Optimizing dosing frequencies for bisphosphonates in the management of postmenopausal osteoporosis: patient considerations

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Abstract: Postmenopausal osteoporosis is common and underrecognized among elderly women. Osteoporotic fractures cause disability and disfigurement and threaten patients' mobility, independence, and survival. Care for incident fractures in this age group must go beyond orthopedic repair, to assessment and treatment of the underlying bone fragility. Fracture risk can be reduced by vitamin D and calcium supplementation along with antiresorptive drug treatment. First-line osteoporosis pharmacotherapy employs nitrogen-containing bisphosphonates. The inconvenience of daily oral treatment has motivated development of weekly, monthly, and intermittent oral regimens, as well as quarterly and yearly intravenous (iv) regimens. Ibandronate is the first bisphosphonate to have shown direct anti-fracture efficacy with a non-daily regimen; it was approved for once-monthly oral dosing in 2005 and for quarterly iv dosing in 2006. Intermittent oral risedronate and yearly iv zoledronic acid were approved in 2007. Newly available regimens with extended dosing intervals reduce the inconvenience of bisphosphonate therapy and provide patients with a range of options from which to select a maximally sustainable course of treatment. This review discusses the development, efficacy, safety, and tolerability of extended-interval bisphosphonate regimens and examines their potential to improve patient acceptance and long-term success of osteoporosis treatment.

Keywords: ibandronate, alendronate, risedronate, zoledronic acid, adherence, persistence

Background

Osteoporosis – a progressive loss of bone strength and quality that multiplies fracture risk – is a common and underrecognized hazard to postmenopausal women. Its prevalence among US women ranges from 26% at age 65 years and older to over 50% at age 85 years and older (US Department of Health and Human Services 2004), reflecting an altered balance of bone turnover that begins immediately upon menopause and increases steadily with age (Garnero et al 1996b). Fortunately, osteoporosis is eminently preventable and treatable. Lifelong attention to nutrition and exercise, bone density monitoring after menopause, and appropriate treatment of diagnosed osteoporosis can reduce the burden of disability, cost, and mortality.

Bone densitometry by dual-energy X-ray absorptiometry (DXA), which measures bone mineral density (BMD), is the canonical method for diagnosing osteoporosis (Briot and Roux 2005). The relationship between low BMD and fracture is stronger than the relationship between cholesterol and heart attacks (US Department of Health and Human Services 2004). Judicious BMD testing should be considered in at-risk postmenopausal women, in younger women with multiple risk factors, and in all patients who present with fragility fractures or take medications that can reduce BMD (US Department of Health and Human Services 2004). At a minimum, BMD screening of all men and women should be considered at 65 years of age.

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The World Health Organization (WHO) defines osteoporosis as a BMD T-score of ≥2.5 standard deviations below the gender-specific young adult mean, as measured by DXA (World Health Organization 1994). However, total fracture risk reflects both BMD-dependent and BMD-independent risk factors (Kanis et al 2007). The 2008 National Osteoporosis Foundation practice guidelines (National Osteoporosis Foundation 2008) (Table 1) utilize FRAX™, the new WHO absolute fracture risk algorithm (Kanis 2008), which takes into account BMD, age, smoking, alcohol intake, personal or parental history of fracture, body mass index, corticosteroid use, and rheumatoid arthritis to predict individual patients' 10-year probability of sustaining osteoporotic fractures.

Osteoporotic fractures, with an estimated annual incidence of 2 million among US citizens aged 50 years or older (Burge et al 2007), have severe physical, economic, and psychosocial consequences. Direct physical consequences include temporary or permanent disability and disfigurement. If fracture sufferers become bedfast, indirect consequences such as decubitus ulcers, pneumonia, and urinary tract infections may result (US Department of Health and Human Services 2004). Mortality risk increases 2.8- to 4-fold during the first 3 months after a hip fracture (US Department of Health and Human Services 2004). In the US, 500,000 hospitalizations, 800,000 emergency room visits, and 180,000 nursing home placements yearly are attributable to osteoporotic fractures (US Department of Health and Human Services 2004), requiring annual direct care expenditures estimated at US$16.9 billion and total costs exceeding US$19 billion (2005 dollars) (Burge et al 2007). A 2007 case-control study reported incremental costs of US$4,007 per Medicaid beneficiary or US$5,370 per Medicare beneficiary during the first post-fracture year (Rousculp et al 2007).

A particularly distressing cost of osteoporosis to elderly patients and their families is potential loss of independence. Fracture sufferers often lose more mobility through fear than they lose to the direct effects of injury. This effect can synergize with the direct effects of fractures on mobility and morbidity to cause self-perpetuating inactivity, social isolation, and functional dependence, often culminating in institutionalization (US Department of Health and Human Services 2004).

Calcium and vitamin D supplementation are essential in the prevention and therapy of osteoporosis and have been used in all of the major trials of osteoporosis drugs (Sunyecz and Weisman 2005). The US Institute of Medicine's estimated adequate intakes for adults aged ≥50 years are 1200 g calcium (with ≥700 mg preferably derived from diet) and 800–1000 units vitamin D (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 1997). Calcium supplementation (1000 mg/day) prevents BMD loss and may reduce vertebral fractures in postmenopausal women, as shown in a meta-analysis by the Agency for Health Research and Quality (MacLean et al 2008). Vitamin D (700–800 international units/day) with or without calcium reduced hip and non-vertebral fractures versus placebo in another meta-analysis (Bischoff-Ferrari et al 2005).

Table 1 Diagnostic categories of BMD and appropriate clinical responses (World Health Organization 1994; Healy 1998; Hodgson et al 2001; Kanis 2008)

Classification	T-score	Clinical response
Normal	Exceeding −1	• Reassure • Encourage adequate calcium and vitamin D intake and weight-bearing exercise
Osteopenia	< −1 to > −2.5	• Maintain nutrition and exercise • Assess risk factors (personal or family history of fracture, smoking, alcohol intake 3 units/day, low body weight, corticosteroid use, rheumatoid arthritis) • Consider bisphosphonate treatment if 10-year hip fracture probability is ≥3% or probability of any major osteoporotic fracture is ≥20% by regionally appropriate WHO model at http://www.shef.ac.uk/FRAX/index.htm
Osteoporosis	−2.5 or less	• Maintain nutrition and exercise • Assess and reduce risk of falls • Institute bisphosphonate therapy
Severe osteoporosis	−2.5 or less and fragility fracture	• Maintain nutrition and supervised/adapted exercise (avoiding spinal twists, forward bends, and high-impact activities) • Assess and reduce risk of falls • Continue bisphosphonate therapy

In addition to lifelong preventive nutrition and weight-bearing exercise, antiresorptive treatment with nitrogen-containing bisphosphonates has become standard first-line therapy for postmenopausal osteoporosis. Timely diagnosis and effective treatment of osteoporosis can reduce the incidence of fractures and their multifaceted individual and societal costs.
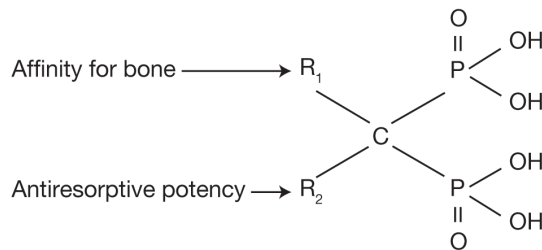
Objective

Bisphosphonates have become the standard first-line treatment for postmenopausal osteoporosis. This paper will trace the evolution of bisphosphonate therapies from daily to monthly or less frequent dosing regimens, outline evidence on efficacy, safety, and tolerability, and examine their potential to improve patient acceptance and clinical outcomes of osteoporosis treatment.

Bisphosphonate pharmacology and dosing frequencies

Two features of bisphosphonate structure determine biological activity (Figure 1). The arrangement of 2 phosphate groups bound to a geminal carbon (rather than an oxygen as in pyrophosphate) creates a non-hydrolyzable pyrophosphate analog (Rogers et al 2000), and the R_1 and R_2 groups occupying the carbon's other bonds mediate high-affinity calcium chelation. Thus, bisphosphonates are readily and tenaciously incorporated into bone mineral surfaces, where they are consumed by osteoclasts at remodeling sites.

Within osteoclasts, non-nitrogen-containing bisphosphonates are metabolized to apoptosis-inducing compounds. Nitrogen-containing bisphosphonates (the focus of this review) inhibit protein prenylation by farnesyl pyrophosphate synthase and thus disrupt the cellular physiology of resorption (Dunford et al 2001). Inhibitory potency, determined by the R_2 group, is increased by tertiary nitrogen (as in ibandronate) or a heterocyclic ring (as in risedronate and zoledronic acid) (Dunford et al 2001). An upstream metabolite that accumulates during prenylation inhibition, isopentenyl pyrophosphate, is further metabolized to an apoptosis-inducing product (Monkkonen et al 2007). Although osteoclast apoptosis is not essential for antiresorptive activity of

Bisphosphonate types	Mechanisms of action	Agents	R_1 Side Chain	R_2 Side Chain
Simple bisphosphonates	Nonhydrolyzable pyrophosphate analogs; induce osteoclast apoptosis	Etidronate	-OH	$-CH_3$
Nitrogen-containing bisphosphonates	Nonhydrolyzable pyrophosphate analogs and prenylation inhibitors; inhibit osteoclast recruitment and resorptive activity	Alendronate	-OH	$-(CH_2)_3-NH2$
		Ibandronate	-OH	$-(CH_2)_2-N-(CH_3)$ (pentyl)
		Pamidronate	-OH	$-(CH_2)_2-NH_2$
		Risedronate	-OH	$-CH_2$-3-pyridine
		Zoledronic acid	-OH	$-CH_2$-imidazole

Figure 1 Bisphosphonate types and structures.

nitrogen-containing bisphosphonates, it plays a contributory role (Russell et al 2008).

Suppression of bone turnover by nitrogen-containing bisphosphonates manifests in decreased serum and urine levels of bone turnover markers (Table 2). The bone collagen breakdown products cross-linked C-telopeptide (CTX) or N-telopeptide (NTX) are often used in clinical follow-up. The rate and magnitude of their decreases in response to treatment depend on bisphosphonate potency, dose, route, and interval.

Evolution of dosing regimens

Nitrogen-containing bisphosphonates have become the standard of care for osteoporosis. US approval dates for currently available bisphosphonate regimens are shown in Figure 2. Oral bisphosphonate dosing (daily, weekly, or monthly) is popular for first-line treatment in the outpatient setting. Intravenous (iv) regimens (quarterly or yearly), are newer options available to patients with postmenopausal osteoporosis. Intravenous bisphosphonates are particularly helpful for those who are bedfast or have esophageal disorders, cognitive problems, or other dosing challenges.

Alendronate, risedronate, and ibandronate all were initially approved by the Food and Drug Administration (FDA) for daily oral dosing, supported by trials with direct anti-fracture efficacy endpoints (Black et al 1996; Harris et al 1999; McClung et al 2001; Chesnut et al 2004). The burdensome dosing requirements needed for gastrointestinal (GI) protection with daily oral bisphosphonates have motivated development of less frequent oral regimens. Weekly dosing is made possible by the long half-life of bone-bound bisphosphonates, which remain at resorption sites longer than the 2-week lifespan of individual osteoclasts (Bone et al 2000). Weekly oral alendronate and risedronate achieved approval based on

comparisons with the respective daily regimens (Schnitzer et al 2000; Brown et al 2002). Weekly oral ibandronate has also shown non-inferior efficacy to the daily regimen (Cooper et al 2003) but has not been marketed. These weekly regimens, with 7 times the daily oral dose, maintain continuous reduction of bone turnover markers (Papapoulos and Schimmer 2007).

Bisphosphonate pharmacology also makes possible monthly, intermittent, quarterly, or yearly dosing. In the quest for improved adherence and persistence, these extended-interval regimens provide important lifestyle-friendly options. Monthly oral ibandronate, the first approved monthly bisphosphonate regimen, was supported by comparison trials with the daily regimen and has been in use since 2005 (Miller et al 2005; Reginster et al 2006). Pharmacodynamically, monthly oral ibandronate utilizes a non-linear dose increase versus the daily oral regimen (150 mg/month vs 2.5 mg/day), which more than doubles annual cumulative skeletal exposure (ACE; 10.8 mg with monthly vs 5.5 mg with daily oral treatment) (Zaidi et al 2007). Increased ACE maintains efficacy during the interdose periods of extended-interval regimens (Zaidi et al 2007). Bone turnover markers show marked suppression within 3 days after a 150 mg/month oral ibandronate dose and reach a nadir by 7 days postdose (Silverman et al 2007a); although marker levels gradually increase during the interdose period, they remain throughout the month within the premenopausal range required for efficacy (Papapoulos and Schimmer 2007).

An intermittent oral risedronate regimen (2 consecutive days monthly) was approved in April 2007 (Delmas et al 2008a), and a once-monthly risedronate dosing regimen was approved in April 2008 (Delmas et al 2008b). These risedronate regimens provide 30 times the daily oral dose. Comparison to daily oral risedronate shows that they achieve similar bone turnover marker suppression and BMD increases (Delmas et al 2007a; Delmas et al 2007b).

Table 2 Biomarkers of bone turnover (After Leeming et al 2006)

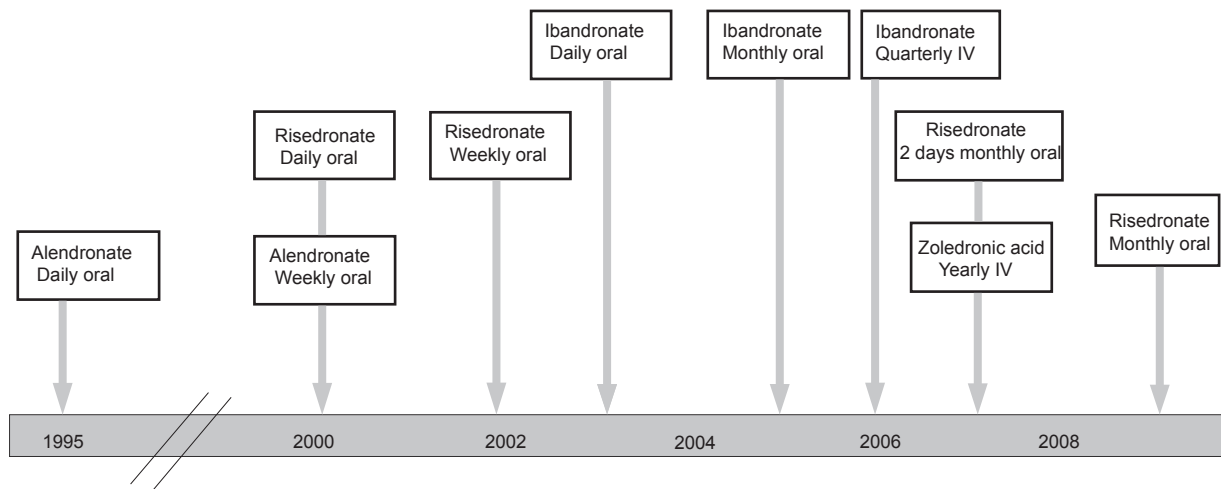| Processes	Biomarkers	Descriptions
Bone resorption	Bone type I collagen N-telopeptide	Collagen breakdown product generated by osteoclast cathepsin K
	Bone type I collagen C-telopeptide	Collagen breakdown product generated by osteoclast cathepsin K
	Deoxypyridinoline	Collagen breakdown product; remnant of cross-links of collagen polypeptides
	Tartrate-resistant alkaline phosphatase	Osteoclastic enzyme; may indicate osteoclast number
Bone formation	Bone-specific alkaline phosphatase	Osteoblastic enzyme involved in bone mineralization
	Osteocalcin	Major non-collagen protein of bone
	Aminoterminal propeptide of type I procollagen	Byproduct of mature collagen formation
	Carboxyterminal propeptide of type I procollagen	Byproduct of mature collagen formation

Figure 2 Timeline of Food and Drug Administration approvals of different bisphosphonate regimens.

Intravenous bisphosphonate regimens decouple bisphosphonate therapy from stringent oral dosing requirements, providing alternative options for any postmenopausal osteoporosis patients and extending the benefits of bisphosphonates to patients unable to take them orally. Quarterly iv ibandronate (3 mg/3 month), approved in 2006, has shown efficacy in postmenopausal osteoporosis with a similar safety profile to the monthly oral regimen (Delmas et al 2006). The lower-dose iv ibandronate regimens investigated during drug development did not achieve clinical efficacy because bone turnover returned toward untreated levels during the interdose periods (Adami et al 2004; Recker et al 2004). The approved 3 mg/3 month iv dose provides the highest annual cumulative skeletal exposure of approved ibandronate regimens (12 mg) (Zaidi et al 2007), resulting in superior efficacy to daily oral ibandronate (Eisman et al 2008).

Zoledronic acid was originally developed as a high-potency agent for single-dose iv infusion to treat hypercalcemia (Major 2002) and skeletal complications (Perry and Figgitt 2004) of malignancy. Suppression of bone turnover in osteopenic or osteoporotic postmenopausal women infused with 5 mg zoledronic acid was more rapid and pronounced than in those receiving 70 mg/week oral alendronate (Saag et al 2007); further investigations in postmenopausal osteoporosis led to the 2007 approval of a yearly iv zoledronic acid regimen (5 mg/year) for this indication (Black et al 2007).

Bisphosphonate efficacy, safety, and tolerability

Key randomized trials evaluating nitrogen-containing bisphosphonates individually and comparatively are summarized in Table 3; their findings on efficacy, safety, and tolerability are described below.

Efficacy studies

Pivotal trials supporting approval of daily oral nitrogen-containing bisphosphonate regimens utilized fracture-based primary endpoints. After these daily regimens attained approval, "bridging trials" supporting less frequent dosing regimens were designed to show non-inferiority or equivalence to daily regimens by means of surrogate BMD endpoints.

Daily oral regimens

The **F**racture **I**ntervention **T**rial (FIT) evaluated oral alendronate (5 mg/day for the first 2 years; 10 mg/day thereafter) vs placebo in women with (Black et al 1996) or without (Cummings et al 1998) baseline vertebral fractures. Alendronate reduced the relative risk of new vertebral fractures by roughly 50% in the group with prevalent vertebral fractures (Black et al 1996); hip and wrist fracture risks also decreased by roughly 50%, and that of non-vertebral fractures by 20% (Table 2). In the group without baseline vertebral fractures (Cummings et al 1998), new vertebral fracture risk decreased by approximately 45%; non-vertebral fracture effects depended on baseline BMD (Table 2).

In the **F**IT **L**ong-term **EX**tension study (FLEX) (Bone et al 2004), FIT participants who received alendronate for 5 years were re-randomized to continue alendronate (5 or 10 mg/day) or to switch to placebo for 5 additional years. In the group who received alendronate for a total of 10 years, BMD increased at multiple sites compared with baseline; lumbar spine BMD continued increasing throughout

Table 3 Overview of bisphosphonate study results by dosing frequency, route, and agent

Frequency	Route	Study, N value, duration, and reference	Patients	Agent and dose	Key results
Daily	Oral	FIT Vertebral Fracture Study (N = 2027, 3 years) (Black et al 1996)	Women aged 55–81 years with femoral neck BMD ≤0.68 g/cm^2 and prevalent vertebral fractures	Alendronate (5 mg/day for 24 months, then 10 mg/day for months 24–36) vs placebo	Relative hazard reductions vs placebo: • New radiographic vertebral fractures: 47% • New clinical vertebral fractures: 55% • Hip fractures: 51% • Wrist fractures: 48%
		FIT Clinical Fracture Study (N = 4432, 4 years) (Cummings et al 1998)	Women aged 54–81 years with femoral neck BMD ≤0.68 g/cm^2 without prevalent vertebral fractures	Alendronate (5 mg/day for 24 months, then 10 mg/day for remainder of study) vs placebo	Relative hazard reduction vs placebo: • Radiographic vertebral fractures: 44% overall Relative hazard reduction vs placebo among women with femoral neck BMD T-scores <–2.5: • Overall clinical fractures: 36% • Hip fractures: 56%
		VERT Multinational (N = 1226, 3 years) (Reginster et al 2000)	Postmenopausal women aged ≤85 years with ≥2 prevalent vertebral fractures	Risedronate (2.5 mg/day or 5 mg/day) vs placebo	Relative risk reduction for 5 mg/day vs placebo after 1 year: • New vertebral fractures: 61% Relative risk reduction for 5 mg/day vs placebo after 3 years: • New vertebral fractures: 49% • Nonvertebral fractures: 33%
		VERT North America (N = 2458, 3 years) (Harris et al 1999)	Postmenopausal women aged ≤85 years with ≥2 prevalent vertebral fractures or with 1 prevalent radiographic vertebral fracture and lumbar BMD T-score ≤ –2.0	Risedronate (5 mg/day) vs placebo (the 2.5 mg/day arm was discontinued after 1 year)	Relative risk reduction for 5 mg/day vs placebo after 1 year: • New vertebral fractures: 65% Relative risk reduction for 5 mg/day vs placebo after 3 years: • New vertebral fractures: 41% • Nonvertebral fractures: 40%
		HIP (N = 9331, 3 years) (McClung et al 2001)	Women aged 70–79 years with femoral neck BMD T-score ≤ –4.0 or women aged ≥80 years with T-score ≤ –3.0 plus poor gait or propensity to fall	Risedronate (2.5 or 5 mg/day) vs placebo	Relative risk reduction for hip fracture vs placebo: • Overall: 30% • Subgroup with non-skeletal sources of fracture risk: 20%
		BONE (N = 2946, 3 years) (Chesnut et al 2004; Chesnut et al 2005)	Postmenopausal women with lumbar BMD T-score ≤ –2.0 and 1–4 prevalent vertebral fractures	Ibandronate (2.5 mg day or 20 mg every other day for 12 doses every 3 months) vs placebo	Relative risk reduction for daily vs placebo: • New vertebral fractures: 62% • New or worsening vertebral fractures: 62% • Clinical vertebral fractures: 49%

Weekly	Oral	Alendronate Once-weekly Study (N = 1258, 1 year) (Schnitzer et al 2000)	Postmenopausal women aged 42–95 years with lumbar spine or femoral neck T-score ≤ −2.5	Alendronate (70 mg/week or 35 mg twice weekly vs 10 mg/day)	Increase of lumbar spine BMD: • 70 mg/week: 5.1% • 35 mg twice weekly: 5.2% • 10 mg/day: 5.4% Once- and twice-weekly regimens demonstrated statistical equivalence to daily treatment
		FACT (N = 1053, 1 year; N = 833, 2 years) (Sebba et al 2004; Bonnick et al 2006)	Women ≥6 months postmenopausal, aged ≥40 years (≥25 years if surgical menopause), with BMD T-score ≤ −2.0 (total hip, hip trochanter, femoral neck, or lumbar spine)	Alendronate (70 mg/week) vs risedronate (35 mg/week)	At 1 year, significantly more alendronate users (p < 0.05) experienced BMD gains at all sites. 2-year increase of hip trochanter BMD: • Alendronate: 4.6% • Risedronate: 2.5% Alendronate demonstrated a statistically greater increase (p < 0.001)
		Cooper et al (N = 235; 48 weeks) (Cooper et al 2003)	Women aged 53–80 years who were ≥3 years postmenopausal with lumbar BMD T-score ≤ −2.0	Ibandronate (20 mg/week vs 2.5 mg/day)	Increase of lumbar spine BMD: • Weekly: 3.53% • Daily: 3.47% Weekly treatment demonstrated statistical non-inferiority to daily treatment.
		Brown et al (N = 1456; 1-year efficacy, 1-year extension) (Brown et al 2002)	Women aged ≥50 years who were ≥5 years postmenopausal with a lumbar or femoral BMD T-score ≤ −2.5 or a T-score ≤ −2.0 plus ≥1 prevalent vertebral fracture	Risedronate (35 or 50 mg/week vs 5 mg/day)	Increase of lumbar spine BMD at 1 year: • 35 mg/week: 3.9% • 50 mg/week: 4.2% • 5 mg/day: 4.0% Both weekly regimens showed statistical non-inferiority to daily treatment
Monthly	Oral	MOBILE (N = 1609; 2 years) (Miller et al 2005; Reginster et al 2006)	Women aged 55–80 years who were ≥5 years postmenopausal with a mean lumbar BMD T-score < −2.5 and > −5.0	Ibandronate (50 mg + 50 mg/month or 100 or 150 mg/month vs 2.5 mg/day)	Increase of lumbar spine BMD after 1 year:* • 50 mg + 50 mg/month: 4.3% • 100 mg/month: 4.0% • 150 mg/month: 4.8% • 2.5 mg/day: 3.8% Increase of lumbar spine BMD after 2 years: • 50 mg + 50 mg/month: 5.3% • 100 mg/month: 5.6% • 150 mg/month: 6.6% • 2.5 mg/day: 5.0% At both study years, all monthly regimens demonstrated statistical non-inferiority to daily treatment; 150 mg/month demonstrated superiority to daily treatment

(Continued)

Table 3 (*continued*)

Frequency	Route	Study, N value, duration, and reference	Patients	Agent and dose	Key results
		MOTION (N = 1760; 1 year) (Miller et al 2008)	Women aged 55–84 years who were ≥5 years postmenopausal with a mean lumbar BMD T-score < −2.5 and ≥ −5.0	Ibandronate (150 mg/month) vs alendronate (70 mg/week)	Increase of lumbar spine BMD after 1 year: • Monthly ibandronate: 5.1% • Weekly alendronate: 5.8% Increase of total hip BMD after 1 year: • Monthly ibandronate: 2.9% • Weekly alendronate: 3.0% Increase of femoral trochanter BMD after 1 year: • Monthly ibandronate: 4.2% • Weekly alendronate: 4.2% Increase of femoral neck BMD after 1 year: • Monthly ibandronate: 2.1% • Weekly alendronate: 2.3% Monthly ibandronate was statistically non-inferior to weekly alendronate at all sites
		Delmas et al (N = 1229; 1 year) (Delmas et al 2008a)	Postmenopausal women aged ≥50 years who had lumbar BMD T-score < −2.5 or T-score < −2.0 and ≥1 prevalent vertebral fracture	Risedronate (75 mg + 75 mg/month vs 5 mg/day)	Increase of lumbar spine BMD after 1 year: • 75 mg + 75 mg/month: 3.4% • 5 mg/day: 3.6% The 2-consecutive-days-monthly regimen showed statistical non-inferiority to the daily regimen
		MERIT-OP (N = 1292, 2 years) (Delmas et al 2008b)	Women aged ≥50 years who were ≥5 years postmenopausal with a lumbar or femoral BMD T-score < −2.5 or a T-score < −2.0 plus ≥1 prevalent vertebral fracture	Risedronate (150 mg/month vs 5 mg/day)	Increase of lumbar spine BMD at 1 year: • 150 mg/month: 3.5% • 5 mg/day: 3.4% The monthly regimen showed statistical non-inferiority to daily treatment
	iv	Heijckmann et al retrospective (N = 117; 3 years) (Heijckmann et al 2002)	Women aged 46–78 years with lumbar spine BMD T-score < −2.5	Pamidronate (iv 60 mg/month vs alendronate oral 20 mg/day)	Increase of lumbar spine BMD: • Pamidronate: 11.6% • Alendronate: 9.3% The groups did not statistically differ
Intermittent	Oral	BONE (N = 2946, 3 years) (Chesnut et al 2004)	Postmenopausal women with lumbar BMD T-score ≤ −2.0 and 1–4 prevalent vertebral fractures	Ibandronate (20 mg every other day for 12 doses every 3 months or 2.5 mg/day vs placebo)	Reduction in new morphometric vertebral fracture risk vs placebo: • Intermittent: 50% • Daily: 62% Reduction in clinical vertebral fracture risk vs placebo: • Intermittent: 48% • Daily: 49%

Quarterly	iv	IRIS (N = 520, 1 year) (Adami et al 2004)	Women aged 55–75 years who were ≥5 years postmenopausal with lumbar BMD T-score <−2.5	Change of lumbar spine BMD after 1 year: • iv 2 mg/quarter: 5.0% • iv 1 mg/quarter: 2.8% • Placebo: −0.04% Both ibandronate regimens increased BMD significantly more than placebo. BMD increase was signifi cantly greater with 2 mg/quarter than 1 mg/quarter
		DIVA (N = 1395, 2 years) (Delmas et al 2006; Eisman et al 2008)	Women aged 55–80 years who were ≥5 years postmenopausal with lumbar BMD T-score <−2.5 and ≥ −5.0	Ibandronate (iv 2 mg/quarter or 1 mg/quarter) vs placebo Ibandronate (iv 2 mg/2 months or 3 mg/3 months vs oral 2.5 mg/day) Increase of lumbar spine BMD after 1 year: • iv 2 mg/2 months: 5.1% • iv 3 mg/3 months: 4.8% • Oral 2.5 mg/day: 3.8% Increase of lumbar spine BMD after 2 years: • iv 2 mg/2 months: 6.4% • iv 3 mg/3 months: 6.3% • Oral 2.5 mg/day: 4.8% At both 1 and 2 years, both iv regimens showed statistical superiority (p 0.001) to daily oral
Yearly	iv	HORIZON Pivotal Fracture Trial (N = 3889, 3 years) (Black et al 2007)	Postmenopausal women aged 65–89 years who had femoral neck BMD T-score ≤ −2.5 or prevalent radiologic vertebral fractures with femoral T-score ≤ −1.5	Zoledronic acid (5 mg/year) vs placebo Relative risk reduction vs placebo: • Morphometric vertebral fracture: 70% • Hip fracture: 41% • Nonvertebral fracture: 25% • Clinical fracture: 33% • Clinical vertebral fracture: 77% BMD increases vs placebo after 3 years: • Total hip: 6.02% • Lumbar spine: 6.71% • Femoral neck: 5.06% p < 0.001 for all fracture and BMD comparisons

Abbreviations: BMD, bone mineral density; BONE, iBandronate Osteoporosis vertebral fracture trial in North America and Europe; DIVA, Dosing IntraVenous Administration study; FACT, Fosamax Actonel Comparison Trial; FIT, Fracture Intervention Trial; HIP, Hip Intervention Program; HORIZON, Health Outcomes and Reduced Incidence with Zoledronic Acid ONce Yearly; IRIS, Intermittent Regimen iv Ibandronate Study; MERIT-OP, Monthly Evaluation of RIsedronate Trial in Osteoporosis; MOBILE, Monthly Oral IBandronate in LadiEs; MOTION, Monthly Oral Therapy with Ibandronate for Osteoporosis INtervention; VERT, Vertebral Effi cacy with Risedronate Trial.

treatment, whereas from 5 years onward other sites showed stable or decreasing BMD (Bone et al 2004). Clinically evident vertebral fractures were less common than in the group who switched to placebo, who experienced hip and spine BMD declines after discontinuing alendronate (Black et al 2006).

Placebo-controlled trials supporting the approval of daily oral risedronate (5 mg/day) evaluated hip fractures among women with osteoporosis or non-skeletal risk factors (the **H**ip **I**ntervention **P**rogram [HIP]) (McClung et al 2001) or new vertebral fractures among women with prevalent vertebral fractures (**V**ertebral **E**fficacy with **R**isedronate **T**rial [VERT]) (Reginster et al 2000). In HIP (McClung et al 2001), relative hip fracture risk was significantly reduced with risedronate vs placebo in the overall patient set and among osteoporotic patients, but did not differ significantly among non-osteoporotic patients with risk factors for falling (Table 2). Non-vertebral fracture risk, similarly, significantly decreased with risedronate overall and in osteoporotic patients. In the multinational VERT study (Reginster et al 2000), new vertebral fracture risk in risedronate recipients was reduced by 61% during the first year and by 49% over 3 years, whereas non-vertebral fracture risk was reduced by 33% over 3 years (Table 2). Risedronate recipients in the North American VERT study (Harris et al 1999) showed 1-year vertebral fracture risk reduction of 65%, 3-year vertebral fracture risk reduction of 41%, and non-vertebral fracture risk reduction of 40% (Table 2).

In the oral i**B**andronate **O**steoporosis vertebral fracture trial in **N**orth America and **E**urope (BONE) (Chesnut et al 2004), oral ibandronate given daily or intermittently to women with prevalent vertebral fractures significantly reduced the relative risk of new vertebral fractures and clinical vertebral fractures compared with placebo (Table 2). Lumbar BMD significantly increased and rates of height loss decreased in both ibandronate groups as compared with placebo (Chesnut et al 2004). Non-vertebral fracture risk also decreased by 69% in daily oral ibandronate recipients with low baseline femoral neck T-scores <−3.0 (Chesnut et al 2004). BONE supported the initial approval of daily oral ibandronate in 2005. Its vertebral fracture data provided the first evidence for anti-fracture efficacy of a non-daily oral bisphosphonate regimen.

Weekly oral regimens

In the Alendronate Once-Weekly Study (Schnitzer et al 2000), a 70 mg oral once-weekly dose of alendronate resulted in statistically equivalent lumbar spine BMD gains to those seen with the 10 mg daily treatment or 35 mg twice-weekly treatment (Table 2); the 70 mg/week oral alendronate regimen was approved in 2000. A bridging trial of risedronate at 35 or 50 mg/week showed non-inferior increases of lumbar BMD with both regimens as compared with the 5 mg/day approved dosing (Brown et al 2002), resulting in 2002 approval for 35 mg weekly oral risedronate.

Monthly oral regimens

The currently available monthly oral ibandronate regimen was approved in 2005 on the basis of the 2-year **M**onthly **O**ral **IB**andronate in **L**adi**E**s (MOBILE) bridging trial (Miller et al 2005; Reginster et al 2006). In the MOBILE trial, monthly oral ibandronate regimens (100 or 150 mg/month) proved as effective as the approved daily regimen at improving lumbar BMD (Table 2). The 150 mg/month regimen subsequently showed superiority to 100 mg/month and 2.5 mg/day at lumbar spine and total hip BMD improvement (Miller et al 2005; Reginster et al 2006). Significantly greater percentages of patients achieved measurable 2-year BMD gains at lumbar spine, total hip, or both with the 150 mg/month regimen vs 2.5 mg/day (p ≤ 0.004) or 100 mg/month (p < 0.01) (Reginster et al 2006). Additionally, 150 mg/month ibandronate resulted in significantly higher percentages of patients achieving target BMD gains (≥3% or ≥6%) at these sites (Reginster et al 2006).

An oral risedronate regimen consisting of 75 mg/day for 2 consecutive days monthly received US approval in April 2007, based on a bridging study showing its non-inferiority to the approved daily risedronate regimen (Table 2) (Delmas et al 2008a). The **M**onthly **E**valuation of **R**isedronate **T**rial in **O**steo**P**orosis (MERIT-OP) (Delmas et al 2008b) subsequently reported similar non-inferiority results for a 150 mg/month risedronate regimen approved in April 2008 (Table 2).

Quarterly iv regimens

Quarterly iv ibandronate received FDA approval in 2007 on the basis of the **I**ntermittent **R**egimen iv **I**bandronate **S**tudy (IRIS) (Adami et al 2004) and **D**osing **IV** **A**dministration (DIVA) (Delmas et al 2006; Eisman et al 2008) trials (Table 2), whose lumbar BMD endpoints demonstrated non-inferiority to the approved daily oral ibandronate regimen. Both iv regimens in the DIVA trial achieved lumbar BMD increases statistically superior to oral dosing (Table 2) (Delmas et al 2006; Eisman et al 2008). Efficacy against non-vertebral fractures was subsequently demonstrated for the quarterly iv and monthly oral ibandronate regimens in pooled analyses (Cranney et al 2007; Harris et al 2008).

Yearly iv regimen

The **H**ealth **O**utcomes and **R**educed **I**ncidence with **Z**oledronic Acid **ON**ce Yearly (HORIZON) trial showed significant reduction of vertebral, non-vertebral, and hip fractures with yearly iv zoledronic acid vs placebo in post-menopausal osteoporosis patients with or without prevalent vertebral fractures (Table 2) (Black et al 2007). A subsequent study, the HORIZON Clinical Fracture Trial (Lyles et al 2007), included women and men who underwent surgical repair of low-trauma hip fractures within 90 days before enrollment. Yearly zoledronic acid recipients in this high-risk population showed relative risk reduction vs placebo of 35% in new clinical fractures and 28% in 2-year all-cause mortality (Lyles et al 2007).

Comparative trials

The **F**osamax **A**ctonel **C**omparison **T**rial (FACT) (Bonnick et al 2006) compared weekly oral alendronate (70 mg/week) and risedronate (35 mg/week) regimens in a 1-year head-to-head study with a 1-year extension (Table 2). At all time points alendronate produced significantly greater BMD increases than risedronate at the hip trochanter, lumbar spine, total hip, and femoral neck. Significantly more alendronate than risedronate recipients attained measurable BMD gains (Sebba et al 2004; Bonnick et al 2006). Fractures were reported only as adverse events (AEs) in the FACT studies.

The 1-year randomized, double-blind, double-dummy **M**onthly **O**ral **T**herapy with **I**bandronate for **O**steoporosis I**N**tervention (MOTION) trial recently demonstrated that monthly oral ibandronate provides similar efficacy to weekly oral alendronate, as assessed by BMD improvements at the lumbar spine, total hip, trochanter, and femoral neck (Table 2) (Miller et al 2008). Fractures were reported only as AEs in the MOTION study.

Meta-analyses of non-vertebral fracture efficacy

The FDA requires direct anti-fracture endpoints to approve new bisphosphonate agents; initial trials are often designed and powered for primary endpoints of vertebral fracture. All approval trials for currently used nitrogen-containing bisphosphonates except HIP (risedronate) and HORIZON (zoledronic acid) were designed with primary vertebral fracture endpoints. In contrast, regimen extensions of existing agents can be approved on the basis of bridging trials. Thus, no direct anti-fracture efficacy trials exist for weekly, monthly, or quarterly bisphosphonates.

Non-vertebral fractures are infrequent events; their use as a trial endpoint requires large or high-risk populations and is affected by methodological variations (Miller 2008). Meta-analyses are thus often used to explore treatment effects on non-vertebral fracture risk. Daily alendronate has been associated in such meta-analyses with non-vertebral fracture risk reductions of 14%–49% (Karpf et al 1997; Cranney et al 2002b; Boonen et al 2005), and daily risedronate with non-vertebral fracture risk reductions of 19%–59% (Karpf et al 1997; Cranney et al 2002a; Harrington et al 2004; Liberman et al 2006). No currently published meta-analyses have specifically examined weekly oral bisphosphonate regimens.

Meta-analyses of extended-interval ibandronate regimens based on their achieved ACE have shown significant non-vertebral fracture risk reduction. Patients receiving ACE ≥10.8 mg (ie, approved monthly oral or quarterly iv ibandronate regimens or an investigational bimonthly iv regimen) achieved relative risk reductions versus placebo of 29.9% for all non-vertebral fractures, and 34.4% for a set of 6 important non-vertebral fractures (clavicle, humerus, wrist, pelvis, hip, leg) (Harris et al 2008). Ibandronate regimens with ACE ≥10.8 mg showed 38% relative risk reduction for all non-vertebral fractures versus daily oral ibandronate (ACE 5.5 mg) (Cranney et al 2008). These meta-analyses provide the first evidence of non-vertebral fracture efficacy for any weekly, monthly, or quarterly bisphosphonate regimen.

Safety and tolerability

The most common AEs reported with bisphosphonates affect the upper GI (UGI) system. In part such events may reflect the increased baseline incidence of UGI disorders among elderly patients and the synergistic effects of non-steroidal anti-inflammatory drugs (NSAIDs) used for comorbid arthritis. Adherence to oral dosing requirements (taking bisphosphonates with ≥8 fluid oz (237 mL) water after an overnight fast and not reclining, eating, or drinking for 30–60 minutes after dosing) reduces UGI AEs and enhances absorption. AEs affecting other body systems are somewhat less frequent.

Oral ibandronate (daily or intermittent) shows UGI AE frequencies similar to placebo, even among patients with histories of UGI disorders or concomitant anti-ulcer or NSAID treatment (Epstein et al 2006). Head-to-head studies indicate that safety and tolerability profiles, and in particular UGI tolerability, appear not to vary greatly among different oral bisphosphonates. In the FACT (Bonnick et al 2006), overall AEs, serious AEs, and discontinuations due to AEs were similar between 70 mg/week alendronate and 35 mg/week risedronate. UGI AEs (predominantly dyspepsia, nausea, and reflux) affected 24.8% of alendronate recipients

and 22.9% of risedronate recipients; and 1.7% and 1.2%, respectively, discontinued because of UGI AEs (Bonnick et al 2006). In the MOTION trial (Delmas et al 2007b), the incidence of UGI AEs was similar between weekly oral alendronate (17.2%) and monthly oral ibandronate (17.5%); however, more alendronate users withdrew because of treatment-related UGI AEs (1.7% vs 1.0% of ibandronate users). Because UGI AEs generally result from topical irritation, agents designed for less frequent oral dosing may reduce cumulative risk (Epstein et al 2006).

Osteonecrosis of the jaw (ONJ) is an infrequent but troublesome bisphosphonate-related AE thought to result from antiangiogenesis (Migliorati 2003; Migliorati et al 2006), impaired circulation, or excessive osteoclast suppression (Carter et al 2005). Most ONJ reports are associated with iv pamidronate or zoledronic acid prescribed for hypercalcemia of malignancy or skeletal metastases (indications requiring higher and more frequent doses than are used in osteoporosis). Cumulative worldwide ONJ reports with oral bisphosphonates (as of 2006) have included 170 with alendronate, 12 with risedronate and a single patient who had received both ibandronate and iv zoledronic acid (American Dental Association Council on Scientific Affairs 2006). A 2007 systematic review (Pazianas et al 2007) collected 26 ONJ cases in adult osteoporosis patients receiving bisphosphonates (alendronate, 23; alendronate and zoledronic acid, 1; pamidronate, 1; risedronate, 1; ibandronate, 0). Advancing age, dental extractions, and corticosteroid use showed significant associations with ONJ risk.

Reports of atrial fibrillation in trials of yearly iv zoledronic acid (Black et al 2007) and daily oral alendronate (Cummings et al 2007) recently prompted an FDA safety review of this AE among bisphosphonate users (Food and Drug Administration 2007). Although serious atrial fibrillation events in these studies (Black et al 2007; Cummings et al 2007) were significantly more frequent in drug recipients, no significant difference was seen between bisphosphonates and placebo when *all* atrial fibrillation events were considered. Neither serious nor overall atrial fibrillation events significantly differed between zoledronic acid and placebo in the HORIZON Recurrent Fracture trial, which enrolled an older patient population than the pivotal HORIZON study (Lyles et al 2007). Postdose electrolyte imbalances (hypocalcemia, hypophosphatemia, or hypomagnesemia) have been suggested to be responsible for atrial fibrillation during bisphosphonate use (de Nijs and Westgeest 2007; Poole et al 2007); however, the causality of this AE is not known with certainty. An October 2007 early communication

about the ongoing safety review stated that bisphosphonate prescribing patterns need not change at this time (Food and Drug Administration 2007).

Reduced kidney function has been reported in 9% to 15% of patients receiving iv zoledronic acid or pamidronate (Chang et al 2003). In the HORIZON trial (Black et al 2007), increases of serum creatinine >0.5 g/dL occurred at 9–11 days postdose in significantly more zoledronic acid recipients (iv 5 mg/year) than placebo recipients (1.2% vs 0.4%, p = 0.001). In 85% of cases, levels reverted in 30 days to within 0.5 g/dL of baseline, and by the third year of the study, there was no significant difference between study groups. Although iv ibandronate labeling includes a precaution regarding hypocalcemia and renal impairment, iv ibandronate has shown no evidence of affecting renal function in patients with cancer-related bone disease (Strampel et al 2007) or in DIVA trial participants (Rizzoli and Reid 2007). In a pooled analysis of 4 trials comprising 6815 patients with osteoporosis and estimated glomerular filtration rates >30 mL/min/1.73 m², changes in estimated creatinine clearance throughout study duration were modest and similar among iv ibandronate, daily oral ibandronate, and placebo groups (Miller et al 2007). Patients receiving iv bisphosphonate medications should have their serum creatinine measured regularly.

Ocular inflammatory AEs (conjunctivitis, episcleritis, uveitis, or scleritis) are occasionally associated with nitrogen-containing bisphosphonates (particularly with regimens used in cancer) and may be mediated by tumor necrosis factor-α and interleukins 1 and 6 (Fraunfelder 2003; Fraunfelder 2007). Patients experiencing eye pain during bisphosphonate use require immediate referral to an ophthalmologist. Conjunctivitis and episcleritis may be treated topically; uveitis and scleritis require bisphosphonate discontinuation (Fraunfelder 2003; Fraunfelder 2007).

A transient flu-like illness (fever, myalgia, arthralgia, and malaise) may occur upon initial bisphosphonate use (especially with iv use or the oral dose levels used in monthly or intermittent treatment) and is thought to represent an acute phase reaction to accumulated by-products of prenylation inhibition (Bukowski et al 2005). Generally, symptoms are mild, last only 1–3 days, and diminish in incidence and severity with subsequent doses.

Patient perspectives: improving treatment uptake, adherence, and persistence

Osteoporosis prevention is a lifelong endeavor, and osteoporosis treatment ideally starts at or before the initial

BMD decline after menopause. Care of elderly patients presenting with incident fractures must go beyond emergent repair to assessment and reduction of recurrent fracture risk. In one Midwestern community care system, process improvements utilizing follow-up of orthopedic billings provided osteoporosis evaluation and treatment to 58% of incident fragility fracture patients in 2003, in contrast to only 5% in 1999 (Harrington et al 2005). Patients with incident hip or spine fractures face increased future fracture risk (Black et al 1999; Lindsay et al 2001) as well as acute risk of disability and mortality. Treating underlying osteoporosis in such patients may conserve medical and financial resources, functional capacity, and life expectancy.

The achievement and maintenance of fracture prevention benefits requires continuity of osteoporosis treatment. Unfortunately, adherence and persistence with treatment are problematic in all chronic diseases and pose particular challenges in osteoporosis. Oral bisphosphonate dosing requirements are inconvenient for patients; thus, less frequent treatment intervals are conducive to better patient acceptance, adherence, and persistence. The US Surgeon General's Report on Bone Health and Osteoporosis (US Department of Health and Human Services 2004) has highlighted the need for interventions that improve adherence and for research specifically exploring the impact of dosing regimens on adherence. By making therapy less intrusive to daily life, oral regimens with less frequent dosing may provide improved real-world effectiveness.

Patient preferences and adherence: obstacles and opportunities

Patient inconvenience in osteoporosis treatment is not just a nuisance but a real hazard to effective clinical outcomes, as disruption of maintenance regimens can have severe physical consequences. Premature discontinuation of bisphosphonate therapy has been associated with up to 26% increase in fracture risk (Chesnut 2006; Gold et al 2007), and frequent oral dosing strongly predicts earlier discontinuation (Cramer et al 2005). Adherence and persistence with bisphosphonate therapy are important not only for direct anti-fracture benefits, but also for reduced overall healthcare requirements. In a retrospective study of 32,944 women initiating bisphosphonate treatment, those remaining adherent and persistent had significantly lower total healthcare costs than those with gaps or discontinuation of therapy (Curtis et al 2006). Adherence to weekly dosing is improved over daily regimens (Cramer et al 2005; Gold et al 2007), but remains suboptimal. Only 45% of weekly bisphosphonate recipients

in a large longitudinal study maintained adherence and only 57% maintained persistence over 1 year (Chesnut 2006). Thus, though once-weekly therapy represents a move toward a more patient-friendly regimen, it still presents obstacles to sustained treatment.

Once-monthly oral ibandronate may reduce the cumulative inconvenience of an oral bisphosphonate regimen and help patients maintain continuity of treatment. Once-monthly ibandronate users in 2 recent retrospective database studies (N = 17,479 and N = 11,664) were respectively 25.1% and 37.7% less likely than once-weekly oral bisphosphonate users to discontinue therapy before 1 year (Silverman et al 2007b). The naturalistic **PER**sistence **S**tudy of **I**bandronate ver**S**us alendrona**T**e (PERSIST) study in the UK (Cooper et al 2006) compared persistence times among women in primary care randomized to 6 months of open-label treatment with monthly oral ibandronate or weekly oral alendronate. Ibandronate recipients were offered a patient support program (PSP) available to all UK patients prescribed ibandronate; no similar program existed at the time of the study for alendronate users in the community. Kaplan–Meier analysis showed a significantly higher probability of persistence in the ibandronate/PSP group (p < 0.0001); mean (± SD) persistence times were 122 ± 2.5 days for ibandronate/PSP and 109 ± 2.5 days for alendronate (Cooper et al 2006). However, conflicting results are reported in different persistence comparisons (Weiss et al 2007). Once-monthly ibandronate was preferred over once-weekly alendronate by 66.1% of patients in the randomized, crossover Boniva Alendronate Trial in Osteoporosis (Emkey et al 2005).

Patients who cannot tolerate or do not prefer oral dosing may opt for quarterly iv ibandronate injection (Rizzoli and Reid 2007) or yearly iv zoledronic acid infusion (Black et al 2007). These regimens abrogate oral dosing requirements, but require periodic visits to a physician's office or infusion center for administration. Outpatients with adverse GI histories on daily or weekly oral bisphosphonates achieved improved adherence to quarterly iv ibandronate (Lewiecki et al 2008). Yearly iv zoledronic acid has been preferred by a majority of trial outpatients who switched to it from weekly oral alendronate (McClung et al 2007; Saag et al 2007). Intravenous regimens may be particularly advantageous for elderly patients residing in long-term care facilities or those with impairments affecting medication self-management. The availability of multiple oral and iv options gives patients the opportunity to decide which attributes of a bisphosphonate regimen they consider most important for long-term sustainability.

Physiologic assessments of adherence and response

The clinical silence of osteoporosis until fractures occur may create challenges in sustaining patients' motivation for treatment. BMD change is clinically measured no more often than every 2 years (Bonnick and Shulman 2006). Earlier demonstration of therapeutic response may help to motivate patients and to detect non-adherence. Biomarkers of bone turnover (Table 2), measured in serum or urine, change much more rapidly than BMD (Bonnick and Shulman 2006), and thus may provide early objective feedback on adherence and response. Decreased CTX at various time points during bisphosphonate therapy is strongly correlated with BMD increases at 6 months and 1 year (Leeming et al 2006). Conversely, high CTX levels may predict fracture risk; in the Epidemiology of Osteoporosis study (Garnero et al 1996a), elderly women with elevated urinary CTX had a 4.8-fold increased risk of hip fractures.

Patients' responses to biomarker-based feedback showed unexpected patterns in a 1-year prospective study of risedronate treatment (5 mg/day orally for 1 year) with and without a reinforcement program (urinary NTX testing and patient education at weeks 13 and 25) (Delmas et al 2007a). In addition to the biomarker follow-up, persistence was measured directly with electronically monitored pill dispensers; overall persistence over 1 year was 77% in the reinforcement group and 80% in the non-reinforcement group. Counterintuitively, patients who were informed of a poor NTX response (>30% increase, indicating poor adherence) were roughly twice as likely to discontinue therapy prematurely. In contrast, patients informed of a good NTX response (>30% decrease) showed improved persistence rates after the reinforcement visit (Delmas et al 2007a). Patients in the reinforcement group had less than half the incidence of new vertebral fractures as in the non-reinforcement group. Interventions that increase persistence with bisphosphonates improve fracture protection.

Recent developments thus allow a multipronged approach to maintaining the continuity of bisphosphonate treatment. Monthly or less frequent regimens lessen lifestyle disruption, preference assessments identify the attributes patients value, and bone turnover markers provide physiologic accountability.

Conclusions

Nitrogen-containing bisphosphonates have become the standard of care for postmenopausal osteoporosis, in company with calcium and vitamin D supplementation and weight-bearing physical activity. Oral bisphosphonate dosing requires stringent dosing guidelines to maximize bioavailability and minimize UGI irritation. The inconvenience this poses to patients has motivated the development of weekly and monthly oral regimens to enhance adherence, as well as quarterly and yearly iv regimens for patients unable to tolerate oral dosing. Ibandronate is the first bisphosphonate to have shown direct anti-fracture efficacy with a non-daily regimen; it was approved for once-monthly oral dosing in 2005 and for quarterly iv dosing in 2006. Yearly iv zoledronic acid was approved in 2007; it has shown improvement of fracture rates and post-fracture mortality, although the recent FDA early communication about atrial fibrillation and bisphosphonate use certainly warrants ongoing safety review. The availability of once-monthly and less frequent bisphosphonate regimens promises to improve patient satisfaction and adherence, and thus to increase the real-world effectiveness of osteoporosis therapy.

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