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NEWSLETTER

Spring 2012

AUCKLAND Bonedensity Managing Bone Health

Bisphosphonate Treatment Strategies

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Executive Summary

1. Though drug therapy may need to be stopped and started in osteoporotic patients, both the patient and doctor should regard osteoporosis as a lifelong condition which will need continuous management and monitoring, even if it does not require continuous medication.
2. Reassessment includes ongoing fracture history, bone density by DXA, absolute fracture risk and serum P1NP.
3. Prescribe alendronate 70mg weekly for five years, then reassess; no longer osteoporotic - take a two year break; good response but still osteoporotic - continue alendronate each two weeks and reassess at year eight; persisting severe osteoporosis - continue for 10 years, then take a two year break.
4. Administer intravenous zoledronate annually x 3 in severe osteoporosis and then each 18 months x 3 and each two years thereafter, if response has been positive. In early to moderate osteoporosis, administer each 18 months x 3 and each two years thereafter if response has been positive.
5. If fractures continue despite adequate inhibition of bone turnover, then a different treatment strategy, such as teriparatide, should be considered.

Drug holidays – why, when and for how long?

Bone resorption increases substantially at the menopause, leading to postmenopausal bone loss. Oestrogen replacement is a physiological way of restoring bone turnover rates to normal, and it is considered safe, from the bone point of view, to continue oestrogen treatment indefinitely. Bisphosphonates however, are more potent inhibitors of resorption which progressively accumulate in the skeleton (albeit at very low concentrations). Therefore, from the time of their introduction as medicines to manage osteoporosis, there has been concern regarding their long-term safety. There are now large follow-up cohorts of patients treated with alendronate for 10 years, risedronate for seven years, and zoledronate for six years, without clear-cut evidence of skeletal toxicity. However, case reports of stress fractures developing in the subtrochanteric region of the femur have suggested that this rare phenomenon may be bisphosphonate-related, reinforcing concerns regarding the safety of continuous long-term therapy with these drugs. Furthermore, it has become clear that the inhibition of bone resorption continues for several years after the discontinuation of long-term bisphosphonates, suggesting that their continuous administration is unnecessary, whether or not the safety concerns are well founded. Studies following-up patients treated with alendronate or zoledronate have indicated that continuation of therapy is probably not necessary in individuals whose hip bone density is no longer in the osteoporotic range. Such studies also show that, beyond five years, alendronate 5mg/day has the same effects on bone density and fractures as alendronate 10mg/day (equivalent to 70 mg/fortnightly or 70 mg/weekly with the current preparations).

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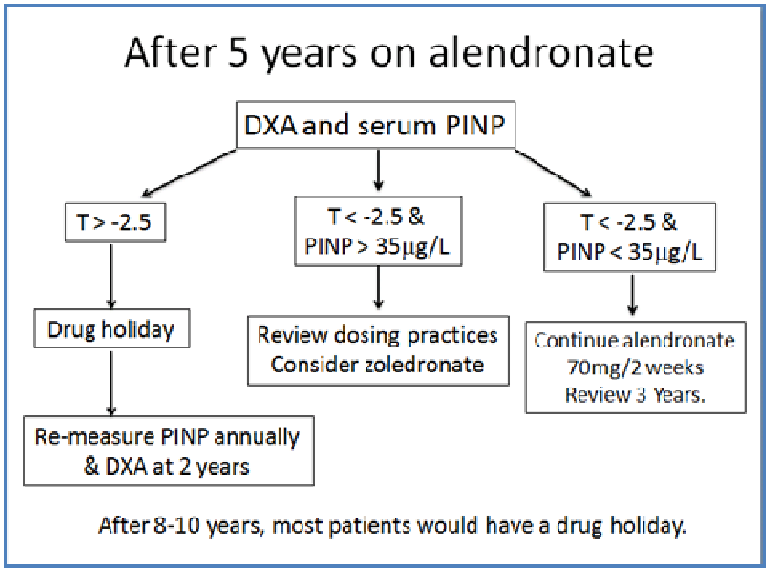
In light of these findings the following is a pragmatic approach to the long term management of the bisphosphonate-treated patient, which is in accord with what many international experts recommend.

ALENDRONATE

1. Assess alendronate-treated patients with DXA bone density and serum P1NP at 5 years (P1NP is a serum marker of bone turnover and = procollagen 1 N terminal peptide)
2. If P1NP is > 35ug/L, this suggests noncompliance or malabsorption of alendronate, the latter possibly due to inappropriate dosing practices. Discussion of appropriate procedures 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 < 35ug/L, then continue alendronate in a dose of 70mg every fortnight, with a plan to review in a further three year's 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 two years later.
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 1-2 years without any further drug administration.
6. During such a drug holiday, it is sensible to measure P1NP at the time of drug cessation, and then one and two years after cessation. Once P1NP is > 35ug/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.
7. In patients who have continued to fracture while receiving therapy, ensuring that P1NP is <35ug/L (after the fracture has healed) 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.



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ZOLEDRONATE

Zoledronate also has a very prolonged duration of action so the same general considerations apply. However, it is already being administered intermittently so simply increasing the inter-dose interval, as discussed below, seems a simpler approach. There is no definitive answer to the question of how often to give intravenous zoledronate.

The phase 2 trials of zoledronate showed comparable efficacy for doses given at three, six and 12 month intervals, so the latter option was taken into the phase 3 trials. 5mg given every 12 months is, therefore, what the authoritative fracture data are based on. However, changes in bone density after a single infusion of zoledronate are comparable to those from annual infusions out to 18 months, and a single infusion is still producing a > 40% reduction in bone resorption five years later. A post hoc analysis of individuals from the phase 3 trial who only received a single infusion of zoledronate or placebo, suggests that the reduction in fractures at three years is comparable to that found in the individuals who took all the annual infusions. Therefore, infusions at 12 or 18 month intervals do produce the greatest changes in bone density but less intense regimens do have antifracture efficacy, which may indeed be similar to that of the annual doses. Therefore, it is my practice to start patients with osteoporosis on infusions at 18-month intervals, but to dose annually in those who have severe osteoporosis. Rather than have a drug holiday in zoledronate-treated patients, it is my practice to gradually increase the inter-dose interval (e.g. to two or three years in patients treated for longer than five years) as long as they have shown the expected improvements in bone density.

RISEDRONATE

Risedronate is a further potent oral bisphosphonate which is widely used around the world. It has a shorter duration of action, and drug holidays with risedronate should probably not last longer than one year.

Change of Takapuna address

WE have moved from 15 Shea Tce, Takapuna
to
Waitemata Cardiology, 1 Shea Tce, Takapuna

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