Osteoporosis treatment: choices and options

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During the last two decades, several medications have been granted a marketing authorization for the management of osteoporosis. Bisphosphonates are the most widely prescribed drugs in this area, worldwide. Alendronate and risedronate are given daily or weekly and have demonstrated their ability to reduce fracture rate at the spine and hip [1]. However, the bisphosphonates are associated with stringent dosage and administration procedures, and some patients may experience upper gastrointestinal adverse effects, following administration. Consequently, about half of patients discontinue daily bisphosphonate therapy within one year, which negatively affects treatment outcomes, leading to a reduced anti-fracture effect. Improving patient adherence to osteoporosis therapy is a complex process that involves effective patient/provider communication, association of treatment with expected benefits and/or positive treatment feedback (i.e. using measurement of marker of bone turnover or bone mineral density measurements). Another primary component of improving adherence is to use simplified or user-friendly treatment programs [2]. It has been found across a range of therapeutic areas that adherence to medication is inversely related to frequency of administration. Therefore, all currently marketed or developed bisphosphonates are now offering formulation with intermittent dosage regimens [3].

Weekly alendronic acid and risedronic acid provide similar benefits in terms of bone mineral density and changes in biochemical markers, as those seen with their daily formulations. Oral ibandronic acid was the first compound to demonstrate anti-fracture efficacy with interval between dosing greater than weekly (20 mg every other day for 12 doses every three months). In a 2-year trial, once-monthly ibandronic acid was compared to daily ibandronic acid administration at the dose that had previously been demonstrated to reduce spine fracture risk compared with placebo. Once-monthly 150 mg regimen proved to be superior to daily, in terms of increases in spinal and proximal femur BMD, as well as serum C telopeptide of type I collagen suppression. Ibandronic acid was well tolerated, with a similar incidence of adverse events across groups [4].

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Intermittent intravenous administration of ibandronic acid, in postmenopausal osteoporotic women, at the dose of 3 mg every three months was also demonstrated to be superior to the oral regimen, for bone mineral density changes. Spine and hip BMD increases were greater in the group receiving medication intravenously than in the group receiving ibandronic acid orally. The intravenous regimen was well tolerated and did not compromise renal function [5].

Zoledronic acid is one of the most potent bisphosphonates that is currently available for clinical use. In Paget's disease of bone, a single infusion of zoledronic acid has been shown to produce more rapid, more complete and more sustained response than daily treatment with risedronic acid. In an exploratory study, performed in post-menopausal women with low BMD, increases in BMD were recorded for various intravenous doses of zoledronic acid, higher than those in the placebo group. Biochemical markers of bone resorption were significantly suppressed throughout the study, in all of the zoledronic acid groups. The most important finding of this study was that a single baseline dose of zoledronic acid, 4 mg, produced equivalent suppression of bone turnover and increase in bone mass to the more frequently administered smaller doses of the same agent. These findings strongly suggested that this agent may be able to be given as infrequently as once a year for osteoporosis therapy. Subsequently, the effects of annual infusions of zoledronic acid on fracture risk, during a 3-year period were assessed in post-menopausal women with osteoporosis. In this double-blind, placebo-controlled trial, treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70%, as compared with placebo and reduced the risk of hip fracture by 41%. Non-vertebral factures, clinical fractures and clinical vertebral fractures were reduced by 25%, 33% and 77% respectively. Zoledronic acid was also associated with a significant improvement in bone mineral density and bone metabolism markers. Adverse event, including change in renal function, were similar in the two study groups [6]. Whereas serious a trial fibrillation occurred more frequently in the zoledronic acid group, no increase in deaths from cardiovascular causes, strokes or deaths from stokes were recorded. No other study conducted with zoledronic acid did confirm any causative link between zoledronic acid administration and increase in serious atrial fibrillation.

Another way of handling poor adherence linked to bisphosphonate administration is to use other type of drugs, which are more user-friendly and for which the administration is not linked to constrains decreasing the willingness of the patient

to take them for a long time [2]. Strontium ranelate, given as a once-daily sachet, has been shown to reduce vertebral, non-vertebral and hip fractures in a wide scatter of patients, ranging for osteopenia to elderly women (over the age of eighty years) with established osteoporosis [7]. Compliance to strontium ranelate, which is deprived of gastrointestinal site-effects and can be taken at bedtime, was shown to be significantly improved compared to daily or weekly oral bisphosphonates.

In conclusion, compared to where we were, 10 years ago, several medications are now available to treat osteoporotic patients, that have unequivocally demonstrated their ability to significantly reduce fracture rates, at the spine and non-spine locations. The major challenge for the management of osteoporosis is to significantly increase long-term observance and persistence to treatment. Both patients and medication factors are involved. Bisphosphonate formulations, either orally administered with intervals between dosing greater than weekly (ibandronate) or used trough the intravenous route (ibandronate quarterly or zoledronate yearly) are major steps towards meeting the patients needs and requests. The better results obtained, in terms of bone mineral density changes (ibandronate) or fracture reduction (zoledronate) compared to what was previously observed with daily oral administration confirmed the predominant role of adherence in the long-term efficacy and efficiency of these medications. An alternative, is to use daily oral medications (strontium ranelate) which are convenient and harmless to use and for which may also be linked to a high degree of adherence, hence contributing to effects in real life similar to those observed in clinical trials.

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