OSTEOPOROSIS AND BISPHOSPHONATE THERAPY: NEW OPTIONS TO IMPROVE ADHERENCE

KEY MESSAGES

- Osteoporosis is characterised by low bone mass and micro-architectural deterioration of bone tissue, resulting in increased risk of fracture
- A T-score ≤ -2.5, as determined by dual energy X-ray absorptiometry (DXA) bone densitometry, is diagnostic for osteoporosis
- The National Osteoporosis Foundation of South Africa (NOFSA) recommends first-line therapy with a nitrogenous bisphosphonate (BP) or denosumab
- Oral BPs are poorly absorbed and need to be taken with tap water on an empty stomach, 30 minutes before other medications, food or drink
- BPs compromise osteoclast function and survival by blocking the mevalonic (HMG-CoA) pathway
- Oral BPs are effective in reducing the risk of osteoporosis-related fractures
- A drug holiday may be considered in those where BMD increases to a T-score > -2.5 and in the absence of any fracture
- Poor adherence to oral BPs significantly reduces drug efficacy
- A preference for monthly over weekly oral BPs has been demonstrated
- Risedronate 150mg monthly is non-inferior to risedronate 5mg daily
- Major but rare side effects of oral BPs include osteonecrosis of the jaw (ONJ) and atypical femur fracture (AFF)
- Risedronate is a first-line medicine for the treatment of postmenopausal osteoporosis, since meta-analyses of large randomised controlled trials have demonstrated its efficacy against vertebral, nonvertebral, and hip fractures
- Risedronate has desirable pharmacological characteristics in terms of its low affinity for bone, and its strong inhibition of farnesyl pyrophosphate synthase, which leads to rapid reduction and reversal of bone turnover
- Risedronate is the first monthly oral bisphosphonate to offer both vertebral and non-vertebral fracture reduction, based upon non-inferiority studies of daily risedronate.

Introduction

Bone is a living tissue, constantly undergoing renewal to repair microcracks from daily life and to maintain mechanical integrity of the skeleton. The process of bone remodelling is regulated by osteoblast-mediated bone formation and osteoclast-mediated bone resorption.

Osteoporosis is a systemic skeletal disease characterised by low bone mass (measured as bone mineral density (BMD)) and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (wrist, spine, hip, pelvis, ribs or humerus). The incidence of osteoporotic fractures is significantly greater than that of other common diseases (heart attack, stroke, breast cancer) and places a significant burden on the medical system.

BMD is determined by dual energy X-ray absorptiometry (DXA) bone densitometry and is expressed as a T-score compared to peak bone mass. The National Osteoporosis Foundation of South Africa (NOFSA) recently revised its treatment guidelines. Recommendations for therapy of mild osteopenia, without any fractures present and
no likelihood of ongoing bone loss, are non-pharmacological (lifestyle) measures, calcium and vitamin D supplementation (if deficient) and regular follow-up. Hormone therapy should be considered in suitable patients with more significant osteopenia. In DXA-confirmed osteoporosis (T-score ≤-2.5), NOFSA recommends first-line therapy with a nitrogenous bisphosphonate (BP) or denosumab (currently not registered in South Africa). For those patients unable to take these medications and in whom there are no contraindications, strontium ranelate can be used. Raloxifene is used for the prevention of vertebral fractures, especially in younger women at risk of breast cancer. Teriparatide is the only available anabolic drug and is reserved for more severe cases of osteoporosis, especially when fractures occur in patients on BPs. BPs are potent inhibitors of bone resorption and have been used in the treatment of osteoporosis for 40 years, representing 70-80% of total osteoporosis drug prescriptions. Commonly prescribed oral BP agents include alendronate, risedronate and ibandronate. Intravenous BP agents are ibandronate and zoledronate.

Pharmacokinetics and pharmacodynamics of oral BPs

Oral nitrogenous BPs are poorly absorbed through the stomach and have a rapid half-life with no circulating metabolites. Of the ingested dose, about 1% is absorbed into circulation, 49% of which is excreted unmetabolised by the kidney while 51% is rapidly redistributed to the bone surface.2

Dr de Villiers has the following advice for taking oral BPs properly:

• Take the dose in the morning on an empty stomach, preferably with overnight fasting. Wait 30 minutes before ingesting the first food, drink or other medicine of the day.
• Swallow the tablet whole (do not suck or chew), with one full glass of tap water. Do not use bottled water as the higher calcium content will inhibit BP absorption.

To avoid gastrointestinal symptoms, remain upright (sitting or standing) for 30 minutes after swallowing medication. The acidic environment of the bone surface enables BP molecules to bind strongly to hydroxyapatite. BPs are subsequently ingested by osteoclasts, compromising cell function and survival through inhibition of the mevalonic (HMG-CoA) pathway that is responsible for the production of cholesterol and isoprenoid lipids. The farnesyl pyrophosphate synthase enzyme is blocked by BPs, thereby inhibiting prenylation of the intracellular farnesyl pyrophosphate signalling proteins Ras, Rho and Rab. These proteins regulate a variety of important cell processes such as cell morphology, membrane ruffling, trafficking of endosomes and prevention of apoptosis.3

Reduction of osteoporosis-related fractures

Dr de Villiers summarised published pivotal efficacy trials of different osteoporosis medications on reduction of vertebral, non-vertebral and hip fractures (Table 1).

Risedronate fracture protection

The Vertebral Efficacy with Risedronate Therapy (VERT) studies, using risedronate 5mg daily or placebo, were conducted multinational in Europe, Australia and New Zealand (VERT-MN) and in North America (VERT-NA). Vertebral fracture was the primary endpoint of these studies. Secondary endpoints included non-vertebral fractures, BMD at several sites, bone turnover markers and safety. After three years, vertebral fractures were reduced by 49%. In an extension study, the effect was sustained over seven years.4 Daily use of risedronate 5mg resulted in a 60% reduction in incidence of hip fracture in postmenopausal osteoporotic women over three years, including those who had existing vertebral fractures.5, 6
Osteoporosis

Side effects of oral BPs

Osteonecrosis of the jaw (ONJ)

Medication-related ONJ is associated with all BPs and denosumab; it is also associated with dental procedures, poor oral hygiene, use of steroids, radiation, antiangiogenic drugs and chronic diseases such as HIV/AIDS. BP-related ONJ is a rare complication and in general only a risk when high dosages, i.e. greater than those recommended for fracture prevention, are used. In BP-related ONJ, 96% of cases are associated with high intravenous doses administered for the prevention of malignancy-related problems. In current literature, only three cases of ONJ have been associated with oral risedronate. Currently, use of BPs is not a contraindication to planned dental procedures.7

Atypical femur fracture (AFF)

BPs are known to reduce the incidence of femur neck fractures (typical osteoporotic fractures). AFF occurs in the femur shaft (subtrochanteric). It is often preceded by pain and may occur bilaterally.8 Radiological features of AFF are displayed in Figure 1. AFF may be associated with over-suppression of bone turnover in patients exposed to prolonged BP use (3-5 years, depending on the agent). However, a direct causal relationship has not been proven.9 According to the NOFSA guidelines, after five years (oral) or three years (intravenous) of BP therapy, if the patient is considered to still be at risk of fracture, she can be switched to a different agent. She may, however, continue with a BP as the benefit of preventing a typical femur fracture far outweighs any risk of causing an AFF.

Table 1. Osteoporosis-related fracture reduction in published pivotal trials

<table>
<thead>
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<th>Study</th>
<th>Vertebral RR</th>
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<th>Hip RR</th>
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*All values shown are statistically significant

Figure 1. Radiological features of AFF

- Subtrochanteric
- Thickened cortices
- Clean transverse fracture
- Beaking
- Bilaterality
Drug holiday – cessation of BP therapy

If after 3-5 years of BP therapy the patient is not considered at high risk of fracture, a drug holiday can be considered. There is no consensus within the scientific community, neither is there any conclusive evidence to support a prescribed drug holiday for all patients at a specific time point or for a specific duration. BPs remain in the bone for a long time after discontinuation of therapy, usually with BMD being maintained. Therefore, a drug-free period may be considered following 3-5 years of BP therapy, provided that BMD increases to a DXA-derived T-score >-2.5 and in the absence of any fracture. The patient should be followed up and BMD monitored after 18-24 months.

Adherence

Long-term and highly compliant treatment with oral BPs is necessary to achieve optimal fracture protection. An 80% compliance rate decreases fracture protection by 50%, whereas a 50% compliance rate decreases BP efficacy to 10%. Dosing intervals do affect adherence to medication. Despite better compliance in weekly compared with daily regimen users, the absolute rate of persistent patients still remains below 50% after only one year of a weekly dose. Preference for monthly over weekly oral BPs has been demonstrated.

A non-inferiority trial compared risedronate 150mg monthly against risedronate 5mg daily for BMD, bone turnover markers, and adverse events. The once-a-month regimen was determined to be non-inferior to the daily regimen. Similar changes in BMD and biochemical markers of bone turnover were observed. Incidence of adverse events leading to withdrawal from medication and upper gastrointestinal tract side effects were similar.

References