For appointments at
Albany, Takapuna, Epsom,
Botany and Henderson
Ph: 09-623-2301
Fax: 09-623-2302
Healthlink: akldbone
Email: admin@bonedensity.co.nz
www.bonedensity.co.nz

NEWSLETTER

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AUCKLAND Bonedensity
Managing Bone Health

What to do after a first dose of zoledronate?

Most clinicians in New Zealand are familiar with the indications for treatment of oesteoporosis, where therapy is aimed at reducing the risk of future fracture. The criteria used by Pharmac for funding the potent bisphosphonates alendronate and zoledronate, and the technique for delivery of intravenous zoledronate (if this is the chosen therapy) are also well known. However, Auckland Bone Density fields a number of queries concerning the best strategy for deciding on further treatment after an initial infusion of zoledronate.

In the patient where the decision is made to treat with IV zoledronate the following issues are relevant:

1. Mode of action of zoledronate: Intravenous zoledronate is absorbed onto bone surfaces and then taken up by bone-resorbing cells (osteoclasts) where it inhibits enzymes involved in bone resorption. Bone resorption is thus markedly reduced, bone formation is subsequently decreased to a lesser degree, and modest increases in bone density occur.
2. Duration of action of zoledronate: Zoledronate absorbed into bone has a very long tissue half-life. Bone turnover markers remain lower by an average of 40% at five years after a single infusion of 5mg, and improvements in bone density (BMD) persist for at least 3-5 years (after three years, average 6.8% improvement in spinal BMD compared with placebo infusion, and average 4% improvement at the hip).
3. Reduction of fracture risk with zoledronate: Trial data indicate annual infusions of zoledronate in osteoporotic subjects reduce the risk of fracture by 33% over three years. However, post-hoc analysis of the same trials indicates fracture risk is reduced by the same amount (1/3) in those who received a single dose of 5 mg zoledronate compared with those who received three annual doses. After three annual doses of zoledronate, no additional benefit for reduction in clinical fractures occurred in those who received a further three annual zoledronate doses compared to those who received placebo.

Decision on further zoledronate treatment after an initial infusion:

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In the light of the above trial data it remains uncertain what dosing strategy of zoledronate is optimal for delivery of the agent in the most clinically effective and cost-efficient manner. Local practice varies, and for many patients a less frequent than annual zoledronate administration can be considered. A pragmatic approach might be to prescribe annual infusions for three years for patients with recent hip or clinical spinal fracture, where the short-term risk of fracture is likely to be high, particularly if confirmed by bone density assessment. These infusions could be followed by longer intervals of 2-3 years thereafter. In those who have had no recent fractures but who have a medium fracture risk on BMD assessment, treatment every 2-3 years from the start may be sufficient. Patients with no recent fracture but a high fracture risk as judged by BMD measurement could have infusions every 18 months, with progress judged by follow up BMD after several years.

Specific issues:

1. When using zoledronate there is little point in using bone turnover markers such as P1NP to guide further treatment. This is in contrast to the use of P1NP levels when using alendronate, where low or low-normal levels of P1NP may help determine that intake and absorption of the agent is adequate.
2. The acute flu-like reaction seen with an initial infusion of zoledronate in about 10-20% of cases has a much lower frequency (1-2%) with successive infusions.
3. Renal function: a serum creatinine and eGFR should be measured prior to using zoledronate. Zoledronate should not be used at eGFR < 35 because of the risk of renal damage.
4. If there is any suspicion of vitamin D deficiency (elderly, rest home resident, ethnic skin pigmentation, sun avoidance etc) then a tablet of 1.25mg calciferol (vitamin D) should be given immediately prior to the zoledronate infusion to avoid hypocalcaemia (which can sometimes occur in vitamin D-deficient patients given zoledronate).