Latest Innovation in the Treatment of Osteoporosis: SERMs and the Role of Parathyroid Hormone

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Anti-resorptives (Bisphosphonates, Estrogens and SERMs) are the drugs used in the treatment of osteoporosis. They reduce the rate of bone remodeling. Raloxifene is a non steroidal (non hormonal) design compound called Selective Estrogen receptor Modulator (SERM) that acts as estrogen agonist on bone. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, 7705 postmenopausal women (≤ 80 years) with osteoporosis were randomized to placebo or raloxifene[1]. Raloxifene reduced bone remodeling, increased bone mineral density (BMD) and decreased the incidence of new clinical vertebral fractures (VF) during the first year by about 68%, and reduced the risk of all new vertebral fractures by 35% during three years (RR = 0.65 [95%CI 0.53, 0.79]. The risk reduction was sustained during the 4th year (RR 0.61 [95%CI 0.43, 0.88][2]. In the 3204 postmenopausal women with osteopenia (based on NHANES hip T-score at baseline) raloxifene 60 mg/day reduced the risk of new vertebral fractures at 3 years by 47% (RR=0.53 (95% CI, 0.32-0.88). In an analysis of patients with severe osteoporosis, women with severe prevalent VF, raloxifene 60mg/day decreased the risk of new VF [RR 0.73 (95% CI 0.54, 0.99)] and all new non vertebral fractures [RR 0.53 (95% CI 0.29, 0.99)] and similarly in women with baseline 2 or more VF.

In the raloxifene Asian osteoporosis trial, 1000 healthy postmenopausal women from 10 Asian countries were randomly assigned to RLX 60 mg/day or placebo[3]. Raloxifene reduced serum osteocalcin (-16% vs placebo, $p < 0.001$) and N-telopeptide cross-links (-15% vs pl, $p < 0.001$), improved serum lipid profiles (-7.7% vs pl, $p < 0.001$). No differences occurred in any adverse event relative to placebo.

As mentioned before anti-resorptive agents stabilize skeletal structure, but they do not restore the structure. Parathyroid hormone (PTH) is a new therapy that may overcome these limitations, because it stimulates bone formation depending upon its mode of administration. As shown recently in a few studies, PTH 1-34 increases bone formation and bone mass and restores bone micro-architecture, when given intermittently by subcutaneus injection once daily. PTH 1-34 was shown to increase periosteal and endocortical bone formation producing cortical thickening, while trabeculae bone formation increases trabecular thickness[4]. Some evidence suggests that PTH can restore trabecular connectivity and increase trabecular numbers.

In a fracture prevention trial, 1637 ambulatory postmenopausal women with atraumatic vertebral fractures, were randomly allocated to once-daily, self-administered subcutaneous injections of placebo, 20 mg or 40 mg of recombinant human parathyroid hormone (1-34) [rhPTH] for a median of 21 months[5]. Compared to placebo, rhPTH treatment reduced the proportion of women developing a new vertebral fracture 65 to 69%, the proportion developing multiple and moderate-severe vertebral fractures 77 to 90% and reduced fracture-associated height loss and the frequency of back pain. The proportion of women with non-vertebral fractures was reduced by 40% and for non-vertebral 'fragility fractures' by 53%. Compared with placebo, bone mineral density increased by 9 to 13% at the spine, 3 to 6 percent at the proximal femur. The 20 mg dose was very well tolerated, whereas the higher rhPTH dose occasionally caused transient hypercalcemia, nausea and headache. In conclusion, daily treatment of osteoporotic women with rhPTH rapidly decreases the risk of vertebral and non vertebral fractures with very good tolerability, and may restore skeletal structure.

Recent analysis in large evidence based osteoporosis trials of the anti fracture efficacy of several anti-resorptives, such as alendronate, risedronate and raloxifene showed that all decrease the incidence of new vertebral fractures by 35 to 45%. In contrast, their

Keywords: *Osteoporosis, SERMs, Parathyroid Hormone*

J Med Assoc Thai 2004; 87(Suppl 3): S124-5

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ability to increase spinal BMD varies greatly from 2 to 8% depending on the agent. As confirmed by further analysis, the changes in BMD were poor predictor of anti-fracture efficacy[6,7]. For instance in the MORE study, the increase in BMD was poorly correlated with the reduction in vertebral fracture, and less than 10% of the anti-fracture efficacy of raloxifene could be explained by changes in BMD. Similarly, a small fraction (less than 25%) of the anti-fracture efficacy of any bisphosphonate is explained by changes in BMD. Furthermore, recent studies showed that most of the increase in BMD observed after bisphosphonates is due to an increase in density of mineral per unit of bone, and not an increase in bone mass or volume.

Hence, the National Institute of Health (NIH) has reworded the definition of Ostepororis (2001), to focus on Bone strength, which is the result of the integration of bone mass and bone quality. Bone quality encompasses a series of properties not captured by the densitometric techniques, which comprises at least 5 components: (1) Architecture and geometry, (2) Turnover rate, (3) Degree of Mineralization, (4) Damage Accumulation, (5) Others properties of the Bone Matrix.

Both raloxifene as an antiresorptive and teriparatide as a bone forming agent seem to improve various components of bone quality, which would contribute to fracture reduction.

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