Management of Established Osteoporosis

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Abstract: Patients with established osteoporosis should deserve early treatment as the risk of subsequent fracture is very high resulting in significant morbidity and mortality. Effective treatment modalities are those which have been proven to have consistent anti-fracture efficacy. This article attempts to make an overview of the current pharmacological options in the treatment of established osteoporosis. Studies on anabolic and antiresorptive agents and their combination and sequential therapy will be reviewed. The role of auxiliary therapy with calcium and vitamin D supplementation and non-pharmacological management will be emphasized.

Keywords: Anabolic, antiresorptive, fracture, osteoporosis

Introduction

Osteoporosis has been previously defined in 1993 as a disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk.\(^1\) This definition has been revised in 2001 as a skeletal disorder characterized by compromised bone strength with an increased risk of fracture.\(^2\) The reason for the revision is that bone mass only plays a part in the determination of bone strength which is the most important single endogenous factor that determines the propensity of a bone to fracture. The other important elements are the structural properties, the material properties, the microarchitecture and the degree of bone remodeling of the bone.

Bone mass can be quantitatively measured with the dual energy X-ray absorptiometry (DXA) which is the current international gold standard for bone mineral density (BMD) measurement.\(^3\) The other elements which contribute to bone strength cannot be quantitatively measured by equipments or tools in general clinical use, with the exception of the use of biochemical bone markers to reflect the degree of bone remodeling.

Because of the limitation of current clinical instruments in the assessment of bone strength, the clinical diagnostic criteria of osteoporosis is conventionally based on the T-score values obtained by DXA (Table 1).\(^4\) Severe or established osteoporosis is defined by the World Health Organization (WHO) as a T-score of $\leq -2.5$ in the presence of one or more fragility fractures.

Despite the existence of the WHO clinical diagnostic criteria of osteoporosis since 1994, this disease is underdiagnosed and undertreated globally and locally.\(^5,6\) This article gives an overview on the medical management of established osteoporosis with an aim to arouse the awareness of clinicians on the notion that effective osteoporosis therapies are currently available.

Clinical Importance of Established Osteoporosis

The most important clinical consequence of osteoporosis is a fracture. Vertebral fracture is the most common type of osteoporotic fracture but up to a half of the vertebral fractures are asymptomatic. Patients may have a loss of height and
deformity of the spine notably kyphosis with the resultant acceleration of the age-related decline of the lung function. Symptomatic patients may develop severe disabling back pain. Quality of life measures have shown a significant decline in all domains in patients with vertebral fractures.7

Hip fractures are the most important clinical fracture since only half of the fractured patients can return to the pre-morbid ambulatory state. The remaining half may require walking aids for ambulation or even become chair or bed-bound. The one-year mortality has been up to 20% related to both immediate mortality as well as secondary complications from the decrease in ambulatory level.8 Data from the Hong Kong Hospital Authority (HA) showed that there had been more than 3600 cases of hip fractures in the year 2000. The estimated cost of acute care of each case amounted to HK$80,000 not including the cost of rehabilitation. The total cost of the acute care of hip fracture was HK$270 millions, constituting 1% of the HA annual budget.9

More importantly, a history of prior fracture at any site predicts the occurrence of future fractures. Studies have reported that the presence of one or more prevalent vertebral fractures increased risk of sustaining a new vertebral fracture by 5-fold in the following year and almost 20% of patients with an incident vertebral fracture would sustain a new vertebral fracture within a year.10 A history of distal forearm fracture not only predicts a more than 3-fold increase in subsequent distal forearm fracture but also a 1.9-fold increase in hip fracture and 1.7-fold increase in new vertebral fracture.11 Overall, women with prior fractures at any sites had two times increase in risk of subsequent fracture compared with women without prior fractures.11 This group of patients with established osteoporosis should deserve high priority of aggressive clinical attention since effective and safe treatment therapies that reduce fracture risk are currently available.

Pharmacological Management of Established Osteoporosis

The primary objective of any medical intervention for osteoporosis therapy would be a reduction in the risk of future fracture. My personal opinion would be that patients with established osteoporosis should be offered the treatment which has been proven to have the greatest anti-fracture efficacy preferably with long-term safety data. Agents with anabolic property appear to be superior to antiresorptive agents in the former aspect but long-term safety data are lacking. Antiresorptive agents such as hormone replacement therapy (HRT) and calcitonin are out of favour because HRT imposes an unnecessary health risk to postmenopausal women12 whereas calcitonin has inconsistent anti-fracture efficacy.13

(1) Teriparatide [Recombinant-human Parathyroid Hormone (PTH) 1-34]

Although PTH physiologically accelerates bone resorption, intermittent administration of PTH or its 1-34 fragment, teriparatide, has anabolic effect. In the landmark multi-centre Fracture Prevention Trial of teriparatide in 1637 postmenopausal women with prior vertebral fractures, daily subcutaneous injection of teriparatide at a dose of 20 µg increased BMD by 9% at the lumbar spine and 3% at the femoral neck after 21 months. It reduced the risk of new vertebral and non-vertebral fractures by 65% and 53% respectively.14 Histomorphometry and microcomputerised scanning of 51 paired iliac crest biopsy specimens obtained from women from the same trial revealed significant increases in cancellous bone volume, bone connectivity density and bone plate-like structure, cortical thickness and a reduction in marrow star volume,15 all of which indicated an

**Table 1. The World Health Organization criteria for osteoporosis**4

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Bone mineral density (BMD) within 1 standard deviation (SD) of the young adult mean (T-score ≥ -1.0)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>BMD more than 1 SD below the young adult mean but less than 2.5 SD below this value (T-score &lt;-1.0 and &gt;-2.5)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>BMD being 2.5 SD or more below the young adult mean (T-score ≤ -2.5)</td>
</tr>
<tr>
<td>Severe or established osteoporosis</td>
<td>BMD being 2.5 SD or more below the young adult mean (T-score ≤ -2.5) in the presence of one or more fragility fractures</td>
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improvement in bone quality. Side-effects of teriparatide treatment included nausea, headache, dizziness and leg cramps, which were mild and transient. Transient asymptomatic hypercalcaemia was also observed. The current recommended duration of therapy is 18 to 24 months with periodic monitoring of serum calcium levels. The most important factor that limits its clinical use is the cost which amounts to HK$4,000 a month, being 10 times more expensive than other treatment options.

(2) Strontium Ranelate

Strontium is a trace element that has been shown to uncouple bone remodeling by increasing bone formation and decreasing bone resorption. In the multi-centre Spinal Osteoporosis Therapeutic Intervention (SOTI) trial of 1649 postmenopausal women with ≥1 vertebral fractures, strontium ranelate at an oral daily dose of 2 g increased BMD by 14.4% at the lumbar spine and 8.3% at the femoral neck over a 3-year treatment period but after adjustment of strontium content, the corrected increase in BMD of the lumbar spine was 8.1%. The anti-fracture effect was evident early in the course of treatment with a significant 49% risk reduction of new vertebral fractures after 1 year and the overall risk reduction was 41% after 3 years. Anti-fracture efficacy was accompanied by a decrease in back pain and body height loss. Histomorphometric analysis of 14 bone biopsies in 20 patients showed no evidence of osteomalacia nor any sign of a primary mineralization defect after 3 years of treatment.

To evaluate the anti-fracture efficacy of strontium ranelate on non-vertebral fractures, the Treatment of Peripheral Osteoporosis Study (TROPOS) was conducted in 5091 postmenopausal osteoporotic women who were either aged ≥74-year or aged between 70 and 74 but with one additional risk factor for fracture. Results showed that all non-vertebral fractures were significantly reduced by 16% and major fragility fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle, humerus) were significantly reduced by 19% in strontium ranelate treated patients. However, a significant 36% reduction in the risk of hip fracture was only seen in post-hoc analysis of a high-risk subgroup of 1977 women with age ≥74-year and with femoral neck BMD T-score ≤-3. The corresponding risk reduction for the whole group of women was only a non-significant 15%.

In both studies, incidence of adverse events was similar in both the treatment and placebo groups, the most common being nausea and diarrhoea which subsided after the first three months. Long-term safety remains to be established.

(3) Oral Bisphosphonates

Alendronate and risedronate are the two oral bisphosphonates that have been proven in large-scale prospective randomised double-blind placebo-controlled studies to be able to increase spine and hip BMD by 3-10% with a significant reduction in the risk of both vertebral and non-vertebral fractures (30-50%) in postmenopausal women with osteoporosis. In the Vertebral Fracture Arm of the multi-centre Fracture Intervention Trial of 2027 postmenopausal women aged 55-81 with ≥1 vertebral fractures at baseline, daily 10 mg oral alendronate significantly reduced the risk of new morphological vertebral fracture by 47%, new clinical vertebral fracture by 55%, hip fracture by 51% and wrist fracture by 48% after a treatment period of 3 years. Similar anti-fracture efficacy was also reported with risedronate. In the North America Vertebral Efficacy with Risedronate Therapy (VERT) Study in 2458 postmenopausal women with ≥1 vertebral fractures at baseline, daily 5 mg oral risedronate significantly reduced the risk of new vertebral fracture by 41% and non-vertebral fracture by 39% over 3 years. In the Multinational part of the VERT Study in 1226 postmenopausal women with ≥2 vertebral fractures at baseline, daily 5 mg oral risedronate reduced the risk of new vertebral fracture by 49% and non-vertebral fracture by 33% over 3 years. In the Hip Intervention Program (HIP) Study using hip fracture as the primary endpoint, risedronate reduced the incidence of hip fracture by 40% in a group of 5445 elderly women aged 70 to 79 with documented osteoporosis (either a femoral neck BMD T-score of <-4 or a femoral neck BMD T-score of <-3 with an addition non-skeletal risk factor for hip fracture). Pooled data showed that risedronate achieved a significant reduction in both vertebral and non-vertebral fractures as early as 6-month.

Adherence to therapy has been a major problem in the treatment of chronic, largely asymptomatic disease like osteoporosis. Compliance is more of a problem when oral bisphosphonates are prescribed because of the need for ingestion with a large glass of water on an empty stomach.
after an overnight fast, avoidance of food and lying flat for 30 minutes after ingestion of the tablet and possibility of severe complications such as esophagitis and esophageal ulcers. Weekly preparation appears to be more preferred by patients and studies have confirmed the therapeutic equivalence of weekly and daily preparations.

In view of the need to observe the tedious precautions when ingesting the tablets, bisphosphonates that can be taken with a longer dosing interval are being developed. In the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) study in 2946 postmenopausal women with 1 to 4 prevalent vertebral fractures, intermittent oral dosing (20 mg every other day for 12 doses every 3 months) of ibandronate significantly reduced the risk of vertebral fractures by 50% over 3 years and produced significant and sustained reductions in all the measured biochemical markers of bone turnover. However, risk of non-vertebral fracture was not reduced in the overall cohort. It was only in a post-hoc analysis that oral ibandronate administered daily reduced the risk of non-vertebral fractures in a high risk subgroup of patients with femoral neck T-score <-3.0. Overall frequency of adverse effects in treatment and placebo groups were similar. Currently the approved oral dosing is 150 mg monthly based on the results from the MOBILE Study which showed that once-monthly oral ibandronate was at least as effective as daily treatment.

There is no current consensus on the optimal duration of oral bisphosphonate treatment but data have confirmed the efficacy and safety of long-term treatment with alendronate (10-year) and risedronate (7-year).

(4) Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) that binds with high affinity to the estrogen receptor and exhibit agonistic effects on the skeletal and cardiovascular systems and antagonistic effects on the endometrium and breast. Raloxifene increases BMD in the spine by 2.7% and in the femoral neck by 2.4% over placebo, and reduces bone turnover to premenopausal levels. Anti-fracture efficacy in patients with established osteoporosis was demonstrated in the subgroup of women with prevalent vertebral fractures in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial. Raloxifene at a daily dose of 60 mg reduced the risk of new vertebral fracture by 30% over a period of 3 years and by 35% over a period of 4 years. A risk reduction of 66% in new clinical vertebral fracture was noted in the first year. There was no evidence that raloxifene lowered the risk of any non-vertebral fractures. Besides its antiresorptive property, raloxifene has in addition extra-skeletal benefits. It reduces the serum concentrations of total cholesterol and low density lipoprotein cholesterol. Preliminary results of the Study of Tamoxifen and Raloxifene (STAR) for breast cancer chemoprevention showed that raloxifene was equivalent to tamoxifen in reducing the risk of invasive breast cancer by about 50% in high-risk postmenopausal women treated for 4-year but with a 36% reduction in risk of developing uterine carcinoma and 29% reduction in incidence of deep vein thrombosis as compared to raloxifene. In addition to invasive breast cancer chemoprevention, raloxifene is also being evaluated in the Raloxifene Use for The Heart (RUTH) trial to assess whether it reduces the risk of coronary events in high-risk postmenopausal women.

(5) Calcium and Vitamin D Supplementation

Studies that addressed the effects of calcium and/or vitamin D supplementation on fracture risk were generally performed in elderly patients irrespective of their fracture status. Studies directed to patients with established osteoporosis are sparse. The United Kingdom Randomised Evaluation of Calcium Or Vitamin D (RECORD) Study performed in 5292 elderly aged ≥70-year with prior low-trauma fracture showed that oral 800 IU of vitamin D₃ and/or 1000 mg elemental calcium supplementation daily did not reduce the risk of new low-trauma fracture over a treatment period of 24 to 62 months. In the recently published Women Health Initiative (WHI) cohort of 36,282 postmenopausal women 50-79 years of age irrespective of fracture status, calcium and vitamin D₃ supplementation at doses of 1000 mg elemental calcium and 400 IU vitamin D₃ daily for seven years did not significantly reduce fractures at any sites.

Nonetheless, it should be noted that subjects in all the landmark osteoporosis treatment trials had received calcium supplementation in the dose range of 500 to 1000 mg daily with or without vitamin D₃, 250 to 600 IU daily. Attention should also be paid to the potential problem of
vitamin D inadequacy in the local community. Two local studies in the past had confirmed a low plasma 25-hydroxyvitamin D levels in hospitalised patients with hip fractures.\(^{48,49}\) A recent local study in a cohort of community dwelling subjects aged >50 revealed that 62% had a serum 25-hydroxyvitamin D levels below 30 ng/ml, a level below which is considered vitamin D inadequate.\(^{50}\) Since vitamin D itself plays a role in neuromuscular function and its supplementation has been shown to significantly prevent fall in at risk patients,\(^{31}\) it would be advisable to ascertain the serum level of 25-hydroxyvitamin D in osteoporosis patients when facilities are available. Otherwise, it is generally recommended to prescribe calcium and/or vitamin D\(_3\) when starting on anti-osteoporosis agents in patients with established osteoporosis unless there are contraindications.

Regarding hydroxylated vitamin D (alfacalcidol or calcitriol), current evidences do not support their routine use for the treatment of established osteoporosis as they have a very narrow margin of safety and their effect on fracture reduction was inconclusive.\(^{52}\)

**(6) Combination Therapy**

While it is expected that combining anabolic and antiresorptive therapies may have additive or synergistic effects in the treatment of osteoporosis, combination therapy of PTH and oral bisphosphonate in clinical studies however do not appear to offer advantages over the use of PTH or bisphosphonate alone. Alendronate actually has been demonstrated to reduce the anabolic response to PTH in two types of combination treatment regime: either simultaneous therapy with PTH and alendronate or initiation of PTH shortly after starting alendronate therapy in treatment-naive patients.\(^{53,54}\) On the other hand, sequential therapy of PTH followed by alendronate has been shown to maintain the densitometric gains in BMD obtained with PTH.\(^{35,56}\) Currently it is recommended that teriparatide therapy should be followed by bisphosphonate treatment.

Studies combining teriparatide and raloxifene of 6-month duration showed that markers of bone formation and spine BMD increased similarly with teriparatide alone and combination therapy. However, combination therapy induced a significantly smaller increase in bone resorption than teriparatide alone so that it was suggested that combination treatment with raloxifene may enhance the bone forming effects of teriparatide.\(^{57}\) Further studies are required for documentation of the proposed synergistic effects.

**(7) Other Agents**

Interruption intravenous administrations of bisphosphonates have also been investigated in clinical trials for potential treatment of postmenopausal osteoporosis. Intravenous zoledronic acid appears to be the most potent agent achieving long dosing intervals up to one-year and producing effects on bone turnover and BMD as great as those achieved with daily oral dosing.\(^{58}\) The major concern with intravenous bisphosphonates are renal safety and the potential risk of osteonecrosis of the maxilla and mandible, more than 50 cases of which have been reported with the nitrogen-containing bisphosphonates in particular pamidronate and zoledronate in the treatment of metastatic diseases.\(^{59}\) The use of intravenous bisphosphonates in the treatment of established osteoporosis needs to await further evidence on anti-fracture efficacy and safety.

At the same time, agents targeting at the cellular receptor levels are being developed. One of these targets is the receptor activator of nuclear factor-(kappa) B ligand (RANKL) which is essential for osteoclast differentiation, activation, and survival. Subcutaneous denosumab (AMG-162), a monoclonal antibody against RANKL, when administered every 3-month or 6-month has been shown in a recent study to achieve an increase in BMD at the lumbar spine and total hip by a magnitude comparable to that of oral once weekly 70 mg-alendronate. Near-maximal reductions in bone resorption markers were achieved three days after its subcutaneous administration.\(^{60}\) Denosumab has the potential to become the most potent antiresorptive agent for the treatment of postmenopausal osteoporosis.

**Monitoring of Osteoporosis Therapy**

The value of serial densitometry in the monitoring of therapy in individual patients is a subject of controversy. In general, follow-up BMD measurements are performed when patients have been treated for at least a year to cater for the precision error of DXA. Serial BMD measurements should be performed with the same machine.
Suppression of biochemical bone markers after three to six months of antiresorptive therapy serves as a prognostic guide for response to antiresorptive treatment. This may also help in reinforcing patient compliance. For teriparatide therapy, biochemical markers of bone formation increase early in the course of therapy followed by increase in markers of resorption.

Besides teriparatide which has a recommended 18 to 24-month duration of therapy, there has been no consensus on the optimal duration for antiresorptive therapy. In general, treatment duration should be no shorter than three years based on data from published clinical trials. Safety and efficacy data are available for oral alendronate and risedronate up to 10-year and 7-year respectively whereas raloxifene has also demonstrated its safety profile for up to 8-year.

Non-pharmacological Treatment in Established Osteoporosis

Although evidence from randomised controlled studies is lacking, benefits from pharmacological treatment of osteoporotic fracture may not be as rewarding as measures that prevent fall, the immediate event preceding a fracture notably hip fracture. Fall prevention education programs with attention to home and environmental safety are effective. Fall-prone elderly should be assessed by physiotherapists and occupational therapists for proper exercise, balance training and rehabilitation. Elderly with balance problems should be prescribed appropriate walking aids and gait-training exercises. Traditional Chinese exercises such as Tai-Chi are low impact weight-bearing exercises and has been shown to improve balance and reduce incidence of falls and fall-related injuries.

For elderly with a history of recurrent fall or fractures, hip protectors are useful in the prevention of future hip fractures but their effectiveness is limited by a low degree of acceptance and compliance.

Apart from these, provision of diet and exercise counseling and adequate analgesia should be an indispensable component of the overall management of established osteoporosis. Interestingly, salmon calcitonin, despite its inconsistent antifracture efficacy, has analgesic property when given as a nasal spray, which may be useful during acute painful spinal collapses. Occasionally vertebroplasty or kyphoplasty may be required for persistent painful vertebral compression fractures.

Conclusions

In the light of published data, patients with established osteoporosis should deserve early treatment as the risk of subsequent fracture is very high. Teriparatide with its anabolic property appears to achieve the highest risk reduction in both new vertebral and non-vertebral fractures within a relative short period of time with evidence of improvement in bone quality. While antiresorptive agents are effective in reduction of vertebral fractures, risk reductions in non-vertebral fractures are demonstrated with risedronate in intention-to-treat clinical trials and with alendronate in meta-analysis but not with ibandronate nor with raloxifene. Strontium ranelate may be considered as alternative option when teriparatide and oral bisphosphonates are not feasible. Auxiliary therapies with elemental calcium 500-1000 mg and vitamin D supplementation 400-800 IU daily should be prescribed unless there are contraindications. Adequate attention should be paid to non-pharmacological measures. As many of these patients will be elderly, life expectancy and coexisting medical conditions must also be considered when recommending treatment in order to achieve the best cost-effectiveness. In general, every patient with established osteoporosis should merit individual considerations when deciding on the choice of specific pharmacological therapy as well as the duration of treatment.

References


