

Review Article and Clinical Experience: RECENT ADVANCES IN THE TREATMENT OF OSTEOPOROSIS (THE ROLES OF NEW BISPHOSPHONATE)

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EXTENDED ABSTRACT

Osteoporosis (OST) is a condition characterized by low BMD of the spine (T-Score as values reduced less than -2.5 SD) and associated with micro-architectural deterioration of bone. The latter term refers to the development of loss of trabecular element, leading to enhanced bone fragility and increase in fracture risk. Osteoporosis-Type I = OST-Type I (Post Menopausal Osteoporosis = PMO), Osteoporosis-Type II = OST-Type II (Age Related Osteoporosis = ARO), and Osteoporosis-Type III = OST-Type III (Corticosteroid Induced Osteoporosis = CIO) are the most frequent types of osteoporosis in clinical practice. The cessation of estrogen secretion that coincides with menopause is now well accepted to have major role in the pathogenesis of post menopausal bone loss, and PMO may pursue. Evidence suggests that the influence of estrogen loss may be unequal in different parts of the skeleton, with bone loss occurring at an earlier age in spinal trabecular bone and cortical bone loss during post menopausal period. Declining Estrogen levels at menopause result in "High Bone Turnover" and a loss of bone mass, with subsequent increases in bone fragility and the fracture risk. It has been suggested that estrogen may play a role in regulating bone turnover in men as in women. Recent epidemiological study found that serum estradiol and Sex Hormone Binding Globulin (SHBG) but not testosterone levels were associated with BMD in healthy men over 65 years. SHBG is increased in middle-aged men with primary or secondary osteoporosis and well correlated with bone remodeling markers, hip bone mineral density and vertebral fracture risk. OSTEOPOROSIS-TYPE II (ARO) is best exemplified by hip fractures that occurs in older men (>70 years) and women, which are related more to the loss of cortical and trabecular bone through age-related mechanisms (decreased Bone Formation and reduced 1-alpha hydroxylase with its consequences: reduced $1.25\text{ (OH)}_2\text{D}_3$, reduced Ca^{++} , increased PTH and then increased Bone Loss).

Keywords: osteoporosis, biphosphonate

Glucocorticoids are often used in the treatment of chronic inflammatory disorders and are the most common cause of drug related osteoporosis (CIO). Long term therapy with glucocorticoids induces a dose dependent bone loss, which is most pronounced during the first 3-6 months of treatment and leads to an increased risk of fractures. After low bone mass has developed, besides calcium and vitamin D supplementation, HRT, and exercise to maintain muscle mass, the use of Bisphosphonates has been recommended.

The vision of International Osteoporosis Foundation (IOF) on Osteoporosis is: a World without Osteoporotic Fracture by 2010, and the Missions of IOF are:

1. to support National Osteoporosis Societies in order to maximize their effectiveness,
2. to increase awareness and understanding of Osteoporosis,
3. to motivate people to take action to prevent, diagnosis, and treat Osteoporosis

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The Goals of IOF are:

1. to nurture and enlarge the IOF network of member societies worldwide
2. to promote medical innovation and improved care
3. to expand IOF partnerships with organisations working on similar or complementary issues and projects
4. to lobby for policy change in all countries so that diagnosis and treatment of osteoporosis becomes routine

Bisphosphonates (BISPs) are pyrophosphate analogues, in which the oxygen in P-O-P has been replaced by a carbon, resulting in P-C-P structure. The P-C-P bound together with R^I side chain provides the great affinity of BISPs to the bone mineral (hydroxyapatite). The R^{II} side chain is responsible for the potency of the agents in inhibiting osteoclast activity. Bisphosphonates inhibit Osteoclast activity (lactic acid production, reduce PG formation, reduce Lysosome and other enzymes, increase membrane permeability) and suppress Osteoblast lineage cells (reduction in Osteoclast number: reduction in Osteoclast recruitment), and increase osteoclast apoptosis.

Bisphosphonates investigated in humans, numbered in increasing order potency are:

First generation:

1. Etidronate

Second generation:

2. Tiludronate
3. Clodronate
4. Pamidronate

Third generation:

5. Neridronate
6. Alendronate
7. Olpadronate
8. Risedronate
9. Ibandronate
10. Zoledronate

Alendronate is approximately 10-fold more potent than Pamidronate, 100-fold more potent than Clodronate, and 1000-fold more potent Etidronate; however, Risedronate is 10-fold more potent than Alendronate.

Risedronate therapy in OST-Type 1 has proven to a fracture reduction by 65% after first year and sustains non-vertebral fracture reduction by 39% over 3 years. Vertebral-Efficacy with Risedronate Therapy (VERT)-Multinational Study (one tablet daily: placebo or 5.0 mg Risedronate for 3 years, 1000 mg Calcium/day, Vitamin D 500 IU/day) enrolled almost 4000 postmenopausal women. Summarized results showed that Risedronate 5.0 mg daily significantly reduced the incidence of new and worsening vertebral fractures and of new vertebral fractures. Such a novel Bisphosphonate also shows 74% vertebral fracture reduction after one year of treatment in OST-Type III and prevents bone loss in patient with Corticosteroid therapy.

Bisphosphonates have been also well accepted drugs for treating Osteoporosis in patient over 65 years with fracture risks (OST-Type II). Additionally, Risedronate can be prescribed without dosage adjustment for patients with creatinine clearance > 20 ml/minute. The intestinal absorption of Bisphosphonates is low, ranging from 0.5 to 3%, and is abruptly decreased by the presence of food containing even a small amount of Calcium salts. For this reason, they must be administered in strictly fasting conditions, with no food for at least 30 minutes after administration.

Extend of Risedronate absorption was comparable in subject dosed 2 hours after dinner and 0.5 hour before breakfast; however, a significantly greater extend of absorption occurred when this drug was given 1 hour or 4 hours prior to a meal (1.4 to 2.3 fold greater). Based on clinical experiences a single dose of 20 mg Risedronate/weekly for another 2 years may be administered to the patients who have been already treated with 5.0 mg Risedronate/daily for one year.

CONCLUSIONS

The new bisphosphonate, Risedronate, may offer a wider range of options regarding method and frequency of administration. An impressive amount of data as documented the efficacy of Risedronate for OST-Type I and OST-Type III. These data are rapidly changing the clinical approach towards the prevention and treatment of Osteoporosis, and certainly will support the Vision and Mission of IOF. Single dose 15 mg Risedronate weekly for another 2 years for patients who have already been treated with 5.0 mg Risedronate for one year may result in a better compliance. However, this regimen needs further investigation and evaluation.