosis based on the BMD T-score [7]. The criteria were developed based on the evidence indicating that BMD can predict fracture risk [34–36], although it is now generally accepted that fracture risk is determined not only by BMD but also by other structural and functional factors associated with bone quality. The WHO also defined severe osteoporosis as the presence of fragility fracture in addition to BMD T-score of −2.5 or less. This concept of severe osteoporosis is also supported by the fact that previous osteoporotic fractures increase the risk of subsequent fractures [8,9]. However, the WHO definition of severe osteoporosis does not take into account the number and severity of prevalent vertebral fractures, which have been independently associated with subsequent vertebral or nonvertebral fractures [11,37]. A previous study by Lindsay et al. showed that the presence of one vertebral fracture increased the risk of new vertebral fracture by 2.6-fold during the initial year of the study compared with the incidence in subjects without vertebral

fracture at baseline, while the presence of two or more vertebral fracture was associated with increased risk of new vertebral fracture by as much as 7.3-fold [8]. Furthermore, excess mortality rates following fractures of the vertebrae [38−40] and particularly of the hip [2,3,40,41] were also demonstrated in many studies. Mortality rates following hip fracture were reported to range from 10% to 45% in the first year [41]. The number of prevalent vertebral fractures is also associated with increased mortality. A prospective USA cohort study with a mean follow-up of 8.3 years showed that mortality rose with greater numbers of vertebral fractures, from 19 per 1000 woman-years in women with no fractures to 44 per 1,000 woman-years in those with 5 or more fractures [38]. In contrast, no excess mortality was reported among patients who sustain a distal forearm, foot, or ankle fractures [39−41]. Given these various relationships between fractures and their consequences, many clinicians and researchers believe that the current WHO definition is not sufficient to reflect the diverse spectrum of osteoporosis or severe osteoporosis, which can encompass various number and severity of prevalent fractures. To overcome these shortcomings, we need new criteria that stratify the disease severity in detail to assess the fracture risk more precisely and provide a basis for more aggressive treatment options.

In this regard, we propose a concept of 'advanced severe osteoporosis' to provide more accurate assessment of the disease and allow more aggressive managements. We think that number and location of prevalent fractures should be taken into account to further stratify the concept of severe osteoporosis. Therefore, we defined the advanced severe osteoporosis 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. We expect this new concept of advanced severe osteoporosis will provide a basis for more aggressive managements for osteoporotic patients with multiple fractures [42].

In this topic review of severe osteoporosis, we reviewed the anti-osteoporotic agents and found that four classes of established medications have strong evidence enough to be used in severe osteoporosis or osteoporosis with prevalent fractures. Therefore, we recommend SERMs, bisphosphonates, RANKL monoclonal antibody, and parathyroid hormone for the medical treatment of severe osteoporosis, based on the clinical trials and *post-hoc* analyses. In cases of advanced severe osteoporosis or osteoporosis that does not respond to previous anti-osteoporotic treatments, we also recommend parathyroid hormone as an anabolic agent, and bisphosphonates and RANKL monoclonal antibody as more effective antiresorptive agents, which showed definite anti-fracture efficacy not only for vertebral fracture but also for non-vertebral or hip fracture based on the results of pivotal clinical trials.

In conclusion, we need more precise assessment of osteoporosis and further stratification of the disease by number and location of prevalent fractures in addition to BMD. For those with severe osteoporosis or advanced severe osteoporosis, more effective managements should be warranted to decrease the morbidity and mortality associated with osteoporosis. Considering the detrimental effects of osteoporosis-related fragility fractures on future public health in these aging societies, we desperately need a national policy allowing more aggressive treatment options for this disease.

Conflict of interest

YSC (Yoon-Sok Chung) has received funding and/or honoraria from Pfizer, Takeda, MSD, Sanofi, Yuyu, Hanlim, Kwangdong, and GSK, and is a member of the advisory boards of MSD and Yuyu.

Acknowledgments

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2015R1C1A1A01054333).

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