Journal of Osteoporosis & Physical Activity

Leung, J Osteopor Phys Act 2015, 3:1
DOI: 10.4172/2329-9509.1000129

Commentary Open Access

Current Status of Potent Bone Resorption Antagonists

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Abstract

Since osteoporosis is considered as an important risk factor to the development of bone fractures, the search for effect therapeutic agents for its prevention and maintenance has never stopped. From hormonal replacement, promotion of bone formation, to prevention of bone resorption has all been tried. The most active part has been played by the antiresorptive agents, viz the Bisphosphonates.

Large investments in research have increased the potency of the drug hundreds of folds and remarkably secured a very effective patient compliance to once a year injection. The therapeutic triumph is complicated with serious though infrequent adverse effects with prolonged or high dose administrations. It is therefore appropriate time to realize the exact safety, the favorable dosages, and the duration of treatment of bisphosphonates. Several extended studies on bisphosphonates have given the answers. Bisphosphonate are safe and effective, serious adverse effects are rare and may occur only after prolonged use. Bisphosphonates should be used as preventive agent only for the extreme high risk cases. Preventive therapy could be safer if 3 years of administration could be followed by a rest period of 2-3years.

Keywords: Osteoporosis; Bisphosphonate; Bone resorption

Introduction

The gradual deterioration of bone structure and strength i.e. Osteoporosis, with aging is a natural process. The awareness and concern that Osteoporosis is a risk factor to bone fractures have started since more than 40 years ago. Active preventive and therapeutic measures have taken a colourful course: from hormonal replacement to various forms of bone structure preservation treatments. Over the decades, bone promotion i.e. pro-osteogenic measures have given place to anti-resorptive agents for fear of the adverse effects related [1-3]. Anti-resorptive agents are well represented by bisphosphonates which have demonstrated rapid increases of therapeutic potency over the last two decades.

Looking at the rapid development of bisphosphonates used as effective anti-resorptive agents on bone metabolism, not only the potency has increased hundreds of folds, but the way of delivery has advanced from daily oral administration, to weekly and then monthly intervals. The injection form and intravenous preparation thence appear and is given yearly [4].

While short and medium term effective support of bone mineral densities was observed and fracture incidents among those on bisphosphonate treatment enjoyed significant drops compared with those not on bisphosphonate, it was also observed that severe, though rare, adverse effects might occur after 5-10 years of continuous administration [5]. Looking at the small number of cases reported, the adverse effects included low-energy fracture of long bones at odd sites, avascular necrosis of the jaw bone and atrial fibrillation. Those infrequent adverse happenings could well be acceptable if bisphosphates are used for treating the disease. However, bisphosphonates are used to maintain the structural integrity of bone so as to lower its fracture risk only. The rare adverse effects or complications, therefore, is a real concern for people taking bisphosphonates. While the trust on the drug is still maintained, they want to know which type of bisphosphonate will be safer, what dosage is favourable and how long should it be maintained. To answer those questions, obviously long termed trials are required. There are no long-term data for ibandronate [6]. Limited data for risedronate indicate that its effects wear off faster and residual effects are not obvious [7]. An extension study for alendronate was done 5 years after completion of a preceding 5 years, maintained on 10 mgm per day. In the extension period a small decline of 1-2% at the hip and 2-3% at the spine was found after 3 years. After 5 years no reduction in clinical non vertebral fractures was found [8-10].

The latest intravenous preparation of Zolendronic acid for yearly administration was created to avoid loss of compliance for the oral bisphosphonate takers and was more suitable for observation of extension results. The observations would deserve detailed analysis.

First of all, the yearly infusion during the 3 years period was associated with a significant and sustained reduction in fracture risks in the spine and hip. Bone mineral density increased significantly at the total hip, lumbar spine and hip. Adverse events were negligible [11].

In the first extension of 3 years, safety was found similar, acute responses to intravenous treatment were found milder and there was a persistent decrease in bone turnover (i.e. anti-resorption effects) for 3 years after discontinuation, suggesting a continued fracture risk reduction. Changes in bone density and bone markers showed insignificant differences between continuing and stopping medication for 3 years [12].

The Zolendronate trial was further extended to nine years which was just completed recently. The participants were around 100 for both the 6 years and 9 years groups. Only insignificant increase in Bone Density was found in the 9 years group. The number of fractures was

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Received January 08, 2015; **Accepted** February 05, 2015; **Published** February 12, 2015

Citation: Leung PC (2015) Current Status of Potent Bone Resorption Antagonists. J Osteopor Phys Act 3: 129. doi:10.4172/2329-9509.1000129

low and was not affected by treatment length. The observation made was that medication could be stopped for up to 3 years with persistence of benefits [13].

There is some concern whether bisphosphonate works differently among different ethnic groups. In the 3 yearly study on intravenous Zolendronate, over 300 Chinese women with osteoporosis were included. This group demonstrated after 36 months significant reduction in the risk of vertebral fractures and significant increase of Bone Mineral Density. The data were not different from the main study involving mainly Caucasians [11].

Conclusion

Over two decades of bisphosphonate development has confidently shown their anti-resorptive effects. Research on potency has not only raised its efficacy but has also facilitated the maintenance of user compliance. Serious effects may occur with large doses and prolonged uses, manifesting in odd site long bone fractures, jaw necrosis and atrial fibrillation, which are all rare [14]. The long term extension studies have given further assurance about the rarity of the complications. As a further measure of security, it may be recommended that resting periods of a few years between active treatment periods may be considered except for those already experiencing fragility fractures and those with extremely low bone mineral densities.

Now that the potency of bisphosphonates is so high, those women showing only early tendency of osteoporosis or osteopenia, should not be over-energetic on the therapeutic. Other means to reduce fracture risks like exercises, nutritional supplements, including nutraceuticals, could be reasonable considerations [15].

Future Perspectives

Experts on osteoporosis, since the appearances of complications after long-term administration of bisphosphonates, have already cautioned against over energetic prescriptions. Instead, some of them advise that for preventive and maintenance purposes, bisphosphonates could be administered on alternate or any other year while keeping a close watch on BMD changes.

On the pharmaceutical line selective inhibitors of osteoclast activities like odanacatib, might still lack the ideal effects of osteoblast-osteoclast equilibrium [16]. Hence longer observations would be required for comments and recommendations, although the potency appears very impressive [17].

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