

Zoledronic acid: a once-yearly injection for osteoporosis

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KEY POINTS

- once-yearly zoledronic acid infusion is licensed for the treatment of postmenopausal osteoporosis
- available as 0.05mg per ml solution for infusion, 100ml = £283.74
- compared with placebo, it increases bone mineral density in the hip, lumbar spine and femoral neck
- reduces the risk of vertebral fracture by about 70 per cent and that of hip fracture by about 40 per cent; it also reduces the risk of other fractures
- reduces mortality after hip fracture (in men and women) by almost 30 per cent
- in the pivotal trial, the rate of treatment discontinuation over 3 years was no different from placebo and lower than nonadherence rates reported with other bisphosphonates
- the commonest reported adverse events were postinfusion reactions affecting 30 per cent of patients after the first dose but decreasing to about 3 per cent after the third
- zoledronic acid was associated with an increased risk of serious atrial fibrillation compared with placebo in 1 trial but not a second
- once-yearly administration avoids the poor compliance associated with oral bisphosphonates



Aclasta is a once-yearly injection of the bisphosphonate zoledronic acid that offers much improved adherence compared with oral bisphosphonates. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Elaine Dennison comments on its place in therapy.

The National Institute for Health and Clinical Evidence (NICE) is developing a clinical guideline for the treatment of osteoporosis, and has published draft technology appraisals on primary and secondary prevention of osteoporosis in postmenopausal women. Its recommendations define risk categories for treatment with alendronate, but not other bisphosphonates; women who are already receiving different treatment may continue for as long as clinically appropriate.^{1,2}

The bisphosphonate zoledronic acid (Aclasta) was not licensed for osteoporosis when this guidance was drafted.

The bisphosphonates inhibit bone resorption and increase bone mineral density (BMD) by altering osteoclast activation and function. Zoledronic acid is rapidly distributed to bone; its long duration of action is attributed to high binding affinity for the enzyme farnesyl pyrophosphate synthase and its strong affinity for bone mineral.

Adherence to treatment with a bisphosphonate is often poor,

with estimates of continuation rates at one year ranging between 18 and 78 per cent.³ Poor adherence rates over two years are associated with an increased risk of fracture.^{4,5}

The technology

Zoledronic acid is a bisphosphonate licensed for the treatment of osteoporosis in postmenopausal women at increased risk of fracture. The recommended dose is 5mg by iv infusion once yearly, administered over not less than 15 minutes; this formulation and dose

is also licensed for the treatment of Paget's disease.

Patients should be appropriately hydrated (caution is needed in patients taking drugs that may affect renal function or cause dehydration) and taking calcium and vitamin D supplements if necessary. No dose adjustment is recommended for older patients or those with hepatic impairment; zoledronic acid should not be administered to patients with severe renal impairment (creatinine clearance <4ml per minute) or hypocalcaemia.

Clinical trials

One trial (the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial, HORIZON) provides the key efficacy data for annual zoledronic acid for osteoporosis.⁶ The participants were 7765 postmenopausal women (mean age 73; T-score of ≤ -2.5 or ≤ -1.5 plus vertebral fractures) stratified according to concurrent treatment – including HRT and raloxifene (Evista) – and randomised to placebo or zoledronic acid 5mg annually at 0, 12 and 24 months.

The primary end-points were new vertebral and hip fractures assessed clinically and by X-ray over three years. About 60 per cent of women in each group had at least one vertebral fracture, but end-points were not reported by subgroup.

The three-year incidence of new morphometric vertebral fracture was 10.9 per cent with placebo and 3.3 per cent with zoledronic acid (relative risk 0.30; CI 95% 0.24-0.38); similar reductions were seen after one and two years (see Figure 1). The incidence of hip fracture was 2.5 per cent with placebo and 1.4 per cent with zoledronic acid, (hazard

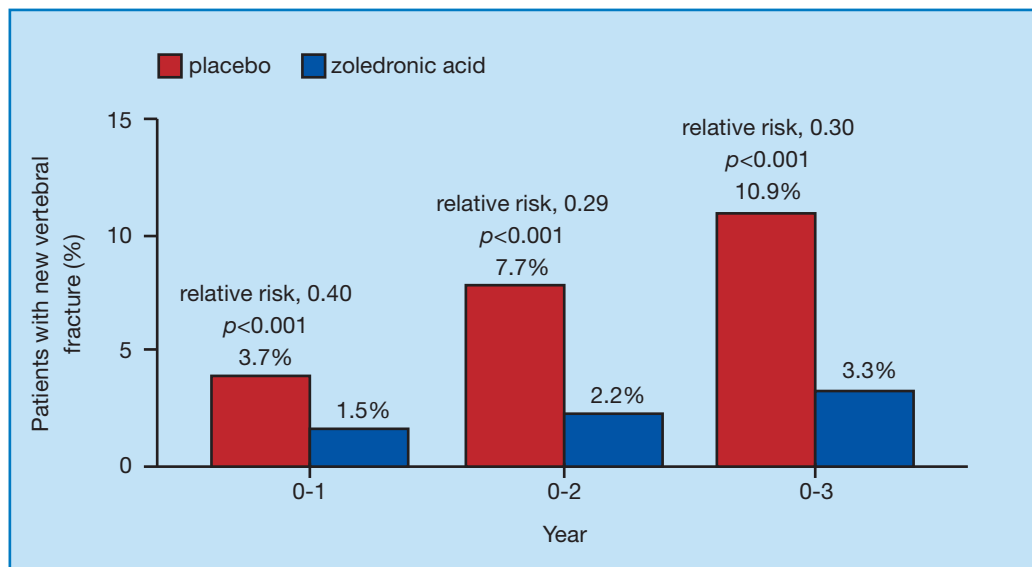


Figure 1. Incidence of vertebral fracture over three years in patients randomised to treatment with zoledronic acid or placebo⁶

ratio 0.59; CI 95% 0.42 - 0.83, see Figure 2).

Zoledronic acid significantly increased BMD at the hip (by 6.0 per cent), lumbar spine (6.7 per cent) and femoral neck (5.1 per cent) and also reduced the incidence of nonvertebral fracture, any clinical fracture, multiple vertebral fractures and height loss.

The proportions of patients who discontinued treatment before

the end of the trial were similar for placebo (15 per cent) and zoledronic acid (16 per cent).

In a second HORIZON study, the Recurrent Fracture Trial,⁷ yearly zoledronic acid reduced the incidence of new fractures and mortality in 2127 men (comprising 24 per cent of the study population) and women who declined treatment with an oral bisphosphonate after hip fracture. About

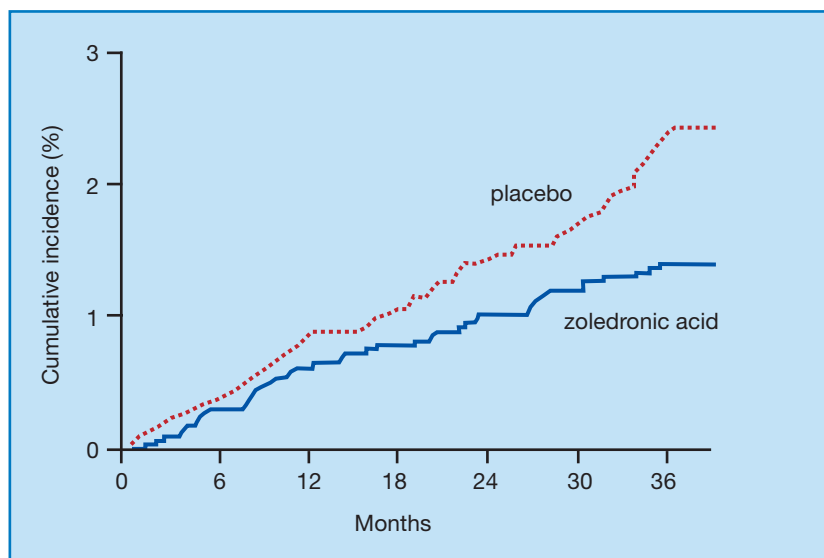


Figure 2. Incidence of hip fracture over three years in patients randomised to treatment with zoledronic acid or placebo ($p=0.002$)⁶

40 per cent of patients had osteoporosis (T-score of ≤ -2.5); median follow-up was 1.9 years.

Compared with placebo, zoledronic acid significantly reduced the risk of new clinical fractures (8.6 *vs* 13.9 per cent) and clinical vertebral and nonvertebral fractures; the incidence of new hip fractures was also reduced but not significantly so (2.0 *vs* 3.5 per cent). Mortality was 9.6 per cent with zoledronic acid and 13.3 per cent with placebo (hazard ratio 0.72; CI 95% 0.56-0.93).

Adverse effects

In the first HORIZON trial,⁶ zoledronic acid was associated with a significantly higher incidence of postdose symptoms (pyrexia, myalgia, flu-like symptoms, headache and arthralgia), affecting 31.6 per cent of patients after the first infusion (*vs* 6.2 per cent with placebo), 6.6 per cent after the second (*vs* 2.1 per cent) and 2.8 per cent after the third (*vs* 1.1 per cent).

It was also associated with more serious cases of atrial fibrillation (1.3 *vs* 0.5 per cent with placebo); these cases usually occurred more than 30 days after administration. There was no difference in the incidence of atrial fibrillation between zoledronic acid and placebo in the second trial.⁷

Changes in renal function were more common with zoledronic acid but transient, with no difference after three years.⁶ There was no significant difference in rates of discontinuation due to adverse effects (2.1 *vs* 1.8 per cent with placebo). Two cases of osteonecrosis of the jaw were reported, one in

Product	Dosage regimen	Cost per year*
alendronate	daily	£94.12
	weekly	£47.58
etidronate plus calcium (Didronel PMO)	daily	£84.48
ibandronate (Bonviva)	monthly	£257.40
	every 3 months	£320.00
risedronate (Actonel)	daily	£209.88
	weekly	£263.90
zoledronate (Aclasta)	yearly	£283.74
*from MIMS/Drug Tariff April 2008		

Table 1. Cost of a year's osteoporosis treatment with current bisphosphonates

each arm of the trial;⁶ no cases were reported in the second trial.⁷

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

It is increasingly recognised that a major limitation in the effective treatment of osteoporosis is poor

compliance with oral therapy, with studies suggesting adherence to oral bisphosphonates of only 39 per cent at six months. In recent years, this has been addressed by the development of

weekly or monthly oral preparations, but until last year the use of intravenous therapies has been limited.

One of these new iv agents is zoledronic acid, a potent

bisphosphonate with proven efficacy against vertebral and non-vertebral fracture, and delivered as an annual infusion. Clearly an annual iv injection will appeal to some, but not all, patients; it also means that 'noncompliers' are identifiable and appropriate action can be taken to ensure they benefit from treatment. Intravenous therapy may be particularly appropriate for those individuals who have experienced gastrointestinal side-effects on oral preparations, or who find it difficult to remember to take an oral preparation.

There have been concerns regarding the safety of potent iv

bisphosphonates. An unexpected finding in one trial was a significant increase in the risk of atrial fibrillation – the cause is uncertain, with no obvious biological explanation, and was not observed in the other major trial.

Another particular concern was the risk of osteonecrosis of the jaw, a rare condition more commonly seen in malignant conditions treated with bisphosphonates – there was no increased risk in the treated group in the two major trials. Finally, while a mild influenza-like syndrome lasting one to three days is common after treatment with iv bisphosphonates, this is usually easily

treated with paracetamol and tends not to recur with subsequent infusions.

Hence the advent of an intravenous infusion with proven reduction in the risk of hip and vertebral fractures is a most welcome addition to the osteoporosis therapy armamentarium. While its place in secondary care seems assured, it will be interesting to see how feasible it is to deliver this therapy in primary care, particularly on a large scale.

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