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NEWSLETTER

Winter 2011

AUCKLAND Bonedensity
Managing Bone Health

2011 BISPHOSPHONATE UPDATE

Bisphosphonate treatment for osteoporosis

Intravenous zoledronate therapy is now funded under the Special Authority mechanism for treatment of osteoporosis in New Zealand. The eligibility criteria are the same as for weekly oral alendronate. This means that practitioners and their patients now have a choice of two effective bisphosphonate therapies for fracture prevention.

Intravenous Zoledronate therapy

Intravenous zoledronate, administered as a 5mg dose annually, reduces fracture risk by 35-70% depending upon the skeletal site[1]. The treatment is administered as a minimum 15 minute infusion. It should not be administered to individuals with severe renal impairment (e-GFR <35ml/min). There is a 20% chance of transient acute phase reaction occurring within a few days of administration of the first dose of zoledronate, but the incidence of this side effect following subsequent doses is <5%[2]. Administration of paracetamol at the time of intravenous zoledronate appears to reduce the severity of symptoms of the acute phase reaction, which include fever, musculoskeletal symptoms, gastrointestinal upset and fatigue. If a patient develops symptoms of acute phase reaction, symptomatic management with paracetamol and/or non-steroidal anti-inflammatory medication is sensible. Occasionally, a patient will experience quite debilitating symptoms – it is important to reassure such patients that the symptoms will resolve spontaneously. There is no need to monitor blood tests after the infusion. In patients at risk of vitamin D deficiency, specifically those with pigmented skin who practice sun avoidance, or housebound or institutionalized elderly, it is reasonable to give 100,000 units of cholecalciferol as a stat dose shortly before or at the time of zoledronate infusion.

Recent evidence also suggests that a single dose of zoledronate produces antiresorptive effects that last up to 3 years[3]. It is reasonable to consider a dosing interval of 18-36 months in many patients.

Duration of Bisphosphonate Therapy

Background

In recent years it has become a common practice to limit the duration of continuous bisphosphonate therapy, particularly when using alendronate. Other potent bisphosphonates will eventually need similar strategies. While there is no clear-cut evidence of adverse effects from continuing alendronate to 10 years[4, 5], several considerations have led to this change in practice. First, bisphosphonates

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steadily accumulate in bone, leading to a theoretical concern that this will eventually have toxic sequelae. In recent years, the development of osteonecrosis of the jaw has been described. This was first seen in patients with metastatic cancer treated with doses of zoledronate ten-fold higher than those used in the management of osteoporosis. Similar, though generally less severe, lesions have been described in patients treated with alendronate, but exposed bone in the mouth also occurs rarely in patients in this age group who have never been treated with bisphosphonates. As far as can be determined from currently available evidence, the incidence in osteoporotic patients, whether treated with bisphosphonates or not, is approximately 1 in 100,000 patient-years, so a causal role of the bisphosphonates is not established [6]. Despite this, it has encouraged caution in the long-term use of these drugs.

A second reason for caution has been the syndrome of atypical subtrochanteric fractures[7]. Subtrochanteric fractures have always constituted about 5% of femoral fractures in the elderly but they typically occur without a prodrome and have a spiral appearance on radiographs. Atypical fractures often have prodromal pain for as long as several months, radiological evidence of local cortical thickening, may be bilateral, and the completed fracture tends to be transverse. There are a number of case series of such fractures occurring in bisphosphonate users, often those who are not particularly osteoporotic. However the syndrome is rare and most large databases which have been examined do not show an increase in the total number of subtrochanteric fractures over the 15 years that bisphosphonates have been used. Thus, bisphosphonates might be affecting the presentation of a subset of individuals developing these fractures. These atypical fractures are clearly very rare and current analyses indicate that bisphosphonate use prevents many more fractures than the tiny number of atypical subtrochanteric fractures which they might contribute to. Despite these findings, this has also contributed to caution around the long-term uninterrupted use of bisphosphonates.

Because bisphosphonates have a long residence time in bone, the offset of their effect on bone resorption and bone density is gradual. After use for about 5 years, it can take up to 2 years for bone turnover to return to normal. This suggests that even if it is safe to continue full dose bisphosphonates, it may be unnecessary. Consistent with this, the FLEX study has demonstrated that the alendronate dose can be halved, without any loss of efficacy in terms of either bone density or fracture risk.[8] Thus, simple economics suggest that this should become standard practice in patients entering their second quinquennium of therapy. While the FLEX study was not adequately powered to assess long-term antifracture efficacy with rigour, post hoc analyses do suggest that patients who are no longer osteoporotic (based on their bone density measurement) can actually cease taking alendronate in years 5–10 without an adverse effect on fracture risk.

Strategies for Patient Management

Because there is no clear evidence of harm from continued alendronate use and because there is no authoritative trial evidence to support any one regimen, a number of different practices have arisen for the long-term management of bisphosphonate-treated patients, many of which may be reasonable. One way to handle this situation is as follows:

1. Assess alendronate-treated patients with DXA bone density at 2-3 years and with both a repeat DXA bone density and serum P1NP at 5 years (P1NP is a serum marker of bone turnover).
2. If P1NP is >30 µg/L, this suggests noncompliance or malabsorption of alendronate, the latter possibly due to inappropriate dosing practices. Discussion of appropriate procedures

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for taking alendronate should be initiated with the patient, with consideration of a change to intravenous zoledronate if there are no clearly remediable issues identified.

3. If the BMD T-score in the spine or hip is <-2.5 and P1NP is <30ug/L, then continue alendronate in a dose of 70 mg every fortnight, with a plan to review in 3–5 years' time.
4. If BMD T-score at both sites is >-2.5, then cessation of alendronate is reasonable, with a plan to re-measure BMD and P1NP after 2 years.
5. After 8–10 years of continuous alendronate use it is probably sensible to have a drug holiday whatever the BMD data. This can be justified on the grounds that bone turnover will remain suppressed for about 2 years without any further drug administration. During such a holiday, it is sensible to measure P1NP at the time of drug cessation, and then 1 and 2 years after cessation. Once P1NP is >30 µg/L, consideration of reinstituting some therapy is appropriate. This could be a further course of alendronate, or any other agent of established anti-fracture efficacy.
6. In patients who have continued to fracture while receiving therapy, ensuring that P1NP is < 30ug/L is important so that it is established that an adequate dose of drug is reaching the bone. If this is not the case, then intravenous zoledronate may be appropriate. If fractures continue to occur despite adequate inhibition of bone turnover, then a different treatment strategy should be considered, and teriparatide (parathyroid hormone-[1-34]) could be considered, when available.

The above strategy is a suggested way to manage long-term alendronate patients. None of this is set in stone and individual patient characteristics and preferences will obviously lead to the adoption of a number of variations on this theme.

Role of Calcium Coadministration

Recent evidence suggests that calcium supplementation may slightly but significantly increase the risk of myocardial infarction[9]. There is a reasonable body of evidence that suggests that the skeletal effects of bisphosphonates are not dependent upon co-administration of calcium and/or vitamin D[10]. It is therefore reasonable, and indeed recommended, that calcium supplements not be routinely prescribed to patients who are receiving potent bisphosphonate therapy for fracture prevention.

Summary

1. There are now two potent bisphosphonates available for osteoporosis management in New Zealand.
2. Whilst osteoporosis is a chronic disease, the emerging model of care differs from that of the other chronic diseases.
3. Cycles of therapy may be more appropriate than continuous therapy.
4. Prescribers will need to understand that there are indications to:
   - start therapy
   - lower treatment intensity
   - stop therapy
   - monitor progress
   - restart therapy

References available upon request

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