



## Zoledronic Acid

Intravenous zoledronic acid (brand name Reclast®) was recently approved by the US FDA as the first once yearly therapy for post-menopausal osteoporosis. Zoledronic acid was previously FDA approved for Paget's disease and in oncology for management of hypercalcemia of malignancy and skeletal metastases (Zometa®; 4 mg dose). Osteoporosis approval was based in large part on data published from two large fracture studies. In the HORIZON Pivotal Fracture Trial (HORIZON-PFT), 7736 postmenopausal women were randomized to 3 annual doses of 5 mg of zoledronic acid or placebo<sup>1</sup>. This trial found that over 3 years of follow up, postmenopausal women taking zoledronic acid had a significantly lower rate of new morphometric vertebral fractures (relative risk reduction, RRR = 70%), non-vertebral fractures (RRR = 25%) and hip fractures (RRR = 41%). While this study is not directly comparable with the pivotal studies of oral bisphosphonates, the magnitude and consistency of the fracture risk reduction equaled or exceeded that observed in prior bisphosphonate trials, despite a somewhat less robust increase in lumbar bone mineral density (6.7% over 3 years) compared with that seen in with alendronate (8.8 % versus placebo over 3 years in the phase III study by Lieberman and colleagues)<sup>2</sup>.

A second study, the HORIZON recurrent fracture trial (HORIZON-RFT) examined the effects of once yearly zoledronic acid on recurrent fractures after an initial hip fracture in over 1000 women and men<sup>3</sup>. IV zoledronic acid was associated with a significantly reduced risk of new clinical vertebral fracture (RRR 46%) and any clinical fracture (RRR 35%). All cause mortality was also reduced by 28%, although the mechanism for the mortality benefit is not fully understood. While the population in this trial was a bit younger than that seen in the community traditionally, and the study was too small to look at age and sex affects, this was the first osteoporosis RCT to specifically examine a post-hip fracture population.

Two shorter-term studies compared zoledronic acid with alendronate and examined the onset of action<sup>4</sup> of each and the effects on BMD for patients that switched from alendronate to zoledronic acid<sup>5</sup>. Among new users, intravenous zoledronic acid more rapidly reduced biomarkers of bone resorption compared to new alendronate users and was non-inferior to alendronate in maintaining bone mineral density in patients switched from alendronate to zoledronic acid.

### Adverse Events

In both HORIZON studies, zoledronic acid was generally well tolerated and serious adverse events did not differ significantly from placebo. Up to 18.8% of persons receiving zoledronic acid experienced infusion reactions<sup>4</sup>, consisting most commonly of influenza-like symptoms and fevers within three days of the infusion. Infusions were much less common with subsequent treatments. In the study of patients switched from alendronate to zoledronic acid, no patients experienced an infusion reaction, suggesting a waning of this effect with longer duration of bisphosphonate exposure. In the HORIZON Recurrent Fracture Trial, where patients were pre-treated with acetaminophen with study drug and as needed over 72 hours, only 7% of participants experienced infusion reactions.

Hypocalcemia was seen infrequently (0.2% of subjects using a cutpoint of 7.5 mg/dl and 2.3 % using 8.3 mg/dl as the threshold) at the zoledronic acid dose used for osteoporosis and was seldom symptomatic or sustained when it occurred. It is recommended that all persons receiving zoledronic acid be vitamin D replete. In the HORIZON Recurrent Fracture Study, patients with 25 OH vitamin D levels below 15 ng/ml or those without known vitamin D levels were given 50 to 125,000 IU of ergocalciferol or cholecalciferol 2 weeks prior to infusion to help ameliorate this potential concern. It is also recommended that renal function be considered prior to use of IV bisphosphonates and that they be avoided if creatinine clearances are < 35 ml/min.

Osteonecrosis of the jaw is an uncommon adverse outcome that predominately has been reported in association with frequent intravenous bisphosphonate therapy in the setting of underlying malignancy (see ACR Hotline Bisphosphonate-Associated Osteonecrosis of the Jaw, June 2006), but it has been very rare when bisphosphonates are administered for osteoporosis (current estimated incidence of 1/100,000). Two cases of confirmed osteonecrosis of the jaw were reported in patients in the HORIZON Pivotal Fracture Trial, 1 on active treatment, 1 receiving placebo; none

were seen in the other HORIZON trial, although a specific case finding method was not used. Patients should be informed of this risk, and pending dental work should be completed prior to treatment.

Atrial fibrillation was detected in 2.5% of zoledronic acid patients (96 out of 3862) vs 1.9% (75 out of 3852;  $P < 0.001$ ) of patients on placebo in the HORIZON Pivotal Fracture Trial. Most atrial fibrillation occurred more than a month after the infusion, suggesting that this outcome was not mediated by a transient flux in serum calcium levels shortly after the infusion. An ECG sub-study in 559 patients did not demonstrate an increased risk of atrial fibrillation. The second HORIZON study did not detect an increased risk of atrial fibrillation or cardiovascular events associated with zoledronic acid. This issue is currently under review at FDA, which has not recommended any change in prescribing related to it. ([http://www.fda.gov/cder/drug/early\\_comm/bisphosphonates.htm](http://www.fda.gov/cder/drug/early_comm/bisphosphonates.htm))

There has been concern about fracture healing with bisphosphonate use. The absence of impairment in hip fracture healing when zoledronic acid was administered within 90 days of a hip fracture suggests it may be suitable for post-fracture patients. This concern requires more study.

### **Practical Considerations**

The decision to use zoledronic acid for osteoporosis will depend in part on cost, (currently approximately \$1,264 per infusion wholesale price for 5 mg Reclast and \$700 for 4 mg Zometa) and insurance coverage, as well as on physician and patient preference. Adherence is a major problem with currently available oral anti-osteoporosis therapies, with less than 50% of those starting bisphosphonates continuing them for more than one year. A medication that is administered once a year could potentially improve adherence to therapy. A 15 minute IV infusion time will require that zoledronic be infused by health providers familiar with intravenous medication administration. Pre-medication with acetaminophen may help abrogate infusion related symptoms. While longer-term data is forthcoming, it is likely that IV zoledronic acid will assume a significant role in post-menopausal fracture management.

### **THE BOTTOM LINE**

- Zoledronic acid administered IV once yearly appears to be at least as effective as oral bisphosphonates in reducing the risk of new and recurrent vertebral and non-vertebral fractures in patients with osteoporosis
- Infusion reactions, including myalgias, may occur (particularly following the first dose)
- Vitamin D should be repleted before infusion, and patients should be monitored for hypocalcemia
- The drug should be avoided in patients with a creatinine clearance of  $<35$  ml/min
- Patients who are not candidates for oral bisphosphonates, such as those with severe esophageal disease, inability to remain upright, or severe cognitive impairment may be particularly suitable patients for the drug.

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**Disclosures:** Dr. Saag has served as a consultant or received honoraria and has served as a clinical investigator for Merck, Novartis, Eli Lilly, Proctor and Gamble, Aventis, Amgen, Roche and Glaxo Smith Kline. Dr. Curtis has served as a consultant or has received honoraria from Merck, Proctor & Gamble, Roche, and Eli Lilly. He has conducted research for Merck, Proctor & Gamble, Amgen, Eli Lilly, and Novartis. Drs. Kavanaugh, Matteson and Ruderman have nothing to disclose.

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**The following are corrections to the Zoledronic Acid Hotline (noted in red):**

- A second study, the HORIZON recurrent fracture trial (HORIZON-RFT) examined the effects of once yearly zoledronic acid on recurrent fractures after an initial hip fracture in over **2000** women and men<sup>3</sup>.
- Atrial fibrillation was detected in **1.3%** of zoledronic acid patients (**50** out of 3862) vs **0.5%** (**20** out of 3852; P < 0.001) of patients on placebo in the HORIZON Pivotal Fracture Trial.
- Costs quoted in the Hotline may not be current or consistent in all regions. The current Wholesale Acquisition Cost (WAC) for Reclast (5 mg) is now quoted as **\$1042**. Prescribers are advised to contact their local carriers or distributors for up-to-date information on the acquisition cost of Reclast and Zometa.
- Osteonecrosis of the jaw is an uncommon adverse outcome that predominately has been reported in association with frequent intravenous bisphosphonate therapy in the setting of underlying malignancy (see ACR Hotline [Bisphosphonate-Associated Osteonecrosis of the Jaw, June 2006](#)), but it has been very rare when bisphosphonates are administered for osteoporosis (current estimated incidence of 1/100,000 **patient-years of therapy**).