

Review

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Bisphosphonates for post-menopausal osteoporosis: are they all the same?

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Summary

The primary goal of treatment for post-menopausal osteoporosis (PMO) is reduction in fracture risk. Therefore, clinicians must recommend therapies that are safe and have proven anti-fracture efficacy. Bisphosphonates have long been established as first-line therapy for osteoporosis and several of these drugs significantly reduce osteoporotic fracture risk. However, choosing among different bisphosphonates can represent a difficult clinical decision. This review outlines the pharmacology of various bisphosphonates, discusses how their pharmacological characteristics affect their efficacy, and summarizes clinical safety and efficacy data. Clinical trial data and the opinions of expert bodies suggest that alendronate, risedronate, ibandronate and zoledronic acid all provide fracture protection for patients with PMO. However, there are differences among these agents. For example, all four agents have demonstrated efficacy in

preventing vertebral fractures, but only zoledronic acid and risedronate significantly reduce non-vertebral fracture risk in pivotal trials. Moreover, reduction in hip fracture risk has only been established for alendronate, risedronate and zoledronic acid. Current data suggest that ibandronate and zoledronic acid have the most persistent antifracture effect. Bisphosphonates have been associated with a number of side effects, the evidence for which is summarized in this review. The most pertinent of these when choosing a bisphosphonate for a particular patient are the well-documented associations between gastrointestinal adverse events and oral administration, and between acute phase reactions and intravenous administration. Ultimately, selection of a specific bisphosphonate for treatment of PMO should be based on efficacy, risk profile, cost-effectiveness and patient preference.

Introduction

The primary goal of treatment for post-menopausal osteoporosis (PMO) is to reduce the risk of fracture.¹ This aim is reflected in the most recent guidelines on the evaluation of medicinal products in the treatment of primary osteoporosis issued by the European Medicines Agency's Committee for

Medicinal Products in Human Use.² This document makes it clear that reduction in fracture risk is the only endpoint that is acceptable in drug registration studies, and that this should be demonstrated for both spinal and non-spinal fractures. Non-spinal fractures are specified as either femoral (hip) fractures or major non-vertebral fractures (pelvis, distal femur, proximal tibia, ribs, proximal humerus,

forearm and hip). Bone mineral density (BMD) is acceptable as the primary end point in bridging studies or as a secondary efficacy endpoint in pivotal trials, but it is not an appropriate surrogate for fracture reduction.²

Post-menopausal women at increased risk of fracture are typically chosen as the population for the pivotal studies associated with registration of a new chemical entity. Once this registration has been achieved, an extension of the indication may be granted on the basis of bridging studies that demonstrate non-inferiority of a new dose, route of administration or formulation. Changes in BMD are acceptable as the primary endpoint in such bridging studies, and in those that aim to demonstrate the efficacy of the drug in a different population (e.g. men with osteoporosis).²

Evidence-based medicine should be the greatest influence on the clinician's approach to treatment. There are two principles of evidence-based medicine. First, there is a hierarchy of evidence in which greater emphasis is given to consistent findings from randomized controlled trials (RCTs). Second, evidence is never enough to make clinical decisions; it should be combined with clinical judgment and the patients' preferences and values. The current availability of highly efficacious bisphosphonates coupled with well-conducted studies allows the principles of evidence-based medicine to be applied to the treatment of PMO. These in turn allow rational choices to be made for the individual patient. A number of different methodologies exist for assessing the evidence base; first, to ensure that the scientific evidence is applicable to real clinical practice, and second, to highlight any significant gaps in the evidence.

Making appropriate treatment decisions can be a complex process. Bisphosphonates are a long-established first-line therapy for osteoporosis and other conditions such as glucocorticoid-induced osteoporosis, Paget's disease and hypercalcemia of malignancy. In recent years, attempts to improve anti-fracture efficacy, moderate side effects and provide optimal convenience to patients have led to the development of newer bisphosphonates, including those that can be administered with longer inter-dosing intervals. For PMO, nitrogen-containing bisphosphonates are currently considered the treatment of choice.¹ These agents increase BMD, and most have been shown to provide fracture protection in RCTs.¹

The RAND (Research and Development) appropriateness method is generally regarded as the most rigorous and systematic methodology.^{3,4} The RAND method rates the appropriateness of medical interventions using the opinions of experts. The

justification for this approach is that RCTs are time-consuming and expensive, sample sizes are limited, and they are conducted under ideal conditions; hence the results are generalized and should be treated as such. By utilizing the knowledge and experience of expert physicians (much of which is derived from RCT data), the principle is that the RAND method can provide a detailed assessment about the appropriateness of a treatment.⁵

In 2007, the RAND evidence-based practice centre prepared a comparative effectiveness review (CER) that compared the fracture reduction benefits among and within classes of treatment for patients with low bone density. They concluded that there is good evidence from RCTs that, compared with placebo, alendronate, ibandronate, risedronate and zoledronic acid prevent vertebral fractures, and risedronate and alendronate prevent both non-vertebral and hip fractures. There is also good evidence that zoledronic acid prevents non-vertebral fractures.⁵

In addition to RAND publications, clinicians can utilize information from the World Health Organization (WHO) to review the evidence base. WHO publishes a series of technical reports that contain the latest scientific and technical advice on a broad range of medical and public health subjects based on the findings of various international groups of experts.⁶

More recently, the Scientific Advisory Board of the European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF) have jointly published guidance on the diagnosis and management of PMO.⁷ These experts concluded that alendronate and risedronate reduce the risk of vertebral fracture in patients with osteoporosis. This protection has been established both in patients who do and in those who do not have a vertebral fracture prior to treatment. Alendronate and risedronate also reduce the risk of non-vertebral fractures, including those of the hip, in patients with a prior vertebral fracture. A similar clinical profile has been established for zoledronic acid, with the exception that evidence for non-vertebral fracture protection has been established only in a mixed group of patients (i.e. those with or without prevalent vertebral fractures). Ibandronate has been shown to provide vertebral fracture protection in patients with a prior vertebral fracture. The ibandronate evidence base for non-vertebral fracture protection is limited to subsets of the population and has been suggested only in *post hoc* analyses. None of these four agents has been shown to be effective in preventing

non-vertebral fractures in patients with osteoporosis who do not have a vertebral fracture at baseline.⁷

Based on the RAND, WHO and ESCEO/IOF recommendations, it would appear that alendronate, risedronate and zoledronic acid all provide various types of fracture protection, and ibandronate vertebral fracture protection, for patients with PMO. A clinician presented with this evidence alone may therefore ask themselves whether either patient satisfaction or outcome is affected by the choice of bisphosphonate.

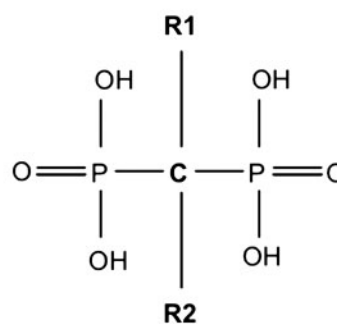
This article aims to address this question by looking at bisphosphonates from a number of different perspectives. We will explore how pharmacological differences among these drugs affect their potency and bioavailability, and whether these characteristics translate into differences in clinical efficacy. We will also examine the differences in clinical trial design and endpoints that add to the complexity of interpreting and comparing reported results. Differences in the safety of bisphosphonates are also considered, as this issue often wields a substantial influence on patient choice and preference. Based on these considerations, we aim to aid clinicians in the complex decision-making process involved in choosing a bisphosphonate therapy, and hope to facilitate a true evidence-based approach to PMO management, with an optimal outcome for all patients.

Distinguishing among bisphosphonates based on pharmacology

Chemical composition and implications

All of the commonly used bisphosphonates are characterized by two phosphate groups sharing a common carbon atom (Figure 1). The P–C–P backbone is responsible for the bisphosphonates' strong affinity for hydroxyapatite, and helps to effect the potent inhibition of bone metabolism that is characteristic of the bisphosphonate class.⁸ Both of the phosphate groups are important, because altering either or both diminishes both the agent's affinity for hydroxyapatite and its biochemical potency (Figure 2a and b).^{8,9} The R1 chain is typically a hydroxyl (OH) group, and this enables the agent to bind strongly to calcium. The composition of the R2 chain, in contrast, varies widely among bisphosphonates, and it is this that determines the agent's anti-resorptive potency. The anti-resorptive action of nitrogen-containing bisphosphonates results from their effects on the mevalonate pathway and, in particular, the enzyme farnesyl pyrophosphate synthase

Generic Bisphosphonate



R1 – enhances binding to hydroxyapatite
 -C- enhances chemical stability
 R2 – determines anti-resorptive potency

Figure 1. The chemical structure of bisphosphonate. The figure shows the structure of a generic bisphosphonate. Bisphosphonates' high affinity for bone is conferred by the phosphonate–carbon–phosphonate (P–C–P) backbone. This affinity can be enhanced by placement of a hydroxyl group in the R1 position. The anti-resorptive potency of the drug is determined by the structure of the R2 side chain.

(FPPS) (Figure 2c).¹⁰ The most potent bisphosphonates have an R2 chain containing a nitrogen atom (e.g. pamidronate, alendronate, risedronate, ibandronate, zoledronic acid). More potent still are those containing a nitrogen atom within a heterocyclic ring (e.g. risedronate and zoledronic acid) (Figure 2a).⁸

Bioavailability

The bioavailability of bisphosphonates has been determined by measuring the 24-h urinary excretion of drug after a single intravenous (IV) dose. The remainder is the amount retained by the skeleton. The bioavailability of bisphosphonates is generally correlated with their affinity for bone mineral. Thus, of the nitrogen-containing bisphosphonates, risedronate is the least bioavailable (65% excreted in the urine),¹¹ followed by ibandronate (50–60%),¹² alendronate (44%)¹³ and zoledronic acid (38%).¹⁴

The mode of administration of the bisphosphonate has a considerable effect on its absorption. As a class, bisphosphonates are poorly absorbed from the gastrointestinal tract. For example, when oral bisphosphonates such as alendronate and risedronate are administered, <1% of the dose is typically absorbed, regardless of the dose given.¹⁵ To maximize absorption, it is generally recommended that oral agents are taken on an empty stomach with plain water and that the patient fast for at least

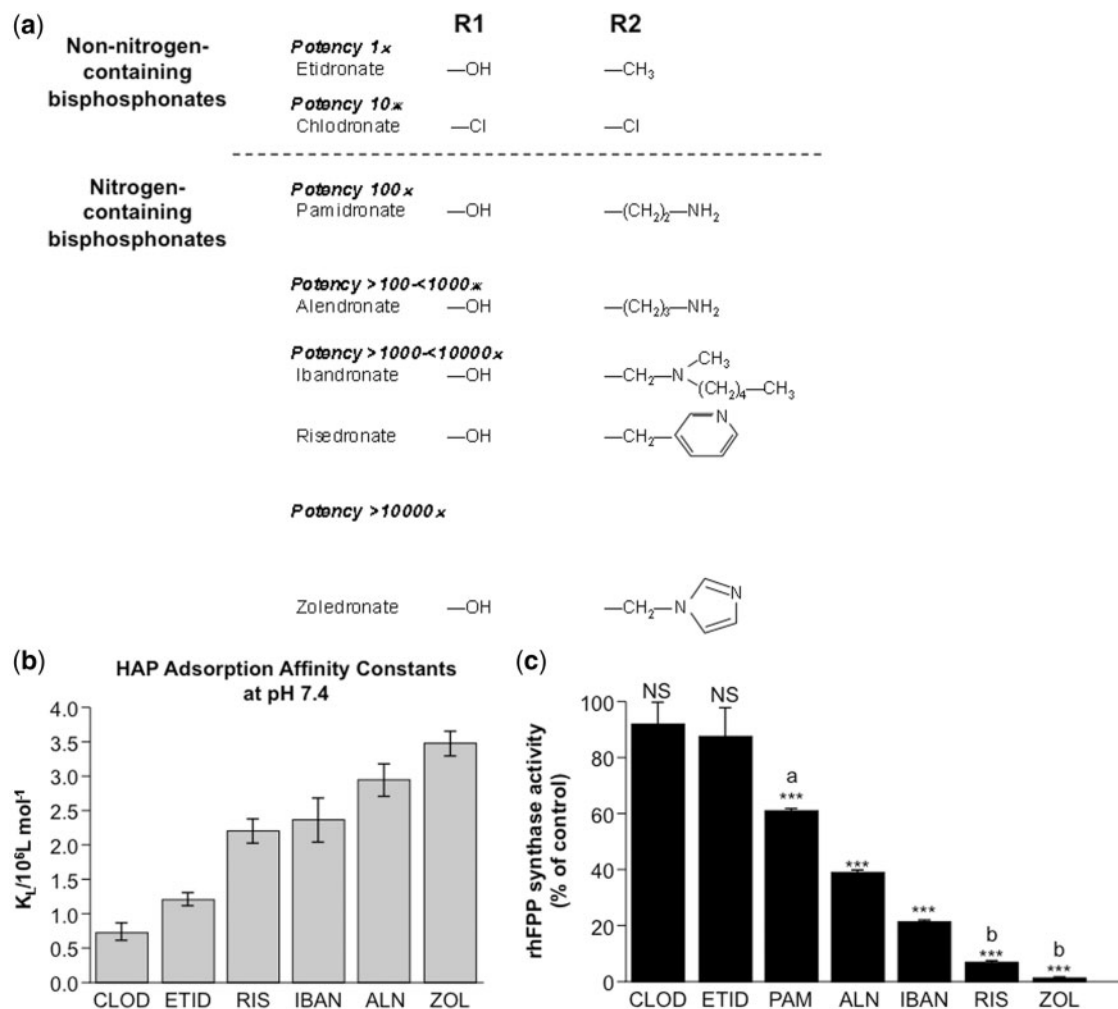


Figure 2. (a) Structure and relative potency of bisphosphonates.⁹⁴ Relative potency at inhibiting bone resorption in rats as compared with etidronate. The majority of the bisphosphonates that have been used in humans have a hydroxyl group in the R1 position. The R2 side chain is more variable in structure. (b) HAP adsorption affinity constants for the bisphosphonates under experimental conditions of growth (adapted from Nancollas *et al.*⁸). The data represent the mean \pm SD. Experiments were performed at pH 7.4 and were initiated by the introduction of known amounts of HAP crystallites to a solution of calcium chloride and potassium dihydrogen phosphate in sodium chloride. The low K_L (adsorption affinity constant) for clodronate is attributed to the absence of a hydroxyl position in the R1 position. Since all other bisphosphonates shown on the graph do have a hydroxyl in this position, it is evident that the configuration of the R2 group also influences binding to HAP. Reproduced with permission from Elsevier. Nancollas *et al.*⁸ (c) Inhibition of FPPS by bisphosphonates (adapted from Dunford *et al.*¹⁰). ALN: alendronate; CLOD: clodronate; ETID: etidronate; HAP, hydroxyapatite; IBAN: ibandronate; RIS, risedronate; ZOL, zoledronic acid; FPPS: farnesyl diphosphate synthase; PAM: pamidronate; NS: not statistically significant. A bacterial lysate containing recombinant human FPPS was preincubated with 0.1 mM bisphosphonate for 10 min before addition of substrate (¹⁴C isopentenyl diphosphate). The data represent the mean \pm SE of the mean of at least three independent experiments, expressed as a percentage of FPPS activity in the absence of bisphosphonate. *** $P < 0.001$ vs. control. * $P < 0.05$ vs. ALN. ** $P < 0.001$ vs. ALN (analysis of variance with Bonferroni's *post hoc* test). Reproduced with permission from the American Society for Pharmacology and Experimental Therapeutics.⁸

30 min afterwards. Patients are also instructed not to lie down for 30 min after taking the tablet. In the case of oral ibandronate, it is recommended that the patients neither eat nor lie down for 60 min after treatment administration.¹² It is important that patients comply with the instruction to fast for 60 min because a 48-week, oral ibandronate

non-inferiority study that evaluated the effects of 30- and 60-min post-treatment fasts on BMD concluded that reducing the post-dose fasting interval was associated with significant reductions in BMD gains.¹⁶

Many patients find the need for such fasting on a daily or even weekly basis to be inconvenient.

Intravenous administration of bisphosphonates (although also considered inconvenient by some) has been introduced in recent years to overcome this problem. When compared with oral dosing, IV administration has the added benefit of limiting systemic exposure. For example, neither IV ibandronate nor IV zoledronic acid are metabolized with ~50 and 62% principally bound to bone tissue, respectively. The remainder of the administered dose is excreted unchanged via the urine.^{12,14}

These data demonstrate how the bisphosphonates, despite possessing identical core structures, differ widely in their affinity for bone mineral, anti-resorptive potency and bioavailability. These differences are due to variations in their structure and mode of administration. In this sense, all bisphosphonates are definitely not the same. But do these largely imperceptible differences actually influence the clinical profile of bisphosphonates in the treatment of PMO? And are there any real, tangible differences among these drugs in anti-fracture efficacy?

Distinguishing among bisphosphonates based on clinical trial results in PMO

Pivotal placebo-controlled trials have demonstrated the efficacy of bisphosphonates in improving BMD at key skeletal sites, and have provided information on reducing the risk of bone fracture.^{17–20} In these trials, bisphosphonates consistently show an ability to increase BMD at key skeletal sites, particularly at the lumbar spine. When compared with placebo, mean improvements in the BMD of the lumbar spine of 6.2–6.6% have been observed with daily alendronate,^{17,20} 5.4–5.9% with daily risedronate,^{21,22} 5.2% with daily ibandronate¹⁹ and 6.7% with once-yearly zoledronic acid.¹⁸ The ability to improve BMD at other sites is more variable. For example, mean improvements in femoral neck BMD of 4.1–4.6 and 5.06% have been observed with daily alendronate^{17,20} and with once-yearly zoledronic acid, respectively;¹⁸ but mean improvements of just 1.6–3.1% have been seen with daily risedronate^{21,22} and 3.4% with daily ibandronate.¹⁹

Femoral neck BMD provides a robust surrogate marker of the risk of hip fracture. However, reduction of fracture risk at vertebral and non-vertebral sites is the most important clinical outcome of treatment with bisphosphonates. Interpretation of such results across trials with different agents is problematic because comparative data are limited. Differences in bone affinity and bioavailability

among agents might be expected to result in differences in clinical outcome, but comparison of trials using different agents is hampered by heterogeneity in patient populations and, in some cases, limitations of trial design.

A number of investigators have attempted to overcome the paucity of comparative data. For example, Rosen *et al.*²³ carried out a 12-month, randomized, double-blind trial that compared the effects of alendronate and risedronate (both administered once weekly) in women with PMO. These investigators found that alendronate was associated with significantly greater gains in BMD and reductions in markers of bone turnover than risedronate. However, the relative effects of these two treatments on fracture incidence were not assessed, and this study thus does not provide us with the data that we need to make a definitive comparison between these two treatments.

A study comparing the effects of a single dose of zoledronic acid with weekly alendronate in post-menopausal women with osteoporosis showed markers of bone resorption were significantly reduced at Weeks 1, 2, 4, 8, 12 and 24 after zoledronic acid treatment compared with alendronate. A significant difference between the two treatments for markers of bone formation was observed at Week 12 but not Weeks 4 or 24. In this study, the effects of either treatment on BMD or fracture incidence were not assessed and so direct comparisons in fracture efficacy between the treatments are not possible.²⁴

Other attempts to generate meaningful comparisons among agents have included use of post-marketing surveillance data. For example, eValuation of ibandronate efficacy (VIBE) was a retrospective, observational claims database study that used eligibility, pharmacy claims and medical claims data to compare fracture rates between female patients treated with monthly ibandronate ($n = 7345$) and those receiving weekly oral alendronate or risedronate ($n = 56\,837$).²⁵ The incidences of hip fracture, non-vertebral fracture and any clinical fracture were similar in the two groups of patients. However, the risk of vertebral fracture was significantly lower in the ibandronate-treated patients than in those who received weekly alendronate/risedronate [relative risk, 0.36, 95% confidence interval (95% CI): 0.18–0.75].

Post-marketing surveillance data were also used in the RisedronatE and ALendronate (REAL) cohort study, a retrospective comparison of the anti-fracture efficacy of once-weekly alendronate and risedronate in women aged ≥ 65 years that was based on health-care utilization records.²⁶ In this study, the 12-month incidences of non-vertebral and hip

fractures were significantly lower in the risedronate-treated group than in the alendronate group (non-vertebral fractures: 2.0% vs. 2.3%; $P=0.03$; hip fractures: 0.4% vs. 0.6%; $P=0.01$).

Another potential strategy to compare the efficacy of different bisphosphonates has been to calculate the number needed to treat (NNT) from each of the pivotal trials. The NNT is the number of patients who need to be treated with a drug over a fixed period of time to prevent the occurrence of one event, such as a fracture. It is the inverse of the absolute risk reduction. In a recently published analysis of treatment efficacy by NNT, zoledronic acid treatment was associated with an NNT of 14 for prevention of vertebral fracture over 3 years.²⁷ Alendronate, risedronate and zoledronic acid appeared to have similar influence on hip fracture with an NNT of 91 for each drug.²⁷ NNT depends mainly on the severity of the disease in the recruited population, hence fracture risk in the placebo group. For instance, NNTs for the same agent could be markedly different if determined in patient groups at low vs. high risk of fracture.²⁸ Thus, as a measure with which to compare treatments, NNT should be interpreted with caution.

Comparisons of outcomes based on post-marketing data and calculations of NNT may have a place in the medical evidence base, but they cannot replace well-designed, randomized, double-blind controlled trials. Table 1 summarizes the designs of the pivotal RCTs that have been performed to determine the efficacy and safety of bisphosphonates, and highlights the similarities and differences among studies.^{17–22,29,30} It is evident from the table that there are key differences among studies, particularly in terms of severity of disease at baseline and whether prior fracture was an inclusion criterion, an exclusion criterion, or neither. Trials were similar with regard to the mean age of patients. In terms of the alendronate trials, this would indicate that, of the patients previously treated in the fracture intervention trials (FIT)-1 and FIT-2, older patients were less likely to receive treatment in the fracture intervention trial long-term extension (FLEX) because of loss to the study or exclusion. In addition, patients in different trials received different regimens of calcium/vitamin D therapy, and in most cases this was given according to baseline parameters within each arm. The health outcomes and reduction in osteoporosis with zoledronic acid once-yearly pivotal fracture trial (HORIZON-PFT) incorporated a formal stratification made according to whether patients were taking osteoporosis medications at baseline (21% of patients in each arm). Table 1 also shows variation in discontinuation rates among trials using daily regimens. Discontinuation

is a particular issue with long-term daily oral therapy.

Most trials have assessed incidence of morphometric vertebral fractures as an endpoint. Morphometric vertebral fractures are radiographically confirmed fractures that cause a protocol-defined decrease from baseline in vertebral height. This decrease in height may be defined as a percentage change (e.g. ≥ 20 or $\geq 15\%$) or an absolute measurement (e.g. ≥ 4 mm). Some investigators use a semiquantitative grading system in addition to, or instead of, a quantitative system. The most widely used grading scheme has four categories that range from 0 (normal) through 1 (mild deformity, 20–25% reduction in height), 2 (moderate deformity, 25–40% reduction) and 3 (severe deformity, 40% reduction).³¹ This grading system relies on visual inspection.

A range of criteria for diagnosis of incident vertebral fractures was used in the studies summarized in Tables 1 and 2. These included quantitative criteria only, semiquantitative criteria only and a mixture of the two systems. Moreover, the quantitative criteria varied among studies ($\geq 20\%$ and ≥ 4 mm decrease in vertebral height in alendronate trials; $\geq 15\%$ decrease in risedronate trials). The European Medicines Agency's guideline on the evaluation of medicinal products in the treatment of primary osteoporosis specifies only that 'a carefully validated method with predefined criteria for diagnosis of fractures' should be used for assessment of vertebral fractures.² However, it is self-evident that differences among studies in the criteria used may affect the results. For example, higher diagnostic sensitivity but more false positives are achieved when fracture is defined as a reduction in vertebral height of $\geq 15\%$ than when the criterion is a reduction in height of $\geq 20\%$.³²

Some trials have also assessed incidence of clinical fractures (vertebral or non-vertebral) as secondary endpoints. These are identified symptomatically and reported as adverse events. Comparing the incidence of non-vertebral fractures among trials is particularly problematic because their definition varies, with several studies defining these fractures according to occurrence at just six sites, and others including almost all non-vertebral fractures (typical exceptions include fractures due to excessive trauma, and those involving the hands, feet, face and skull; Table 1, 2). Non-vertebral fractures are infrequent clinical events and non-vertebral fracture reduction as a primary endpoint in clinical trials requires relatively high-risk patients and very large study samples. Similarly, accurate determination of hip fracture rates also requires highly powered studies. Direct comparisons of clinical trial results

Table 1 Summary of trial designs for randomized, controlled trials of bisphosphonates used in the treatment of osteoporosis

Study (Ref)	ALN	FIT-2 ²⁰	FLEX ²⁹	RIS	VERT-MN ²²	HIP ³⁰	IBAN	ZOL	HORIZON-RFT ⁴¹
N	2027	4432	1099	2458	1226	9331	2946	7736	2127
Study duration (years)	3	4	5 (as extension to 5 years of prior alendronate)	3	3	3	3	3	Median follow up 1.9 years
Primary endpoint	Incidence of new vertebral fractures	Incidence of new clinical fractures	Total hip BMD	Incidence of new vertebral fractures	Incidence of new vertebral fractures	Incidence of hip fracture	Incidence of morphometric vertebral fractures	Incidence of vertebral fractures (stratum 1), hip fracture (all)	Incidence of new clinical fracture
Study treatment	Alendronate 5 mg/day, increased to 10 mg/day at 24 months vs. placebo	Alendronate 5 or 10 mg/day or placebo	Alendronate 5 mg/day plus vitamin D 250 IU/day (offered to all)	Risedronate 2.5 mg/day (discontinued after 1 year) or 5 mg/day or placebo	Risedronate 2.5 mg/day (discontinued after 1 year) or 5 mg/day or placebo	Ibandronate 2.5 mg/day or 20 mg every other day for 12 doses in 3 months or placebo	Ibandronate 2.5 mg/day or 20 mg every other day for 12 doses in 3 months or placebo	Zoledronic acid 5 mg, once yearly	Zoledronic acid 5 mg, once yearly
Supportive treatment	Calcium 500 mg/day plus vitamin D 250 IU/day, in women with low baseline calcium	Calcium 500 mg/day and vitamin D 250 IU/day (offered to all)	Calcium 1000 mg/day (all) and cholecalciferol up to 500 IU/day in women with low baseline vitamin D	Calcium 500 mg/day and vitamin D 400 IU/day (all)	Calcium 500 mg/day and vitamin D 400 IU/day (all)	Calcium 500 mg/day and vitamin D 400 IU/day (all)	Calcium 500 mg/day and vitamin D 400 IU/day (all)	Calcium 1–1.5 g/day and vitamin D 400–1200 IU/day (all)	Calcium 1–1.5 g/day and vitamin D 800–1200 IU/day (all)
Baseline patient and disease characteristics	Age 55–81 years, post-menopausal ≥ 2 years, femoral neck <i>t</i> -score -1.6 or less	Patients who received alendronate in FIT-1 and -2. Excluded if hip BMD reduced from FIT baseline	Age ≤ 85 years, stratified by number of vertebral fractures (one fracture plus lumbar <i>t</i> -score ≥ 2 or less vs. ≥ 2 fractures)	Age ≤ 85 years, and ≥ 2 vertebral fractures	Age ≤ 85 years, and ≥ 2 vertebral fractures	Age 70–79 years, with osteoporosis, or age ≥ 80 years, ≥ 1 non-skeletal risk factor for hip fracture, and low femoral neck <i>t</i> -score	Age 55–80 years, post-menopausal ≥ 5 years, 1–4 vertebral fractures and <i>t</i> -score of -2.0 to -5.0	Age 65–89 years, femoral neck <i>t</i> -score -2.5 or less, with or without fracture, -1.5 or less with two mild or one moderate fracture	Age ≥ 50 years, low-trauma hip fracture surgically repaired within previous 90 days
Fracture at baseline	Required for inclusion	Excluded	Required for inclusion	Allowed	Allowed	Allowed	Allowed	Allowed	Required
Definition of non-vertebral fractures	Any clinical fracture excluding pathological fractures, those due to excessive trauma, and those involving the face and skull	Any clinical fracture excluding pathological fractures, those due to excessive trauma, and those involving the face and skull	Six skeletal sites (clavicle, humerus, wrist, pelvis, hip, leg)	Six skeletal sites (clavicle, humerus, wrist, pelvis, hip, leg)	Six skeletal sites (clavicle, humerus, wrist, pelvis, hip, leg)	Six skeletal sites (clavicle, humerus, wrist, pelvis, hip, leg)	Six skeletal sites (clavicle, humerus, wrist, pelvis, hip, leg)	Any fracture except toe, facial bone, finger and fractures in trauma sufficient to cause fracture in a person without osteoporosis	Any fracture except toe, facial bone, finger and fractures in abnormal bone
Definition of new vertebral fractures	Decrease from baseline of 20% and ≥ 4 mm in vertebral height	Decrease from baseline of 20% and ≥ 4 mm in vertebral height	Decrease from baseline of $\geq 15\%$ in vertebral height and change from 0 (normal) on semiquantitative grading scale	Decrease from baseline of $\geq 15\%$ in vertebral height and change from 0 (normal) on semiquantitative grading scale	Decrease from baseline of $\geq 15\%$ in vertebral height and change from 0 (normal) on semiquantitative grading scale	N/A	Decrease from baseline of $\geq 20\%$ and ≥ 4 mm in vertebral height	Decrease from baseline of 20% and ≥ 4 mm in vertebral height and increase from baseline of ≥ 1 category on semiquantitative grading scale	Decrease from baseline of 20% in vertebral height and new or worsening back pain or decrease in vertebral height of $\geq 25\%$ with no baseline radiograph

(continued)

Table 1 Continued

Study (Ref)	ALN			RIS			IBAN			ZOL	
	FIT-1 ¹⁷	FIT-2 ²⁰	FLEX ²⁹	VERT-NA ²¹	VERT-MN ²²	HIP ²⁰	BONE ¹⁹	HORIZON-PFT ¹⁸	HORIZON-RFT ⁴¹		
Mean age in years \pm SD (Tx vs. placebo)	70.7 \pm 5.6 vs. 71.0 \pm 5.6	67.6 \pm 6.2 vs. 67.7 \pm 6.1	72.7 \pm 5.7 vs. 72.9 \pm 5.5 vs. 73.7 \pm 5.9	69 \pm 7.1 vs. 69 \pm 7.7 vs. 68 \pm 7.2	71 \pm 6.9 vs. 71 \pm 7.0 vs. 71 \pm 7.0	74 \pm 3.0 (stratum 1, both arms) vs. 83 \pm 3.0 (stratum 2 both arms)	69 \pm 6.0 (all arms)	73.1 \pm 5.34 vs. 73.0 \pm 5.4	74.4 \pm 9.48 vs. 74.6 \pm 9.86		
Mean femoral BMD \pm SD (Tx vs. placebo), g/cm ³ or t-score	0.57 \pm 0.07 vs. 0.56 \pm 0.07	0.592 \pm 0.06 vs. 0.593 \pm 0.06	0.62 \pm 0.07 vs. 0.61 \pm 0.07 vs. 0.61 \pm 0.07	0.597 \pm 0.103 vs. 0.593 \pm 0.105 vs. 0.602 \pm 0.102	0.583 \pm 0.105 vs. 0.573 \pm 0.098 vs. 0.576 \pm 0.093	t-score; 2.0 \pm 0.9 vs. 2.0 \pm 0.9 vs. 2.0 \pm 0.9	0.53 \pm 0.062 vs. 0.53 \pm 0.064	0.65 \pm 0.127 vs. 0.65 \pm 0.122			
Discontinuation rate	11–13%	17–19%	19–23%	42%	42%	50%	32–35%	N/A	23–25%		
Notes	Stratified according to risk (high risk: \geq 1 morphometric vertebral deformity or clinical fracture during FIT)						Stratified by concomitant osteoporosis therapy at baseline, stratum 1; no, stratum 2; yes			Patients were only required to have experienced a hip fracture and not have a diagnosis of osteoporosis	

ALN: alendronate; BMD: bone mineral density; BONE: oral ibandronate osteoporosis vertebral fracture trial in North America and Europe; FIT: fracture intervention trial; FLEX: fracture intervention trial long-term extension; IBAN: ibandronate; IU: international units; PFT: pivotal fracture trial; RFT: recurrent fracture trial; RIS: risedronate; HIP: risedronate-hip intervention program; SD: standard deviation; Tx: treatment; VERT-NA: vertebral efficacy with risedronate therapy-North America; VERT-MN: vertebral efficacy with risedronate therapy-multinational; ZOL: zoledronic acid.

should therefore be made with caution. It should also be noted that, with regard to daily bisphosphonate regimens, the required dosing over time may not be achieved in clinical practice, due to poor compliance.

In the FIT-1 and -2 studies, the 3- and 4-year risk reduction achieved with alendronate for morphometric vertebral fractures reached significance ($P \leq 0.001$ in each study; Table 2). Significant risk reduction for clinical vertebral fractures was also reported in FIT-1 ($P \leq 0.001$). However, the risk reduction did not reach significance for non-vertebral fractures (FIT-1, $P=0.063$; FIT-2, $P=0.13$), was just significant for hip fractures in FIT-1 ($P=0.047$), and not significant in FIT-2 ($P=0.44$). It should be noted that these studies were underpowered to assess these secondary endpoints. Limited benefit was seen with long-term alendronate therapy. In the FLEX extension study, the risk reduction for morphometric vertebral fractures was only 14% over years 5–10,²⁹ and this did not reach clinical significance (P -value not provided). These findings were supported by changes in markers of bone turnover such as alkaline phosphatase, C-telopeptide of type I collagen, and N-terminal propeptide of type I collagen, which declined during FIT-1 and remained relatively constant during FLEX. While benefits were not apparent for most endpoints, a significant risk reduction for clinical vertebral fractures was observed (5.3% with placebo vs. 2.4% with alendronate, relative risk reduction 55%) and women with a history of repeated clinical vertebral fractures may benefit from extended bisphosphonate therapy.

In the two key trials using risedronate that were carried out in North America [Vertebral Efficacy with Risedronate Therapy (VERT-NA)] and worldwide (VERT-MN), risedronate 5 mg significantly reduced the risk of new vertebral fractures ($P=0.003$ and <0.001 , VERT-NA and VERT-MN, respectively) and non-vertebral fractures ($P=0.02$ and 0.06 , VERT-NA and VERT-MN, respectively). Hip fracture was not a primary endpoint in either of these studies and neither study was powered to assess this endpoint. However, in the Risedronate Hip Intervention Programme (Risedronate-HIP), although hip fracture risk reduction did not reach significance in patients aged ≥ 80 years, the risk reduction was 40% ($P=0.009$) in the cohort of women aged ≤ 79 years who had osteoporosis at baseline.

In the oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe (BONE), ibandronate significantly reduced the risk of morphometric vertebral fracture when used daily ($P=0.0001$) or intermittently ($P=0.0006$). A significant risk reduction was also seen for clinical

vertebral fractures when ibandronate was used daily ($P=0.0117$) or intermittently ($P=0.0143$), but reductions in non-vertebral fractures were not significant in either treatment arm.

In the HORIZON-PFT, zoledronic acid 5 mg significantly reduced the risk of morphometric vertebral fractures ($P<0.001$), non-vertebral fractures ($P<0.001$) and hip fractures ($P=0.002$). The risks of other secondary fracture end points (all clinical fractures and clinical vertebral fractures) were also reduced in the zoledronic acid group (reductions of 33 and 77%, respectively; $P<0.001$ for both).

Assessment of markers of bone turnover in the HORIZON-PFT and VERT-MN indicated that effects occur early with a marked decline in the first 6 months and maintenance of this effect thereafter.^{18,22}

These data indicate that all of the bisphosphonates demonstrate efficacy in preventing vertebral fractures (Table 2), although it should be noted that patients with more severe disease (i.e. those with baseline vertebral fractures) were not included in the FIT-2 trial (Table 1). Ibandronate and zoledronic acid demonstrated the most persistent anti-fracture effect over time. The alendronate and zoledronic acid trials were both adequately powered to establish that treatment can reduce the risk of hip fractures (Table 2). Only zoledronic acid and risedronate significantly reduced the risk of non-vertebral fractures; this effect was not seen with alendronate or ibandronate treatment in the FIT-1/2 and BONE trials (Table 2).

Distinguishing among bisphosphonates based on safety data

As a class, bisphosphonates are associated with a number of side effects. Mode of administration has a major influence on the incidence of some of these adverse events. This is most notable for gastrointestinal adverse events (which predominate after oral administration) and infusion reactions (which predominate after IV administration). The following discussion uses standard designations to describe the incidence of side effects: very common (affects more than 1 user in 10); common (affects 1 to 10 users in 100); uncommon (affects 1 to 10 users in 1000); rare (affects 1 to 10 users in 10 000); very rare (affects <1 user in 10 000).

Gastrointestinal side effects

Gastrointestinal side effects that may occur after oral administration include dysphagia, oesophagitis and

Table 2 Incidence of fracture in randomized, double-blind, placebo-controlled trials

	ALN		RIS		IBAN	ZOL		
	FIT-1 ¹⁷	FIT-2 ²⁰	FLEX ²⁹	VERT-NA ²¹		VERT-MN ²²	HIP ³⁰	HORIZON-PFT ¹⁸
Vertebral (morphometric) Fracture incidence (%)								
Control	15	3.8	11.3	16.3	9.6	NA	10.9	3.8
Tx	8	2.1	9.8	11.3	Daily: 4.7 Intermittent: 4.9		3.3	1.7
RR (95% CI)	0.53 (0.41–0.68)	0.56 (0.39–0.80)	0.86 (0.60–1.22)	0.59 (0.43–0.82)	RRR—Daily: 62% (41–75%) Intermittent: 50% (26–66%)		0.30 (0.24–0.38)	0.54 (0.32–0.92)
Non-vertebral Fracture incidence (%)								
Control	14.7	13.3	19	8.4	8.2	11.2	10.7	10.7
Tx	11.9	11.8	18.9	5.2	Daily: 9.1 Intermittent: 8.9	9.4	8.0	7.6
RR (95% CI)	0.80 (0.63–1.01)	0.88 (0.74–1.04)	1.00% (0.76–1.32)	0.6 (0.39–0.94)	In patients with baseline femoral neck t-score <–3: Daily: 69% Intermittent: 37% (CI not stated)	0.8 (0.7–1.0)	0.75 (0.64–0.87)	0.73 (0.55–0.98)
Hip Fracture incidence (%)								
Control	2.2	1.1	3.0	N/A	NA	All: 3.9 Age group ≤79 years: 3.2	2.5	3.5
Tx	1.1	0.9	3.0	N/A	NA	All: 2.8 Age group ≤79 years: 1.9	1.4	2.0
RR (95% CI)	0.49 (0.23–0.99)	0.79 (0.43–1.44)	1.02 (0.51–2.10)	N/A	NA	All: 0.7 (0.6–0.9) Age group ≤79 years: 0.6 (0.4–0.9)	0.59 (0.42–0.83)	0.70 (0.41–1.19)

ALN: alendronate; BONE: oral ibandronate osteoporosis vertebral fracture trial in North America and Europe; FIT: fracture intervention trial; FLEX: fracture intervention trial long-term extension; IBAN: ibandronate; NA: not available; PFT: pivotal fracture trial; RIS: risedronate; RFT: recurrent fracture trial; RIS: risedronate-hip intervention program; RR: relative risk; RRR: relative risk reduction; Tx: treatment arm; VERT-NA: vertebral efficacy with risedronate therapy-North America; VERT-MN: vertebral efficacy with risedronate therapy-multinational; ZOL: zoledronic acid.

oesophageal or gastric ulcers, all of which have been reported after use of ibandronate, risedronate and alendronate.^{21,22,33–35} Clinical trials involving administration of ibandronate (150 mg monthly or 2.5 mg daily) describe oesophagitis, gastritis, gastro-oesophageal reflux disease, dyspepsia, diarrhoea, abdominal pain and nausea as common events, whereas oesophageal ulcerations, oesophageal strictures, dysphagia, vomiting and flatulence are classified as uncommon.¹² Clinical trials using alendronate have reported similar rates of upper gastrointestinal adverse events to those seen with oral placebo.³⁶ Local irritation of the upper gastrointestinal mucosa is believed to underlie the association between these events and bisphosphonate administration.¹² Gastrointestinal adverse events are also common after IV administration of bisphosphonates, but the incidence is similar in bisphosphonate- and placebo-treated patients.³⁷

It has been proposed that the gastrointestinal adverse events observed in association with bisphosphonate use may be related to the ability of these drugs to inhibit the enzyme FPPS, the action that produces their anti-resorptive efficacy. An *in vitro* study of the effects of alendronate and risedronate on normal human epidermal keratinocytes (NHEK), a model system of squamous epithelium of the type that covers the oesophagus, showed that both bisphosphonates inhibited growth of NHEKs without inducing apoptosis. The concentrations at which growth was inhibited were similar to those that might occur in oesophageal reflux after clinical dosing.³⁸

For all oral bisphosphonates, an important way to minimize the risk of gastrointestinal adverse events is by using a stringent administration regimen. The typical dosing regimen specifies that tablets are taken on an empty stomach with 200 ml (6–8 fluid ounces) of water and, as described previously, patients must fast and remain upright for at least 30 min (Table 3) to avoid epigastric pain. Failure to observe these precautions can expose patients to events such as oesophagitis, mucositis, nausea, vomiting and diarrhoea.

Acute phase reactions

An 'acute phase reaction' characterized by myalgia, arthralgia, fever, flu-like symptoms and mild headache is common/very common after IV administration of bisphosphonates.³⁷ The mechanism underlying this symptom complex is not fully understood but is thought to involve direct and indirect stimulation of $\gamma\delta$ T cells, which may lead to increased circulating levels of interleukin-6 and tumour necrosis factor- α .³⁹ The indirect stimulation

of $\gamma\delta$ T cells may be the result of the inhibition of FPPS by nitrogen-containing bisphosphonates and *in vitro* studies have shown that the potency of individual bisphosphonates to inhibit FPPS directly correlates with their ability to stimulate $\gamma\delta$ T cells. Inhibition of FPPS causes the accumulation of isoprenoid lipids, upstream of FPP in the mevalonate pathway, which then stimulates the proliferation and activation of $\gamma\delta$ T cells.⁴⁰

Symptoms of the acute phase reaction can be reduced with over-the-counter anti-inflammatory medications and usually resolve within 3 days of onset.^{12,18,41} All aspects of the acute phase reaction become substantially less frequent following the first dose. For example, in the HORIZON-PFT, the net rate (zoledronic acid minus placebo) of the acute phase reaction was 30% after the first dose, but 7 and 3% after the second and third infusions, respectively.⁴² Transient, flu-like symptoms with IV ibandronate given every 3 months are also typically associated with the first injection only.¹²

Acute phase reactions are typically reported in association with IV administration of bisphosphonates but are also described as common after monthly oral administration of ibandronate and as rare after daily and weekly oral administration of alendronate.^{12,33}

Cardiac side effects

Both oral and IV bisphosphonates have been associated with increased incidence of atrial fibrillation (AF). For example, secondary analyses of data from the Fracture Intervention Trial have suggested a greater risk of serious AF adverse events with alendronate than with placebo (1.5% vs. 1.0%).⁴³ Similarly, in the HORIZON-PFT, serious AF was more frequent in patients who received IV zoledronic acid than in those who received placebo (1.3% vs. 0.5%; $P < 0.001$).¹⁸ However, subsequent extensive analyses of other RCTs involving zoledronic acid, including the HORIZON-recurrent fracture trial (RFT),⁴¹ failed to demonstrate an increase in risk for AF. Moreover, a recent analysis of new data from the HORIZON-PFT/RFT trials found the increase in the risk of AF or atrial flutter with zoledronic acid treatment to be non-significant (hazard ratio = 1.25, $P = \text{NS}$). The only treatment-factor interaction that was statistically significant was age [HR = 0.963, $P < 0.067$ (significance threshold, $P < 0.10$)]. This interaction could be due to a greater increase in risk with age in the placebo group than in the zoledronic acid group (difference in risk between patients aged 75–84 years and those ≥ 85 years: placebo, 2.7%; zoledronic acid, 1.9%).⁴⁴

Table 3 Bisphosphonates approved for use in post-menopausal osteoporosis by the European Medicines Agency

Bisphosphonate	Indications in PMO	Route of administration	Dose and frequency of administration	Administration requirements
Alendronate	<ul style="list-style-type: none"> • Treatment of PMO to reduce the risk of vertebral and hip fractures • Treatment of PMO to prevent fractures • Treatment of glucocorticoid-induced osteoporosis and prevention of bone loss in post-menopausal women considered at risk of developing the disease • Treatment of osteoporosis in post-menopausal women at increased risk of vertebral fracture 	Oral	One 70 mg tablet once a week	<p>Must be taken with water only at least 30 min before the first food, beverage, or medicinal product of the day. Patients should not eat or lie down for at least 30 min after dosing.</p> <p>Must be taken with water only at least 30 min before the first food, beverage, or medicinal product of the day. Patients should not eat or lie down for at least 30 min after dosing.</p>
Ibandronate	<ul style="list-style-type: none"> • Treatment of osteoporosis in post-menopausal women at increased risk of vertebral fracture 	Oral	One 150 mg tablet once a month	<p>Should be taken after an overnight fast (at least 6 h) with plain water, at least 1 h before the first food, beverage, or medicinal product of the day. Patients should not eat or lie down for at least 1 h after dosing. Ibandronate should be taken on the same date each month.</p> <p>Administered as an intravenous injection (3 mg in a prefilled 3 ml syringe of solution) over 15–30 s.</p> <p>Should be taken at least 30 min before the first food, beverage, or medicinal product of the day. Alternatively, risedronate can be taken between meals (2 h before and at least 2 h after any food, medicinal product or drink other than plain water), or in the evening (at least 2 h after the last food, medicinal product or drink, other than plain water, of the day, and at least 30 min before going to bed). Patients should not eat or lie down for 30 min after dosing.</p>
Risedronate	<ul style="list-style-type: none"> • Treatment of PMO: <ul style="list-style-type: none"> ◦ To reduce the risk of vertebral fractures ◦ To reduce the risk of hip fractures • Prevention of osteoporosis in post-menopausal women at increased risk of osteoporosis • To maintain or increase bone mass in post-menopausal women undergoing long-term (>3 months) systemic glucocorticoid treatment at doses ≥ 7.5 mg/day prednisone or equivalent • Treatment of PMO: <ul style="list-style-type: none"> ◦ To reduce the risk of vertebral fractures ◦ To reduce the risk of hip fractures 	Intravenous injection Oral	3 mg every 3 months 5 mg once a day	<p>Should be taken at least 30 min before the first food, beverage, or medicinal product of the day. Patients should not eat or lie down for 30 min after dosing.</p> <p>Risedronate 35 mg should be taken on the same day each week.</p> <p>Administered via a vented infusion line (5 mg in 100 ml ready-to-infuse solution) over 15 min or more. In patients with a recent, low-trauma hip fracture, administration is recommended ≥ 2 weeks after hip fracture repair.</p>
Zoledronic acid	<ul style="list-style-type: none"> • Treatment of PMO • Prevention of PMO • Treatment and prevention of osteoporosis associated with long-term (≥ 12 months) systemic glucocorticoid therapy 	Intravenous infusion	5 mg once a year	<p>Administered via a vented infusion line (5 mg in 100 ml ready-to-infuse solution) over 15 min or more. In patients with a recent, low-trauma hip fracture, administration is recommended ≥ 2 weeks after hip fracture repair.</p>

It has been suggested that the conflicting data on AF risk in the HORIZON studies, with an increased incidence seen in HORIZON-PFT, could be an artefact induced by the multiple comparisons.⁴⁵ In the HORIZON-PFT, in 47 of the 50 zoledronic-acid treated patients with an adjudicated serious adverse event of AF, the event occurred >30 days after infusion, by which time zoledronic acid is undetectable in the circulation.¹⁸ The link between oral alendronate administration and serious AF adverse events has also been called into question by the results of a recent population-based case-control study involving data from 13 586 patients with AF or atrial flutter and 68 054 controls.⁴⁶ The adjusted relative risk for these conditions associated with current use of bisphosphonates (etidronate or alendronate) was 0.95 (95% CI: 0.84–1.07), thus refuting the suggestion that oral bisphosphonates increase the risk of AF or atrial flutter.

To date, no convincing mechanism has been proposed to account for the potential association between bisphosphonate use and risk of AF, and no effect of dose or duration of therapy on the incidence of AF has been shown.⁴⁷ These findings, combined with the clinical trial data, led the United States Food and Drug Administration (FDA) to conclude in 2008 that there is no clear association between overall bisphosphonate exposure and the rate of serious or non-serious AF and that health-care professionals should not alter their bisphosphonate prescribing patterns on the basis of this purported association.⁴⁸

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported as a complication of both oral and IV bisphosphonate administration. Most cases have occurred in oncology patients who have received high-dose IV bisphosphonates as part of their chemotherapy, although the condition has also been reported in patients with benign bone diseases such as PMO or Paget's disease. Current risk estimates for bisphosphonate-associated ONJ in osteoporosis patients range from 1 per 20 000 to 1 per 100 000 patient-years.^{49–51} However, it is difficult to make accurate frequency estimates because ONJ remains a poorly defined condition. In the HORIZON-PFT (the only bisphosphonate clinical trial to have included adjudication for ONJ), this condition was reported in one patient treated with zoledronic acid and one patient who received placebo (incidence of 0.026% for both). Both patients recovered.^{18,52}

Osteonecrosis of the jaw is also very rare after oral administration of bisphosphonates. The low incidence of this event is demonstrated by the results

of a 2009 systematic review that identified 1850 cases of ONJ in 92 publications between 1966 and 26 January 2008. Of these, only 59 cases (3.2%) involved the use of oral bisphosphonates (alendronate, clodronate or risedronate), with the remainder involving treatment with IV ibandronate, pamidronate or zoledronic acid.⁵⁰

The pathogenesis of ONJ is poorly understood and the mechanism for involvement of bisphosphonates—if any—is unknown. Alterations in angiogenesis or bone turnover, delayed epithelialization, immunocompromise and infection have all been proposed as causative factors, and a potential role for bisphosphonates in many of these factors has been proposed but not substantiated.⁵² A consensus document that resulted from an expert meeting convened by the ESCEO and the Foundation for Research on Osteoporosis and other Bone Diseases came to a number of conclusions, all of which are relevant to clinicians who prescribe bisphosphonates. The panel concluded that the incidence of ONJ in patients taking bisphosphonates for osteoporosis is very low, that the majority of ONJ cases occur after tooth extraction, that there are no data that unequivocally link the development of ONJ to bisphosphonate intake in osteoporotic patients, and that the underlying risk of developing ONJ may be increased in osteoporotic patients by comorbid diseases and administration of immunosuppressive drugs.⁵²

Atypical subtrochanteric fractures

In recent years, an association between atypical fractures and long-term bisphosphonate therapy has been reported in several clinical case reports and case reviews. In particular, these involve fractures of the subtrochanteric or diaphyseal femur, predominantly following long-term oral alendronate use.^{53–59} Secondary analysis of data from three large, randomized bisphosphonate trials (FIT, FLEX and HORIZON-PFT) identified fractures of the subtrochanteric or diaphyseal femur in 10 patients [six bisphosphonate treated (0.077%), four placebo treated (0.053%)] and an overall incidence of 2.3 per 10 000 patient-years.⁶⁰ Compared with placebo, the relative hazard in bisphosphonate-treated patients was 1.03 (95% CI: 0.06–16.46) for oral alendronate use in the FIT trial, 1.50 (95% CI: 0.25–9.00) for IV zoledronic acid use in the HORIZON-PFT trial, and 1.33 (95% CI: 0.12–14.67) for continued oral alendronate use in the FLEX trial. Black *et al.*⁶⁰ concluded that the incidence of fracture of the subtrochanteric or diaphyseal femur was very low, even among women who had received bisphosphonate therapy for 10 years, but that their study was

underpowered to reach definitive conclusions regarding an association with bisphosphonate use.

Further insight is available from a recently published systematic literature search of case/case series studies that summarized data from 141 cases of atypical femoral fracture in women who had been treated with a bisphosphonate at a dosing regimen suitable for the prevention or treatment of osteoporosis.⁶¹ This article, which defines these fractures predominantly as insufficiency fractures, summarizes some of the clinical features that may allow identification of the bisphosphonate-treated patients who are at the greatest risk of developing atypical fractures and shows that long-term bisphosphonate therapy is not a prerequisite for their development. It also highlights the use of glucocorticoids and proton pump inhibitors as important risk factors.

A 2008 bisphosphonate class review by the Committee for Medicinal Products for Human Use (CHMP) concluded that there is an association between atypical stress fractures and long-term use of alendronate, but uncertainty concerning the existence of a class effect.⁶² This led to a new special warning/precaution being included on the alendronate label that advised discontinuation of therapy in patients with stress fracture pending performance of an individual benefit-risk assessment.⁶³ Possible mechanisms by which alendronate may predispose to atypical femoral fractures include accumulation of microdamage/microfractures, decreased repair and impaired healing in bone, suppression of bone turnover, increased mineralization leading to development of brittle bones, and inadequate mineralization.⁶² However, we do not know whether these mechanisms apply to all nitrogen-containing bisphosphonates and/or other strong resorption inhibitors. An association with atypical subtrochanteric fractures may only have been found for alendronate thus far because it has been on the market for longest, and therefore has the greater volume of follow-up data available. A recently published position statement by the European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, and International Osteoporosis Foundation (ECCEO-IOF) Working Group concluded that, although bisphosphonate use may be associated with atypical subtrochanteric fractures, the case thus far remains unproven.⁶⁴

Bone pain

Bisphosphonates are widely used for the control of bone pain in patients with cancer.⁶⁵ However, somewhat ironically, bone pain may also be a side effect of bisphosphonate use. Such bone pain may occur as part of the acute phase reaction that occurs

in some patients after IV administration of bisphosphonates or may occur as an uncommon isolated symptom after oral administration of bisphosphonates.¹² Placebo-controlled trials involving IV administration of bisphosphonate to patients with osteoporosis have shown that this adverse event is of variable incidence, but may be common in both zoledronic acid- and placebo-treated patients (2-year post-low trauma hip fracture study: bone pain recorded in 3.2 and 1.0% of zoledronic acid- vs. placebo-treated patients, respectively; 3-year study in PMO patients: bone pain recorded in 5.8 and 2.3% of patients, respectively).³⁷

Renal dysfunction

Renal dysfunction is a known class effect of bisphosphonates and both oral and IV administration are contraindicated in patients with severe renal impairment.^{12,33,37,66} As a result, patients with creatinine clearance of <30 ml/min are usually excluded from bisphosphonate clinical trials and the effects of bisphosphonates on this group have not been quantified. Trials involving zoledronic acid have recorded a transient increase in serum creatinine levels within 10 days of dosing in 1.8% of zoledronic acid-treated patients and 0.8% of placebo-treated patients, all of which resolved without specific therapy.³⁷ Moreover, a renal safety analysis carried out as part of HORIZON-PFT found no cumulative impact on renal function of long-term (over 3 years) zoledronic acid administration and no difference in mean calculated creatinine clearance between zoledronic acid- and placebo-treated patients.⁶⁷ However, recent post-marketing data from the FDA show that 24 evaluable cases of renal impairment and acute renal failure associated with use of zoledronic acid in osteoporosis and Paget's disease of bone were reported in the 17 months to February 2009. Fourteen of the 24 patients had underlying medical conditions associated with risk of renal impairment or acute renal failure, or had been exposed to nephrotoxic drugs. Many patients improved following IV fluid administration or other supportive care. Seven patients died, although no association between zoledronic acid use and these deaths has been established. Based on these reports, the zoledronic acid label in the USA has been updated to include data on acute renal failure and advice for physicians, with recommendations that serum creatinine should be monitored before and after each infusion in patients with pre-existing renal compromise or other risk factors such as concomitant nephrotoxic medications or diuretic therapy.⁶⁸

The mechanism by which bisphosphonates cause renal compromise has not been established. Renal precipitation of bisphosphonate aggregates or calcium complexes has been suggested, but is poorly supported by preclinical studies.⁶⁹ In nitrogen-containing bisphosphonates, the adverse effect on renal function may be mediated *via* inhibition of FPPS (i.e. the same mechanism by which these agents affect osteoclast function).^{69,70}

Oesophageal cancer

Cases of oesophageal cancer in oral bisphosphonate-treated patients have been reported by an official letter from the FDA.⁷¹ Twenty-three cases of oesophageal cancer following alendronate use were reported to the FDA between October 1995 and May 2008. Eight of these patients died. The median time to diagnosis of oesophageal cancer from the start of alendronate use was 2.1 years. During the same period, a further 31 cases—of which six were fatal—were reported in Europe and Japan following alendronate use. Six of these cases also involved use of risedronate, ibandronate, or etidronate. Thus, physicians should avoid prescribing oral bisphosphonates to patients with known risk factors for oesophageal cancer, such as Barrett's oesophagus.⁷¹

However, these limited data should be interpreted with caution due to the lack of a control group. Also, the median time to diagnosis was too brief to be suggestive of a causal relationship between the drug and the disease,^{72,73} and little comparison is provided in the form of expected rates of oesophageal cancer in, for example, post-menopausal women. In addition, no data on the patients' medical history are presented.⁷⁴ Therefore, it is possible that some or all of the affected patients had pre-existing disease.

Retrospective studies of registry data, where bisphosphonate-treated patients were compared with bisphosphonate-naïve patients, have since shown that there is no increase in the incidence rate of oesophageal cancer with bisphosphonate use, and that there may even be a significant protective effect.^{75,76} Thus, it is clear that large RCTs are required to further elucidate this relationship, with a sufficient exposure time and follow-up, and with analyses for confounding variables.

Mortality benefit

It has only recently become evident that the reduction in fracture risk associated with effective management of osteoporosis is associated with a reduction in mortality. For example, in the HORIZON-RFT trial, annual administration of

zoledronic acid was associated with a significant 28% reduction in all-cause mortality in patients who had undergone surgical repair of hip fracture prior to treatment initiation.⁴¹ This finding is supported by the results of a recent meta-analysis of randomized, placebo-controlled trials in which patients with osteoporosis received approved doses of medications with proven efficacy in preventing both vertebral and non-vertebral fractures.⁷⁷ Synthesis of data from eight studies that involved administration of risedronate, strontium ranelate, zoledronic acid, or denosumab revealed that treatment was associated with an 11% reduction in mortality ($P=0.036$). This beneficial effect of therapy on mortality was not related to either patient age or the incidence of fracture (hip or non-vertebral), but was most substantial in the trials with higher overall mortality rates. This led the authors to conclude that osteoporosis therapies with proven anti-fracture efficacy reduce mortality in older, frailer individuals who are at high risk of fracture.⁷⁷

This summary of adverse event data shows that all bisphosphonates are not the same regarding safety. In particular, oral risedronate and alendronate differ in some aspects from IV ibandronate and zoledronic acid; for example, they are more associated with gastrointestinal adverse events, while the latter are more associated with the acute phase reaction.

Treatment decisions and selecting the appropriate therapy

When pharmacological properties, efficacy and safety are collectively taken into account, evidently all bisphosphonates are not the same. The RAND CER, WHO and ESCEO/IOF recommendations all state that risedronate and alendronate provide comprehensive fracture protection.^{5–7} Yet clinical trial data suggest that zoledronic acid provides the most comprehensive fracture protection, and is the only bisphosphonate with proven anti-fracture efficacy in the post-hip fracture population.⁷⁸ Furthermore, all bisphosphonates reviewed in this article are highly effective in preventing the most common type of fracture—vertebral fracture⁷⁹—in women with PMO. Therefore, how does a clinician choose a first-line treatment?

The answer is that all of the bisphosphonates reviewed in this article are a suitable first-line treatment for women with PMO. The clinical data reveal no evidence to suggest that a particular therapy should be elevated to first-line status, or indeed relegated to second- or third-line status. The clinical decision on first-line treatment should therefore be largely based on a combination of clinical judgment

and, where appropriate, patient preference. Data that should be borne in mind, however, are the documented differences in efficacy and compliance between generic and branded bisphosphonates. For example, a recent retrospective study found that 1 year of treatment with generic alendronate was associated with significantly lower increases in BMD at the lumbar spine (2.8%) and total hip (1.5%) than treatment with branded alendronate (Fosamax: 5.2 and 2.9%, respectively) or branded risedronate (Actonel: 4.8 and 3.1%, respectively).⁸⁰ The persistence of patients who received generic alendronate (68% still taking treatment after 12 months) was also significantly lower than with either of the branded products (Fosamax, 84%; Actonel, 94%). This study was not designed to determine the reasons why the BMD increases associated with the generic product were 40–50% lower than the branded products, although the difference in persistence is likely to be a factor. These data should be of concern to clinicians in countries such as the UK, where the National Institute of Health and Clinical Excellence guidance requires patients to be prescribed alendronate in the first instance. Clinicians are advised that alternative treatments such as risedronate or etidronate should only be prescribed if patients are intolerant of alendronate or unable to comply with the dosing instructions.⁸¹ Differences between generic and branded bisphosphonates led the National Osteoporosis Foundation of South Africa to issue a statement in 2006 expressing concern that available information on generic alendronate may not be sufficient to determine its long-term efficacy and safety, and noting that the South African Medicines Control Council had placed alendronate on its 'non-substitutable' list for similar reasons.⁸² Until more data become available, it therefore seems prudent to be cautious in the prescription of generic bisphosphonates.

One of the main considerations faced by clinicians in determining which bisphosphonate to prescribe is the mode of administration. The ability of a patient to adhere to treatment regimens is an important factor in this choice. Oral bisphosphonates are associated with similar costs to IV bisphosphonates (although generic oral bisphosphonates are less expensive); however, oral products are associated with poor compliance/adherence.^{83,84} Several studies have shown that patients with high levels of adherence to osteoporosis medication have significantly lower fracture rates than those with low levels of adherence, with risk reductions for overall fractures averaging ~20%.^{83,85–87} Thus, oral medications are useful for patients who have disciplined lifestyles, who are therefore more likely to be adherent to treatment.

The IV bisphosphonates may improve adherence to therapy, and they are useful for patients who are unable or unwilling to take oral medications or who have experienced a fracture while taking oral medications, as this is likely to be due to poor adherence. There is evidence to show that it is safe to switch from an oral to an IV bisphosphonate in this way.⁸⁸ Adherence plays a vital role in the economics of fracture protection. There is no real-life effectiveness with oral bisphosphonates if compliance is <50%, and typical compliance with oral bisphosphonates over 2 years is just 43%.⁸³ The difference in adherence between a yearly and weekly administered treatment would result in fewer fractures with IV compared with oral bisphosphonates and therefore lower real-life costs.⁸⁹ Cost calculations of poor adherence and 'wasted' oral bisphosphonates led Sheehy *et al.*⁹⁰ to suggest that bisphosphonates with less frequent dosing regimens, such as a once-yearly medication, should be investigated further as these would constitute the equivalence of 'perfect adherence with weekly or monthly presently available oral bisphosphonates'. In fact, IV bisphosphonates are proven to be more cost effective than branded oral bisphosphonates in women with PMO.⁹⁰

Another crucial aspect of choosing a bisphosphonate is the patient's medical history. Oral bisphosphonates should be used with caution in patients with a history of oesophageal disorders that delay oesophageal transit or emptying, or who have a history of oesophageal or upper gastrointestinal problems. The patient must also be capable of maintaining an upright position for at least 30 min after taking the tablet.

Ibandronate should not be used in patients with a history of, or risk factors for, non-vertebral (including hip) fractures, as there is no clinical evidence to support its use in such patients. Similarly, clinical evidence suggests that in patients with a history of, or at high risk of, hip fracture, alendronate and zoledronic acid are more efficacious than risedronate in reducing hip fracture risk.^{17,18,20–22}

The only data that we currently have that give efficacy comparisons among bisphosphonates are from post-marketing surveillance studies. As discussed above, the VIBE study found a significantly lower risk of vertebral fracture in patients treated with monthly ibandronate than in those who received weekly alendronate/risedronate²⁵ and the REAL study showed that weekly risedronate is associated with significantly lower incidences of non-vertebral and hip fracture than weekly alendronate.²⁶

Another major factor in treatment choice is patient preference. In patients who are already taking

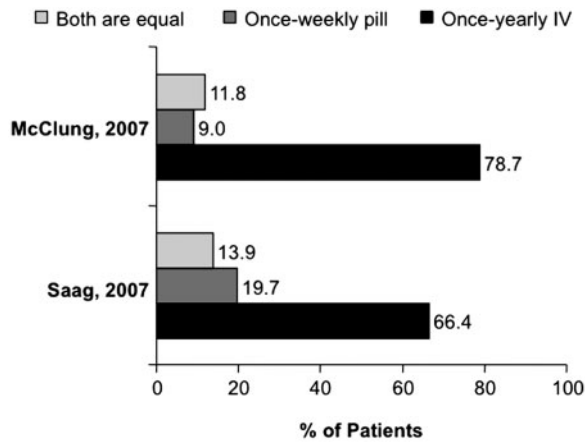


Figure 3. Patient preference for once-yearly intravenous therapy.^{24,88} Two separate studies have demonstrated that the majority of post-menopausal women with low bone density prefer an annual intravenous treatment to once-weekly oral treatment.

a number of concomitant medications, or who have lifestyles that do not accommodate frequent, strict dosing regimens, a quarterly or once-yearly intravenous medication may be welcomed. Conversely, many patients prefer oral medications and the control associated with it. A minority of patients—approximately one in five—may have a fear of needles^{91,92} and therefore avoid IV options, although this is more than twice as likely to occur in people aged under 50 years than those over 50.⁹² Clinical trials of bisphosphonate therapy have shown that annual IV dosing is generally preferred by patients to weekly oral regimens. In a 24-week RCT that compared annual infusion of zoledronic acid 5 mg and oral weekly alendronate 70 mg in post-menopausal women with low bone density, 66.4% of the patients who completed an end-of-study questionnaire expressed a preference for the once-yearly IV infusion, compared with 19.7% who preferred a once-weekly pill. Just 13.9% considered both treatment modalities equal.²⁴ Similarly in a 1-year RCT of post-menopausal women with low BMD on alendronate who were randomized to continue with oral weekly alendronate 70 mg or switch to zoledronic acid 5 mg infusion, 78.7% of patients preferred a once-yearly infusion (Figure 3).⁸⁸

Conclusions

International treatment guidelines recommend the use of bisphosphonates as first-line therapy in patients with osteoporosis, with the prime objective of reducing the number of osteoporotic fractures. Selection of a specific bisphosphonate for treating

PMO should be based on a review of efficacy data, risk profile, inclination of the patient and the cost-effectiveness of the therapy.⁹³ The advantages and disadvantages of each viable option should always be presented to the patient and the importance of the patient's preferences acknowledged. Overall, all bisphosphonates are potential first-line treatments for PMO. Their efficacy and favourable risk–benefit profile, as well as their possible mortality benefit, have set high standards in the field, such that emerging drugs for PMO must have equal or better benefits. Ultimately, the choice of bisphosphonate treatment is largely dependent on the individual patient.

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