Differences between the bisphosphonates for the prevention and treatment of osteoporosis

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Abstract: Bisphosphonates, pyrophosphate analogs which potently inhibit osteoclastic bone resorption, are now firmly established as first-line therapy for osteoporosis. Several bisphosphonates of varying antiresorptive potency are either in clinical use or well advanced in clinical trials. Alendronate and risedronate are agents of choice at present because data from randomized controlled trials demonstrate that each of these nitrogen (N)-containing-bisphosphonates reduces the incidence of vertebral and nonvertebral fractures by about 50%, whereas evidence for antifracture efficacy is limited to the vertebral site currently for other bisphosphonates such as etidronate and ibandronate. There have not been direct studies comparing the antifracture efficacy of alendronate with that of risedronate. Intermittent administration of bisphosphonates is now a well established clinical practice, and the potent bisphosphonate zoledronate produces suppression of bone resorption for at least 12 months after a single intravenous dose. Future research will better define how to optimally administer these agents to maximize efficacy and patient compliance. The place in osteoporosis therapeutics of combining bisphosphonate therapy with agents that primarily stimulate bone formation, such as parathyroid hormone, remains to be defined.

Keywords: osteoporosis, fracture, bisphosphonates, bone resorption

Introduction

Osteoporosis is an important public health problem that contributes substantially to morbidity and mortality in an ageing world population. Bone loss is virtually universal in older people and results in osteoporotic fractures in more than 50% of women, and almost 1 in 3 men. Bone loss and a consequent increase in risk of fragility fracture also accompany a variety of disease states (nutritional, endocrinological, and inflammatory) and therapies (glucocorticoids, organ transplantation). As the world population ages, the prevalence of osteoporosis is likely to increase, making fracture prevention one of the principal health concerns of our time.

In the past decade, substantial progress has been made in the pharmacological prevention of osteoporotic fractures, which is currently dominated by the bisphosphonate class of drugs. Several members of this group of agents are either in clinical use or well advanced in clinical trials. This review will focus on differences in potency, route of administration, duration of action, and efficacy between members of this expanding class of drugs. It is important to acknowledge at the outset that only very limited data are available from head-to-head studies of bisphosphonates, and none at all from clinical studies with fracture as a primary end point, meaning that inferences about preferred agents must be drawn with caution.

Antiresorptive potency and mechanisms of action

Bisphosphonates are pyrophosphate analogs which contain a phosphate-carbon-phosphate (P-C-P) core structure that targets them to bone and renders them resistant

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to enzymatic degradation. The initial observations that the bisphosphonate structure had high affinity for bone and inhibited degradation of hydroxyapatite crystals led to confirmation that they could inhibit bone resorption in vitro (Fleisch et al 1969; Francis et al 1969). Manipulation of the composition of the side-chains attached to the P-C-P core, in particular the introduction of a basic nitrogen atom in an alkyl chain, led to the generation of compounds with increased antiresorptive potency (Russell et al 1999). Of the currently available bisphosphonates, etidronate and clodronate are non-Nitrogen (N)-containing-bisphosphonates (which do not contain nitrogen atoms in the side-chains), whose antiresorptive potency is at the lower end of the scale, while pamidronate, alendronate, risedronate, Ibandronate, and zoledronate are N-containing-bisphosphonates which exhibit antiresorptive potencies 100–10 000-fold that of etidronate (Russell et al 1999).

The chemical structure of the bisphosphonates allows them to bind to mineralized bone surfaces, following which they are taken up by osteoclasts during bone resorption. Within these cells, N-containing-bisphosphonates inhibit key enzymes in the mevalonate pathway. Intermediate metabolites of this pathway are necessary for prenylation of intracellular proteins that control the trafficking of key regulatory proteins to the cell membrane (Rogers 2004). With this loss of protein prenylation, osteoclasts undergo apoptosis. This process also occurs in osteoclast precursors, blocking their development into bone resorbing cells (Van Beek et al 2002). In contrast, non-N-containing-bisphosphonates are metabolized to form analogues of adenosine triphosphate (ATP), which interfere with the mitochondrial adenosine diphosphate (ADP)/ATP translocase, and also results in osteoclast apoptosis (Lehenkari et al 2002).

Bisphosphonate deposited on the bone surface may remain there for many years and become incorporated into the structure of bone (Masarachia et al 1996; Bauss and Russell 2004). This long duration of action opens the possibility of intermittent administration, which has been one of the important developments in the field of bisphosphonate therapeutics in recent years (see frequency of administration). The reduction in bone turnover caused by bisphosphonates results in an increased lifespan of skeletal tissue, providing a longer time in which the secondary mineralization of bone can proceed (Boivin and Meunier 2002). This increase in mineral density may contribute to the greater strength of bisphosphonate-treated bone (Borah et al 2000), as may the preservation of trabecular thickness and trabecular connectivity (Borah et al 2004).

Route of administration

All bisphosphonates are very poorly absorbed from the gastrointestinal tract (1%–2% of administered dose). The low bioavailability of orally administered bisphosphonates is a critical issue in their use. They must be taken fasting, or with water alone if they are to be absorbed at all. Fasting for 30 minutes after dosing is adequate in most circumstances, but a 60-minute fast increases the effect of ibandronate on bone density by 60% (Tanko et al 2003). N-containing-bisphosphonates can cause upper gastrointestinal irritation by directly inducing mucosal injury, so patients must not lie down for 30–60 minutes after oral dosing to prevent reflux of the tablet into the esophagus. N-containing-bisphosphonates cannot be used in those with anatomical or motility disorders of the upper gastrointestinal tract (Lanza 2002). The less potent, non-N-containing-bisphosphonates, such as etidronate and clodronate, appear to have better upper gastrointestinal tolerability, but still need to be taken fasting to optimize bioavailability.

One way of circumventing the low bioavailability of bisphosphonates, precluding upper gastrointestinal toxicity, and ensuring patient compliance, is to administer the drug parenterally. This approach has been taken with pamidronate, ibandronate, and zoledronate. Pamidronate was originally developed as an oral preparation, which was withdrawn because of concerns about gastrointestinal toxicity (Lufkin et al 1994). Currently the intravenous preparation of pamidronate is less commonly used for treatment of osteoporosis than in the management of humoral hypercalcemia of malignancy. Ibandronate has been studied in both oral and intravenous forms (Chesnut et al 2004; Recker et al 2004), while zoledronate is being developed as an intravenous therapy. Intravenous administration of potent bisphosphonates can be expeditiously achieved in an outpatient setting (Pecherstorfer et al 1996; Reid et al 2002). Clearly, parenteral administration is associated with the additional costs of medical personnel and equipment, but these may be offset by the need for less frequent dosing (discussed in Frequency of administration). No compelling evidence for antifracture efficacy of intravenous bisphosphonates has yet been published, although intramuscular administration of clodronate reduces vertebral fracture risk in glucocorticoid-treated patients (Frediani et al 2003).

Frequency of administration

Intermittent dosing of bisphosphonates (less frequent administration than traditional daily dosing) has been part of clinical practice for some time. The original studies of fracture prevention using etidronate employed a dosing regimen that involved cyclical therapy with daily administration for 2 weeks every 3 months, ie, 4 cycles of therapy each year (Storm et al 1990). The rationale for this approach was the recognition that continuous therapy with this first-generation bisphosphonate was associated with a risk of impaired mineralization (osteomalacia). Osteomalacia is not a complication of therapy with other bisphosphonates in clinical use. However, the recognition that currently prescribed bisphosphonates may persist on the bone surface for considerable periods of time has led to a widespread use of intermittent dosing in clinical practice. For the oral N-containing-bisphosphonates risedronate and alendronate, this has meant a move from daily ingestion to weekly administration of a dose equivalent to 7 times the standard daily dose. Although no trials were undertaken to confirm the antifracture efficacy of weekly therapy with either alendronate or risedronate, comparative studies demonstrated equivalent increases in bone density and suppression of biochemical markers of bone resorption in response to weekly versus daily administration of each drug (Brown et al 2002; Rizzoli et al 2002). Weekly administration of each of these agents reduces the disruption of the patient's morning routine by the requirement to take the bisphosphonate in advance of eating.

Ibandronate administered by mouth either daily (2.5 mg) or intermittently (20 mg every other day for 12 doses every 3 months) (Chesnut et al 2005) produces equivalent increases in bone density and protection against vertebral fractures, but low-dose intermittent intravenous ibandronate administration (0.5–1 mg every 3 months) did not reduce fracture risk, presumably because either the administered dose was inadequate, or the dosing interval was too long to maintain suppression of bone resorption (Recker et al 2004). These data attest to the importance of careful optimization of both dose and dosing frequency in investigating the antifracture efficacy of bisphosphonates. Further investigation of intermittent ibandronate therapy, using monthly administration, is in progress (Miller et al 2005).

Recent results from a phase II study of the potent bisphosphonate zoledronate suggest that intravenous administration of this agent as infrequently as once each year may be an effective therapy for osteoporosis. Thus, in postmenopausal women, a single intravenous dose of 4 mg zoledronate produced changes in bone density 1 year later that were equivalent to those observed in women treated with lower doses of the same agent more frequently (Reid et al 2002), and comparable with those seen in response to potent oral N-containing-bisphosphonates. Markers of bone turnover remained suppressed at the end of the 1 year follow-up period. Phase 3 studies of the effect of annual administration of zoledronate on the incidence of fragility fractures are nearing completion.

It is therefore now clear that intermittent administration of potent bisphosphonates (oral or parenteral) is both feasible and efficacious. This mode of therapy appears to be preferred by patients (Simon et al 2002) and may be associated with improved compliance with long-term therapy (Cramer et al 2005). Daily administration of these agents is already receding, and the challenge now is to optimize dosing intervals for maximum patient acceptability without compromising efficacy.

Antifracture efficacy

A substantial body of evidence has accrued over the past 10–15 years that demonstrates that bisphosphonates prevent fragility fractures in osteoporotic populations (Table 1). Potent bisphosphonates usually increase bone density of the spine by about 5% at 2 years, and reduce levels of biochemical markers of bone turnover by more than 50%. By far the largest body of evidence demonstrating antifracture efficacy has been generated in studies of the oral N-containing-bisphosphonates risedronate and alendronate, each of which has been shown to reduce vertebral and nonvertebral (including hip) fractures by 20%–50% in postmenopausal women with osteoporosis (Black et al 1996; Cummings et al 1998; Harris et al 1999; Pols et al 1999; McClung et al 2001). These findings are confirmed in meta-analyses (Cranney, Tugwell, et al 2002; Cranney, Wells, et al 2002), which provide pooled relative risk (RR) reductions of 27%–49% for vertebral and nonvertebral fractures for each agent. Estimates of the numbers of patients at high risk of osteoporotic fracture that need to be treated over 2 years with alendronate or risedronate to prevent a vertebral (72 and 96, respectively) or nonvertebral (24 and 43, respectively) are similar for these agents (Cranney, Guyatt, et al 2002). Trends towards fewer fractures are apparent within months of initiation of these agents, before substantial increases in bone density have occurred. Prevention of vertebral fractures has also been demonstrated

Table 1 Summary of results from pivotal clinical trials with nitrogen-containing bisphosphonates

Trial	N	Osteoporosis inclusion criteria	Study duration	Dosage	Increase in LS BMD %*	Fracture risk reduction %		
						Vertebral	Nonvertebral	Hip
Alendronate								
Phase III, Liberman et al 1995	994	LS T-score ≤−2.5 with or without vertebral fracture	3 y	5 mg/d or 10 mg/d for 3 y, or 20 mg/d for 2 y then 5 mg/d for 1 y	8.8 (10 mg/d)	48 (p=0.03)	NS	—
FIT 1 Black et al 1996	2027	FN T-score ≤−2.1 with vertebral fracture	3 y	5 mg/d for 2 y then 10 mg/d for 1 y	6.2	47 (p<0.001)	NS	51 (p=0.047)
FIT 2 Cummings et al 1998	4432	FN T-score ≤−2.1 with no vertebral fracture	4 y	5 mg/d for 2 y then 10 mg/d for 2 y	6.8	44 (p=0.002)	NS	NS
FOSIT Pols et al 1999	1908	LS T-score ≤−2.0	1 y	10 mg/d	4.9	—	47 (p=0.021)	—
Orwoll et al 2000	241	Men, FN T-score ≤−2.0 & LS T-score ≤−1.0, or FN T-score ≤−1.0 with vertebral or osteoporotic fracture	2 y	10 mg/d	5.3	89 (p=0.02)	—	—
Adachi et al 2001	208	Glucocorticoid therapy	2 y	5 mg/d or 10 mg/d, or 2.5 mg/d for 1y, then 10 mg/d for 1y	4.7 (10 mg/d)	90 (p=0.03)	—	—

*Treatment minus placebo.

Abbreviations: BMD, bone mineral density; BONE, oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe; d, day; FIT, Fracture Intervention Trial; FOSIT, Fosamax International Trial; FN, femoral neck; HIP, Hip Intervention Program; IV, intravenous; LS, lumbar spine; NS, not significant; VERT-MN, VERT-NA, Vertebral Efficacy with Risedronate Therapy-Multinational, -North American trials, respectively; y, year.

Table 1 *Continued*

Trial	N	Osteoporosis inclusion criteria	Study duration	Dosage	Increase in LS BMD %*	Fracture risk reduction %		
						Vertebral	Nonvertebral	Hip
Risedronate								
VERT-NA Harris et al 1999	2458	T-score ≥2 with vertebral fractures or 1 vertebral fracture and T-score ≤–2	3 y	5 mg/d	4.3	41 (p=0.003)	39 (p=0.02)	—
VERT-MN Reginster et al 2000	1226	≥2 vertebral fractures	3 y	5 mg/d	5.9	49 (p<0.001)	—	—
HIP McClung et al 2001	5445	Age 70–79 y with FN T-score <–4.0 or <–3.0 with ≥1 risk factor for hip fracture	3 y	2.5 mg/d or 5 mg/d (pooled data)	—	—	20 (p=0.03)	40 (p=0.009)
Reid et al 2001	184	Men, glucocorticoid therapy	1 y	2.5 mg/d or 5 mg/d	8.2 (5 mg/d)	82 (p=0.008)	—	—
Wallach et al 2000	518	Glucocorticoid therapy	1 y	2.5 mg/d or 5 mg/d	2.9 (5 mg/d)	70 (p=0.01)	—	—
Ibandronate								
Phase III, Recker et al 2004	2862	T-score <–2 with or without vertebral fracture	3 y	0.5 mg or 1 mg iv 3 monthly	2.9, 4.0	NS	NS	—
BONE Chesnut et al 2004	2946	T score <–2 with vertebral fractures	3y	2.5 mg/d20 mg alt d for 24 d, every 3 mo	5.24.4	6250	NS	—

*Treatment minus placebo.

Abbreviations: BMD, bone mineral density; BONE, oral iBandronate Osteoporosis vertebral fracture trial in North America and Europe; d, day; FIT, Fracture Intervention Trial; FOSIT, Fosamax International Trial; FN, femoral neck; HIP, Hip Intervention Program; IV, intravenous; LS, lumbar spine; NS, not significant; VERT-MN, VERT-NA, Vertebral Efficacy with Risedronate Therapy-Multinational, -North American trials, respectively; y, year.

in osteoporotic men treated with alendronate (Orwoll et al 2000), glucocorticoid-treated men taking risedronate (Reid et al 2001), and in glucocorticoid-treated subjects taking either risedronate or alendronate (Wallach et al 2000; Adachi et al 2001). Reanalysis of the pivotal studies with each of these agents confirm antifracture efficacy in subjects who are either osteoporotic in terms of bone density or who have a history of vertebral fractures (Black et al 2000; Heaney et al 2002), and that this effect is independent of age.

Antivertebral fracture efficacy has also been reported for ibandronate in postmenopausal women (Chesnut et al 2004), etidronate in postmenopausal women (Storm et al 1990; Cranney, Guyatt, et al 2002), and clodronate in glucocorticoid-treated subjects (Frediani et al 2003). However, none of these agents has yet been demonstrated to prevent nonvertebral fractures, other than in post-hoc analyses (Chesnut et al 2004). No fracture data are yet available for intravenous zoledronate, which is currently undergoing phase III clinical studies.

Most of the data relating to fracture prevention by bisphosphonates has come from trials of 3 years duration. These studies leave unanswered the important question of efficacy and safety with long-term use, and for how long bisphosphonate therapy should be continued. A 2-year extension to one of the risedronate studies has been reported, during which the double-blind and randomization were maintained (Sorensen et al 2003). The risk of new vertebral fractures was reduced by 59% in years 4 and 5, compared with a 49% reduction in the first 3 years. These trends are reported to continue over a further 2 years of follow-up. Data to 8–10 years from extensions to the phase 3 alendronate studies have been published (Bone et al 2004; Ensrud et al 2004). In the extension study of Bone et al (2004), 10 years of continuous therapy with alendronate was associated with a steady increase in spinal bone mineral density (BMD) and stability of BMD at the hip sites, while women who received alendronate for 5 years and then no further active treatment experienced stable spine BMD and a gradual fall in hip BMD over 5 years of follow-up. The limited fracture data available from this study suggest ongoing low rates of fracture during the extension phase. In the FLEX (Fracture Intervention Trial long-term extension) study, subjects who had completed 5 years of active alendronate therapy were re-randomized to receive ongoing active therapy or placebo. After 3 years of follow-up, bone turnover was lower and bone density at hip and spine was higher in the subjects assigned to continue alendronate therapy, but there were clearly persisting effects on both bone turnover and trabecular bone density in the group assigned to placebo (Ensrud et al 2004). Unpublished 5 year data from the same study suggest lower rates of vertebral fracture in the group that continued alendronate therapy, but no reduction in the rate of nonvertebral fracture (Black et al 2004). Importantly, no unexpected adverse events emerged from the long-term risedronate or alendronate studies.

The available evidence, therefore, supports the use of either alendronate or risedronate as the preferred bisphosphonate for treatment of osteoporosis, since each of these drugs has been shown in randomized controlled trials to decrease rates of both vertebral and nonvertebral fractures. Is there any benefit to using either agent in preference to the other? Two randomized comparisons of the effects of alendronate and risedronate on bone turnover and bone density have favored alendronate (Hosking et al 2003; Rosen et al 2005), but in one of these studies risedronate was administered suboptimally (Hosking et al 2003) and both measured surrogate outcomes only. No studies have directly compared the antifracture efficacies of these two drugs, nor is it likely that such studies will be performed. It has been estimated that a study population in excess of 50 000 subjects would be required to provide sufficient statistical power to detect a 10% difference between vertebral fracture rates in an alendronate versus risedronate study (Kanis et al 2002). In the meta-analyses performed by the ORAG (Osteoporosis Research Advisory Group) group, the relative risk (RR) reduction for both vertebral and nonvertebral fractures was greater in comparison to placebo for alendronate (RR 0.52 and 0.51, respectively) than for risedronate (RR 0.64 and 0.73, respectively), but clearly these studies were performed in different study populations, making direct comparison of RR reductions unwise (Cranney, Guyatt, et al 2002). An attempt to refine a comparison of the alendronate and risedronate data from the ORAG meta-analyses, using epidemiological analytic techniques, concluded that alendronate was superior to all other antiresorptive therapies (including risedronate) in preventing nonvertebral fractures, but was not more efficacious than risedronate in reducing the risk of vertebral fractures (Wehren et al 2004). On the other hand, a review of antifracture studies that focused on studies that included intention to treat analyses suggested a stronger evidence base for efficacy of risedronate in the prevention of nonvertebral fractures (Boonen et al 2005). In the absence of conclusive comparative data, and the

presence of evidence of efficacy of each agent, alendronate and risedronate should be regarded as equally effective in preventing osteoporotic fractures.

Combination with anabolic skeletal therapies

The advent of parathyroid hormone (PTH) as an anabolic agent has enabled systematic evaluation of the effects of combining treatment with an agent which primarily stimulates bone formation with bisphosphonates, which primarily suppress bone resorption. The hope that combination therapy might confer additive effects on bone density and fracture risk reduction has not been confirmed in the clinical studies performed to date. Thus, cotreatment of osteoporotic postmenopausal women with PTH and alendronate results in smaller increases in markers of bone formation and bone density than are seen in subjects treated with PTH alone (Black et al 2003). A similar blunting of the effect of PTH on bone density and markers of bone formation by concomitant exposure to alendronate was observed in men with low bone density (Finkelstein et al 2003). However, anabolic responses are still observed in response to initiation of PTH treatment in subjects who have been taking alendronate for at least 12 months (Ettinger et al 2004; Cosman et al 2005). Pretreatment with a less potent antiresorptive agent, such as raloxifene, may be associated with less blunting of the increase in BMD induced by subsequent therapy with PTH than is observed when PTH therapy follows a period of treatment with alendronate (Ettinger et al 2004). Overall, the available data suggest that the induction of bone resorption by PTH is an important determinant of the potency of its anabolic skeletal effect, and that currently there is no clear-cut rationale for combining PTH and antiresorptive therapies. An alternative approach might be to treat with PTH alone for 18–24 months to achieve substantial increments in bone density, and then withdraw PTH treatment in favor of antiresorptive therapy to maintain the increased bone density. Recent evidence suggests that this sequential approach, in which short-term PTH treatment is followed by treatment with alendronate, produces greater increments in bone density than are observed if PTH treatment is followed by treatment with a placebo (Black et al 2005). No data are yet available from studies of combining PTH therapy with other bisphosphonates, and the place of combination and/or sequential PTH/bisphosphonate therapy in osteoporosis management is not yet clear.

Adverse effects

N-containing-bisphosphonates can cause upper gastrointestinal irritation and mucosal ulceration, so patients must not lie down for 30–60 minutes after oral dosing to prevent reflux of the tablet into the esophagus, and these agents cannot be used in those with anatomical or motility disorders of the upper gastrointestinal tract. In other patients, attention to the dosing regimen outlined above prevents difficulties in most patients (Lanza 2003). Although there was not demonstrable upper gastrointestinal toxicity in the placebo-controlled trials of potent N-containing-bisphosphonates, post-marketing surveys suggest that up to 10% of patients prescribed these agents experience such side-effects (Ettinger et al 1998). Two comparative endoscopic studies have demonstrated a higher incidence of gastric ulceration in alendronate-treated subjects than those treated with risedronate (Lanza et al 2000; Thomson et al 2002), but no differences were observed between the agents in the incidence of gastrointestinal adverse events in a 1 year randomized comparison (Rosen et al 2005).

Intravenous administration of N-containing-bisphosphonates necessarily avoids upper gastrointestinal toxicity. The most common adverse event following parenteral bisphosphonate administration is a transient, self-limited myalgic syndrome. This effect occurs in 10%–15% of zoledronate-treated women (Reid et al 2002). No data are available from comparative studies that address the frequency of this side-effect following exposure to different bisphosphonates.

Muscle and/or bone pain following ingestion of oral bisphosphonates did not emerge as an adverse event from randomized controlled trials, but there have been a small number (in relation to the size of the exposed population) of reports of severe musculoskeletal discomfort in response to alendronate and risedronate in post-marketing surveillance (Wysowski and Chang 2005).

Recently, use of potent bisphosphonate therapy has been associated with jaw osteonecrosis (Durie et al 2005; Hellstein and Marek 2005). This poorly characterized and understood condition is probably attributable to bisphosphonate therapy, but almost all of the described cases have occurred in oncology patients receiving high-dose bisphosphonate therapy for management of metastatic skeletal disease, often following dental surgical procedures (Bagan et al 2005; Purcell and Boyd 2005). Several different bisphosphonates have been implicated in the pathogenesis of this rare disorder in oncology patients, and some

preliminary data suggest that it may occur more frequently in patients treated with zoledronate than in those treated with pamidronate (Durie et al 2005). Jaw osteonecrosis in patients receiving conventional doses of oral bisphosphonates for treatment of osteoporosis is extremely uncommon.

Summary and conclusion

Bisphosphonates currently dominate the pharmacotherapy of osteoporosis. Non-N-containing-bisphosphonates such as etidronate and clodronate have largely been superseded by the more potent N-containing-bisphosphonates, an increasing number of which are entering clinical practice. The long skeletal retention time of these agents allows intermittent administration, and the most potent drugs may be effective when administered as infrequently as annually. At present, the evidence base from randomized controlled trials with fracture as the primary endpoint supports the preferential use of either of two oral N-containing-bisphosphonates, risedronate and alendronate, since each of these drugs has been shown to reduce the incidence of both vertebral and nonvertebral fractures. Comparative studies of risedronate and alendronate have only assessed adverse events or surrogate efficacy outcomes (bone resorption and bone density), so there is no clear rationale for choosing one agent over the other. There is considerable interest in the outcome of studies that are assessing fracture incidence in response to intermittent administration of potent intravenous bisphosphonates such as zoledronate. If these studies demonstrate antifracture efficacy, the clinician will have a greater range of proven therapeutic options available for fracture prevention. In the coming era of anabolic agents for osteoporosis, it remains to be determined whether any of the bisphosphonates might confer greater benefits than other members of the class when used in combination or sequence with drugs that stimulate bone formation.

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