

DRUG UPDATE

No.58

January 2008

WHICH BISPHOSPHONATE?

for osteoporosis

Alendronic acid is recommended as the first-line bisphosphonate for osteoporosis. Risedronate is a useful alternative for patients intolerant of alendronic acid or for male patients who require a once-weekly preparation. Intravenous bisphosphonates represent a further option for patients who cannot tolerate oral treatments or for those with known concordance problems.

What are they?

Bisphosphonates inhibit bone resorption and increase bone mineral density (BMD) by altering osteoclast activity and function. They are used in a range of conditions and five are licensed in the UK for the management of osteoporotic fractures: alendronic acid (generic products available since 2006) and risedronate (Actonel®, Procter & Gamble) are both available as daily and once-weekly oral preparations, etidronate is available in a pack with calcium tablets (Didronel® PMO™, Procter & Gamble), ibandronic acid is available as a once-monthly oral tablet and a 3-monthly injection (Bonviva®▼, Roche), and zoledronic acid is available as an annual infusion (Aclasta®▼, Novartis).¹

What does the evidence demonstrate?

Oral bisphosphonates

Once-weekly formulations of alendronic acid 70 mg and risedronate 35 mg are the most commonly prescribed oral bisphosphonates and two studies have compared them in postmenopausal osteoporosis (PMO). FACT was a 12-month randomised controlled trial comparing once-weekly alendronic acid (n = 520) with risedronate (n = 533).² The outcome measures reported were surrogate markers of efficacy such as BMD and biochemical markers of bone turnover. Alendronic acid demonstrated significantly greater increases in various bone density outcomes and a greater suppression of bone turnover markers. These changes were maintained at 24 months.³ A reduction in fractures was not demonstrated at ≤ 24 months but the study was not designed for this comparison.^{2,3} No differences were observed in the incidence of upper gastrointestinal (GI) adverse effects.³ REAL was a retrospective cohort study comparing the number of non-vertebral and hip fractures during the first 12 months of therapy in women aged ≥ 65 years and taking once weekly alendronic acid (n = 21,615) or risedronate (n = 12,215).⁴ The rate of non-vertebral fractures in the alendronic acid group was 2.3% compared to 2.0% in the risedronate group (absolute risk reduction [ARR] = 0.3%, p = 0.03) and hip fractures occurred in 0.6% and 0.4% respectively (ARR = 0.2%, p = 0.01). The apparently greater efficacy of risedronate compared to alendronic acid can be expressed as preventing an additional two hip fractures and three non-vertebral fractures in the first year of treatment for every 1,000 patients. It is not known whether the apparent

superiority of risedronate over alendronic acid is maintained after 12 months. Note that alendronic acid 70 mg is not licensed for male patients, whereas risedronate 35 mg and alendronic acid 10 mg (daily dose) are licensed for male osteoporosis.¹

The cyclical etidronate plus calcium regimen (Didronel® PMO™) is not considered a clinically equivalent alternative to alendronic acid^{5,6} and this product now accounts for relatively little use compared to other bisphosphonate drugs.

Once-monthly oral ibandronic acid 150 mg has demonstrated improvements in BMD in controlled studies and is as effective as weekly alendronic acid after one year in PMO.⁷ However no assessment of fracture rates has been conducted with this preparation.⁸ Two 6-month studies comparing once-weekly alendronic acid to once-monthly ibandronic acid have evaluated patient preferences for treatment (total n = 1,374) and found improved concordance and greater patient preference with ibandronic acid.^{9,10} In preliminary results from a two-year study, risedronate 150 mg once-monthly demonstrated safety and efficacy comparable to daily dosing (5 mg). Once-monthly risedronate is not currently licensed or available in the UK.¹¹

Intravenous bisphosphonates

Evidence for the 3 mg intravenous dose of ibandronic acid originates from the DIVA study (n = 1,395 PMO patients) which demonstrated greater efficacy of the 3 mg 3-monthly intravenous dose compared to a daily oral ibandronic acid regimen.¹² However the reported outcomes relate to BMD and not fracture or mortality rates. Evidence for zoledronic acid 5 mg annual infusion originates principally from the HORIZON pivotal fracture trial (n = 7,736), a placebo-controlled randomised 3-year study.¹³ This found that vertebral fractures were reduced by 7.6% and hip fractures by 1.1% (both p < 0.01) in postmenopausal women. A separate New Drug Evaluation on zoledronic acid provides a full review of the evidence.¹⁴

How safe are they?

The principal adverse effects associated with oral bisphosphonates are abdominal pain, dyspepsia, and GI ulceration. Specific administration instructions are necessary with all oral bisphosphonate drugs.¹

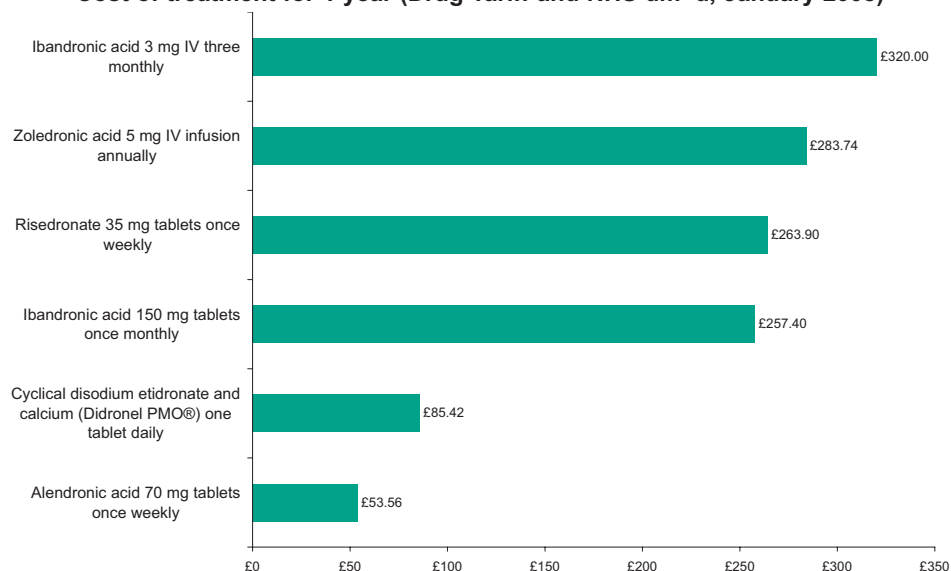
Associations have been made between both oral alendronic acid and intravenous zoledronic acid with atrial fibrillation.^{13,15} It is not known whether this is a class effect. No evidence was identified indicating an increased risk of cardiovascular death with any bisphosphonate drug. Intravenous bisphosphonates are not associated with upper gastric effects but they are associated with transient 'flu-like' symptoms following administration.¹ Osteonecrosis of the jaw (ONJ) has been reported in oncology patients receiving intravenous bisphosphonates.¹⁶ The incidence of ONJ with lower doses of bisphosphonates for the management of osteoporosis is not known and warrants further investigation.¹⁶ The Safer Medication Use bulletin provides a full review of the safety issues relating to bisphosphonates.¹⁶

What does NICE recommend?

The National Institute for Health and Clinical Excellence (NICE) has issued final appraisal determinations for primary and secondary prevention of PMO fractures and these recommend alendronic acid as the first-line agent; ibandronic acid and zoledronic acid are not considered in these reviews.^{5,6} A clinical guideline covering the assessment of

How much do they cost?

Cost of treatment for 1 year (Drug Tariff and NHS dm+d, January 2008)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. These figures relate to drug costs only and do not include the cost of IV administration (where this is conducted in secondary care as a follow-up out-patient appointment this will incur an additional cost of £94).

REFERENCES

- Summary of product characteristics (Aclasta[®], Actonel[®], Bonviva[®], Didronel[®] PMO[™], Fosamax[®]). www.medicines.org.uk (last accessed 31/12/07)
- Rosen CJ et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: A randomized double-blind study. *J. Bone Miner. Res.* 2005;20:141-51 (RCT)
- Bonnick S et al. Comparison of weekly treatment of postmenopausal osteoporosis with alendronate versus risedronate over two years. *J Clin Endocrinol Metab* 2006;91:2631-7 (RCT)
- Silverman SL et al. Effectiveness of bisphosphonates on nonvertebral and hip fractures in the first year of therapy: The risedronate and alendronate (REAL) cohort study. *Osteoporos Int* 2007;18:25-34
- National Institute for Health and Clinical Excellence. Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women. Final Appraisal Determination: Jun 2007 (G)
- National Institute for Health and Clinical Excellence. Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. Final Appraisal Determination: Jun 2007 (G)
- Miller PD et al. Once-monthly oral ibandronate compared with weekly oral alendronate in postmenopausal osteoporosis: results from the head-to-head MOTION study. *Curr Med Res Opin* 2008;24:207-13 (RCT)
- Regional Drug and Therapeutics Centre. Ibandronic acid. New Drug Evaluation No. 74; Mar 2006 (R)
- Emkey R et al. Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Bonviva Alendronate Trial in Osteoporosis (BALTO). *Curr Med Res Opin* 2005;21:1895-903 (RCT)
- Cooper A et al. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. *Int. J. Clin. Pract.* 2006;60:896-905 (RCT)
- Delmas PD et al. Efficacy and safety of risedronate 150 mg once a month in the treatment of post-menopausal osteoporosis. *Bone* 2008;42:36-42 (RCT)
- Delmas PD et al. Intravenous ibandronic acid injections in postmenopausal women with osteoporosis. *Arthritis Rheum.* 2006;54:1838-46 (RCT)
- Black DM et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis: HORIZON Pivotal Fracture Trial. *N. Engl. J. Med.* 2007;356:1809-22 (RCT)
- Regional Drug and Therapeutics Centre. Zoledronic acid. New Drug Evaluation No. 86; Jan 2008 (R)
- Cummings SR et al. Alendronate and atrial fibrillation. *N. Engl. J. Med.* 2007;356:1895-6
- Regional Drug and Therapeutics Centre. Bisphosphonates for osteoporosis. Safer Medication Use No. 2; Jan 2008 (R)

KEY G – guideline, R – review, RCT – randomised controlled trial

Regional Drug and Therapeutics Centre

Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH

Tel: 0191 232 1525 Fax 0191 260 6192

E-mail: nyrdtc.di@ncl.ac.uk Website: www.nyrdtc.nhs.uk

THIS DOCUMENT IS INTENDED FOR USE BY NHS HEALTHCARE PROFESSIONALS AND CANNOT BE USED FOR COMMERCIAL OR MARKETING PURPOSES. PATIENT INFORMATION ON MANY TOPICS CAN BE ACCESSED VIA NHS DIRECT.