Zoledronic acid for the treatment of osteoporosis

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Zoledronic acid (Aclasta) is a major addition to the armamentarium of osteoporosis treatment, being both effective and requiring only annual intravenous infusions, therefore eliminating some of the drawbacks or inconveniences of oral bisphosphonate therapy.

Zoledronic acid (Aclasta) is a potent, intravenous aminobisphosphonate administered once yearly for the treatment of osteoporosis. Bisphosphonates are synthetic analogues of pyrophosphate that bind with high affinity to bone mineral. They are taken up by osteoclasts, the bone-resorbing cells, during bone resorption. Once inside the osteoclasts, they inhibit a critical enzyme called farnesyl pyrophosphate synthase (FPPS).[1] This results in an inhibition of bone resorption through reduction of the activity and recruitment of osteoclasts, and increased apoptosis.[2] Zoledronic acid is the bisphosphonate with the strongest affinity for bone and the highest inhibitory activity of FPPS.[3,4]

A recent study investigating the changes in bone turnover markers for up to two years after a single 5 mg infusion of zoledronic acid in osteopenic postmenopausal women highlighted the prolonged duration of action of this drug.[5] Markers of bone resorption declined markedly within three months of the infusion by about 50 to 80% and increased slowly thereafter, being still 40 to 60% below the levels of the placebo group at 12 and 24 months.

As bone remodelling is a coupled process, a reduction in bone resorption is accompanied by a decrease in bone formation. Although sufficient reductions in bone turnover markers are necessary for therapeutic efficacy of bisphosphonates, oversuppression of bone turnover is not desirable as it may increase bone fragility.[6]

In this regard, recent data are reassuring and show that most postmenopausal women treated with zoledronic acid maintain serum levels of bone turnover markers within the normal premenopausal range, despite significant reductions in both bone formation and resorption markers.[7] Furthermore, there was no association between low serum levels of the bone formation marker P1NP at one year and increased fracture incidence. This is reassuring given recent reports of unusual bone insufficiency fractures in patients taking oral or intravenous bisphosphonates.[6,8-10] However, it is important to keep in mind that these events are rare and that the overall benefits of treating osteoporosis outweigh this small risk. Although the causality between unusual insufficiency fractures and use of bisphosphonates remain plausible, it has not been clearly established.

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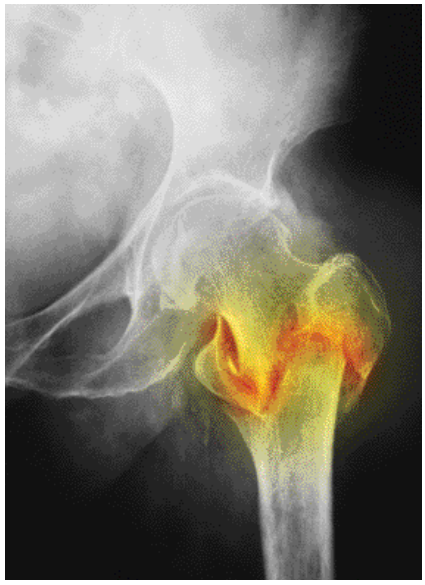

PHOTOLIBRARY

When is it used?

The PBS listing for zoledronic acid has recently been revised, enabling the bisphosphonate to be prescribed (authority required) as the sole PBS-subsidised antiresorptive agent, for:

- osteoporosis in patients aged 70 years of age or older with a BMD T-score of -3.0 or less
- established osteoporosis in patients with a fracture due to minimal trauma
- corticosteroid-induced osteoporosis in patients currently receiving long-term, high-dose corticosteroid therapy with a BMD T-score of -1.5 or less.
- treatment of symptomatic Paget's disease of bone

A streamlined authority prescription is required. The fracture site, or date, site and result of the BMD measurement, as appropriate, need to be documented in the patient's medical records. Only three annual treatments per patient will be subsidised on the PBS.

Zoledronic acid is contraindicated during pregnancy and in women who are breastfeeding. It is not recommended for patients with renal impairment (creatinine clearance <35 mL/min) due to limited safety data in such patients.[11]

How is it administered?

Zoledronic acid is administered via a vented infusion line (5 mg in 100 mL ready to use infusion) over at least 15 minutes once a year. Currently it is only approved for use for a maximum of three years per patient. Patients must be appropriately hydrated prior to the infusion, especially the elderly and those with renal impairment or receiving diuretic therapy. Hypocalcaemia and vitamin D deficiency (serum 25-hydroxyvitamin D level [25-OHD] <50 nmol/L) should be corrected before the infusion. Adequate calcium and vitamin D supplementation should also be recommended after starting therapy.

How effective is it?

Zoledronic acid has been shown to reduce vertebral and nonvertebral fractures by 70% and 25%, respectively, as well as hip fractures by 41%, over three years in postmenopausal women with osteoporosis.[12] It also decreased all-cause mortality by 28% and all clinical fractures by 35% in older men and women receiving 5 mg zoledronic acid versus placebo within three months of sustaining a hip fracture.[13]

The mechanisms responsible for mortality reduction in patients treated with zoledronic acid remain unclear, but may be related to an effect on cardiovascular events and pneumonia.[14] Recently, a single zoledronic acid infusion was reported to be noninferior and possibly superior to daily oral risedronate in the prevention and treatment of glucocorticoid-induced bone loss.[15]

What are the side effects?

Infusion-related, acute-phase reactions are common, occurring in about one-third of patients after the first infusion of zoledronic acid, and only 7% and 3% of patients after the second and third infusion, respectively.[12] Symptoms including fever, myalgia, influenza-like symptoms, headache, nausea and arthralgia can occur within three days and normally last for one to three days. They may be reduced by giving paracetamol shortly after the infusion. Zoledronic acid may also increase serum creatinine concentrations, and rarely it can cause renal failure up to three months after the infusion. Patients at risk are those with pre-existing renal impairment, those being treated for malignancies and those receiving nephrotoxic drugs.

A trial has shown that in postmenopausal women with osteoporosis who were treated with zoledronic acid, the incidence of serious atrial fibrillation events was increased versus placebo (1.3% *v.* 0.5%, P<0.001).[12] However, as this was not found in the other zoledronic acid trials, the association remains uncertain, and a recent FDA report could find no association between bisphosphonates and atrial fibrillation.

Finally, as with oral and other intravenous bisphosphonates, zoledronic acid has been associated with transient hypocalcaemia postinfusion, especially in patients with pre-existing hypocalcaemia and vitamin D deficiency. Rare events reported with both oral and intravenous bisphosphonates include severe ocular inflammation (conjunctivitis, uveitis, scleritis, episcleritis), severe and incapacitating musculoskeletal pain and osteonecrosis of the jaw.[16-20] However, in trials of zoledronic acid in osteoporosis, there was one case of osteonecrosis of the jaw reported in each of the treatment and placebo groups.

What should be monitored?

Serum calcium, 25-OHD and creatinine levels should be assessed prior to starting zoledronic acid. For patients receiving zoledronic acid for osteoporosis, referral to a dentist is not necessary before starting treatment.[21] However, if dental work is planned or suspected, it is desirable that it is performed before the infusion. Maintaining good dental hygiene and regular dentist visits are recommended.[22] If ocular inflammation or severe musculoskeletal pain is suspected to be related to use of bisphosphonates, referral to the appropriate specialist should be considered.

As with other osteoporosis therapies, response to treatment could be assessed by monitoring BMD one to two years after treatment initiation.[23] In the absence of data on which to base our recommendation, we suggest repeating the BMD scan two years after the last dose of zoledronic acid. If the patient experiences a fragility fracture or a significant decrease in BMD (>3% loss at the spine) while taking zoledronic acid, or remains at high risk of fracture (e.g. use of corticosteroids, propensity to fall), after completing three years of zoledronic acid therapy, referral to a bone specialist to discuss further treatment options should be considered.

Conclusion

Zoledronic acid is a major addition to the armamentarium of osteoporosis treatment, being both effective and requiring only annual intravenous infusions, thus eliminating some of the drawbacks or inconveniences of oral bisphosphonates. Low adherence and persistence with daily and weekly oral bisphosphonates is a major issue that impacts on antifracture efficacy. Patients who are considered unsuitable candidates for oral bisphosphonates because of the necessity to remain upright for at least 30 minutes after the ingestion of the drug or who experience gastrointestinal side effects may also benefit from the use of zoledronic acid.

The effects of a single zoledronic acid infusion on BMD and bone turnover markers have been shown to persist for up to two years. Fracture data are needed to ensure that a greater interval between infusions is effective as well as desirable. MT

References

A list of references is available on request to the editorial office.

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