REVIEW

Changes in bone remodelling and antifracture efficacy of intermittent bisphosphonate therapy: implications from clinical studies with ibandronate

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Bisphosphonates reduce the rate of bone resorption and bone remodelling. Given daily, they decrease the risk of fractures in postmenopausal osteoporosis. When bisphosphonates were given at extended drug-free intervals this antifracture efficacy was generally not seen. This may be due to the different pattern of bone remodelling changes. Data from randomised clinical studies of ibandronate, given orally or intravenously, at different doses and for variable time intervals to women with osteoporosis were examined to explore the relationship between intermittent bisphosphonate therapy, changes in bone resorption and fracture risk. The magnitude of the reduction of the rate of bone resorption at the end of the drug-free interval rather than its fluctuation pattern after bisphosphonate administration determines antifracture efficacy, provided that these fluctuations occur within the premenopausal range. Prolongation of the drug-free interval beyond 2 weeks should be compensated by a dose higher than the cumulative daily dose.

remodelling cycle need to be considered. In this paper we explore these relationships using data from clinical studies with ibandronate, a nitrogen-containing bisphosphonate that has been given at different doses and variable time intervals to patients with postmenopausal osteoporosis.

BONE REMODELLING

The skeleton is renewed throughout life, and it has been estimated that the whole skeleton is renewed on average every 10 years by the process of bone remodelling (reviewed by Manolagas³²). This occurs in an orderly fashion through temporary anatomical structures called basic multicellular units. A basic multicellular unit comprises a team of osteoclasts in the front and a team of osteoblasts in the back, supported by blood vessels, nerves and connective tissue. Osteoclasts resorb bone, while osteoblasts move to the resorbed area and lay down new bone matrix that subsequently mineralises, a process known as coupling. The life span of the osteoclasts and osteoblasts differs: that of osteoclasts is about 2 weeks while that of osteoblasts is approximately 3 months. The balance between the supply of new cells and their life span is critical for the maintenance of bone homeostasis and is disturbed in bone diseases.

In osteoporosis, a prolonged life span of osteoclasts and a shortening of the life span of osteoblasts induce an imbalance between bone resorption and bone formation. This imbalance is in favour of resorption and results in bone loss and deterioration of bone architecture. The net outcome of these changes is increased bone fragility.

In clinical practice, bone resorption and formation can be assessed by measurement of collagen type I degradation products and osteoblast products, respectively. Commonly used, sensitive markers of bone resorption include the N- and C-telopeptides of the α chain of type I collagen (NTX and CTX), while for bone formation bone-specific alkaline phosphatase, osteocalcin and procollagen I N-terminal propeptide are used.

DAILY BISPHOSPHONATE AND BONE REMODELLING

The primary pharmacological action of bisphosphonates is the reduction of bone resorption. Bisphosphonates are taken up by the skeleton preferentially at active sites, where they bind strongly to hydroxyapatite crystals of bone

Bisphosphonates are widely used in the management of postmenopausal osteoporosis. When given daily, they suppress bone resorption and turnover, increase bone mineral density (BMD), maintain or improve structural and material properties of bone and thereby reduce the risk of fractures.^{1–19} However, daily administration of nitrogen-containing bisphosphonates is inconvenient because of strict dosing instructions, and may also be associated with gastrointestinal adverse effects. These reduce adherence to treatment and can diminish the therapeutic potential of bisphosphonates.^{20–21}

To overcome these problems, more convenient weekly formulations, the sum of seven daily doses, have been developed^{22–23} and shown to improve patient adherence to treatment.^{24–25} Less frequent bisphosphonate administration is an attractive option that is also preferred by patients.^{26–28} However, earlier attempts to administer bisphosphonates at drug-free intervals of longer than 1 week were mostly unsuccessful in significantly reducing the risk of fractures in patients with osteoporosis.^{29–31} To gain insight into the mechanism of fracture reduction by bisphosphonates given with extended drug-free intervals, determinants of bisphosphonate action in relation to the bone

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Abbreviations: BMD, bone mineral density; IV, intravenous

mineral. During resorption they are liberated from the mineral, taken up by the osteoclasts and inhibit their activity by well documented intracellular mechanisms.^{33–34} They are later embedded in bone, where they remain for a long time.³⁵ Owing to the coupling of bone resorption and formation, the latter will also decrease with bisphosphonate treatment. However, this occurs at a slower rate, so that 3–6 months after the start of treatment a new steady state between bone resorption and bone formation will be reached at a lower level of bone remodelling. These pharmacological responses have been repeatedly shown in clinical studies. For example, during daily bisphosphonate treatment of osteoporosis, bone resorption is reduced to premenopausal levels reaching a nadir about 3 months after the start of treatment, and is maintained thereafter. This response pattern has been shown with alendronate, ibandronate, pamidronate and risedronate given daily for up to 10 years,^{12–36–38} illustrating, in addition, that the accumulation of bisphosphonate in the skeleton is not associated with cumulative effects on bone remodelling.

The reduction of bone resorption by bisphosphonates is followed by a reduction in the remodelling space, a decrease in cortical porosity and an increase in the secondary mineralisation of bone tissue, which consequently lead to increases in BMD. In addition, this action protects the integrity of bone trabeculae and prevents their perforation. The importance of the reduction in bone remodelling for the antifracture efficacy of bisphosphonates has been suggested by meta-analysis of the results of clinical trials³⁹ and was demonstrated for alendronate and risedronate by analysis of individual patient data from the Fracture Intervention Trial (FIT) and the Vertebral Efficacy with Risedronate Therapy (VERT) studies, respectively.^{40–41}

BISPHOSPHONATE DOSING AT EXTENDED DRUG-FREE INTERVALS

Principles and questions

Several factors can contribute to the efficacy and duration of action of less frequently administered bisphosphonates. These include the underlying rate of bone turnover, the degree of bone binding and the antiresorptive potency of the bisphosphonate and, hence, the dose and the dosing interval.

Because the life span of an osteoclast is about 2 weeks and bisphosphonate remains on the bone surface for longer periods, it was suggested that giving the same total dose at weekly intervals would have the same efficacy on bone remodelling and BMD as daily dosing.⁴² It was indeed shown that daily and weekly bisphosphonates induce the same pattern and degree of suppression of bone remodelling and similar increases in BMD.^{22–23} Thus, daily and weekly bisphosphonate administration are pharmacologically equivalent, and we previously proposed (SEP) that the term intermittent or cyclical administration should be reserved for treatment with drug-free intervals longer than 2 weeks.⁴³

Earlier attempts to give bisphosphonates intermittently to patients with osteoporosis in general did not show significant antifracture efficacy. For example, oral etidronate given for 2 weeks every 3 months reduced the risk of vertebral fractures after 2 years⁴⁴ but not after 3 years²⁹ of administration to the same patients. Oral tiludronate given at two different doses for 1 week every month did not significantly reduce the risk of osteoporotic fractures.³⁰ Nitrogen-containing bisphosphonates have also been given intermittently, usually with drug-free intervals of 3 months.^{45–51} However, in no such study was fracture incidence assessed.

The first study to assess fracture incidence with an intermittent nitrogen-containing bisphosphonate regimen was performed with intravenous (IV) ibandronate. This was a double-blind, placebo-controlled study that investigated the

efficacy of two doses (0.5 mg and 1.0 mg) of ibandronate against placebo. The doses were given by IV injections every 3 months for 3 years to women with postmenopausal osteoporosis.³¹ These ibandronate doses provide a total annual cumulative exposure of 2 mg and 4 mg, respectively. Bone resorption markers were measured in samples obtained every 3 months just before ibandronate administration (residual values). There was a dose-dependent reduction of residual values of bone resorption. However, although the pattern of change of residual values was similar to that achieved with daily bisphosphonate administration, the magnitude of reduction was small (10–20% below that achieved with placebo) and values remained above those of premenopausal women (fig 1). These changes in bone resorption were associated with relatively small increases in spine BMD (3.9% (CI 3.6% to 4.3%) and 4.9% (CI 4.6% to 5.3%) for 0.5 mg and 1.0 mg, respectively, after 3 years) and a non-significant trend towards reduction in fracture risk. Clearly the doses used or the drug-free interval, or both, had to be modified for optimal efficacy, illustrating also the main difficulties encountered in the development of intermittent regimens.

This ibandronate study was pivotal for further understanding the efficacy determinants of intermittent regimens as it clearly showed that increases in BMD of a magnitude similar to or greater than that induced by calcitonin or raloxifene failed to decrease fracture risk significantly. This underlines the critical role of adequate reduction of bone resorption for this action. It also raised an additional question about the pattern of response after short bisphosphonate administration. As mentioned, in this study only residual values of markers of bone resorption were measured. It was previously shown, however, that soon after IV bisphosphonate administration, even with the doses of ibandronate used in the study described above, there is a substantial reduction in markers of bone resorption, which gradually increase in the following months of dose-free time, reaching the residual value just before the administration of the new dose.⁵³ The question is, therefore, whether the magnitude of fluctuation of bone resorption is responsible for the inadequate protection of the skeleton, or whether the final actual residual value achieved determines the antifracture efficacy of intermittent bisphosphonate administration, or both. From a theoretical point of view it would have been interesting to explore the relationship between the area under the effect curve and antifracture efficacy of intermittent

Figure 1 Changes in urinary NTX after treatment of women with postmenopausal osteoporosis with single IV injections of placebo, ibandronate 0.5 mg and ibandronate 1.0 mg every 3 months. Geometric means are shown. Samples were obtained before the administration of ibandronate (residual values). Adapted from Delmas *et al.*³⁷ Shaded area depicts premenopausal range (mean (SD)).⁵² BCE, bone collagen equivalent.

Figure 2 Changes in urinary NTX after treatment of women with postmenopausal osteoporosis with placebo or oral ibandronate 2.5 mg/day or 20 mg every other day for 12 doses every 3 months. Geometric means are shown. Samples were obtained before the administration of ibandronate. Additional samples were obtained at months 1, 2, 10 and 11. Adapted from Riis *et al.*⁵⁴ Shaded area depicts premenopausal range (mean (SD)).⁵² BCE, bone collagen equivalent.

regimens but sufficient experimental data for such analyses are not available.

Efficacious regimens

The results of the study with ibandronate,³¹ indicated that dose and dosing intervals of intermittent bisphosphonate regimens need to be carefully assessed before engaging in long-term fracture studies, and that responses should be compared with those of daily administration, when available, which have predictable outcomes.

Such an approach was tested with oral ibandronate. In a phase II study, women with postmenopausal osteoporosis were randomised to receive daily oral (2.5 mg) or intermittent (20 mg every other day for 12 doses every 3 months; between-dose interval >2 months) ibandronate or placebo.⁵⁴ Taking into account the low bioavailability of oral bisphosphonates in general (about 0.6%), these regimens provide essentially an equivalent total systemic annual dose of about 6 mg, greater therefore than the doses given in the study with IV ibandronate (2 and 4 mg annually). In this study, more frequent measurements of bone resorption markers provided information about the pattern of response, additional to those obtained by measuring only residual values. Daily ibandronate reduced bone resorption by 60–70% and well into the premenopausal range, and the pattern of response was that expected from the daily administration of a bisphosphonate (fig 2). The “intermittent” group showed another response pattern. One month after the start of treatment, bone resorption was reduced to a level lower than that found with daily treatment. Thereafter, bone resorption started to increase gradually, but residual values remained within the premenopausal range and there were no marked fluctuations of the values, which stayed close to those achieved with daily treatment.

These changes in bone resorption markers with both ibandronate regimens were associated with significant and equivalent increases in spine BMD after 2 years. It is, therefore, feasible to obtain a pattern of response closely mimicking that induced by daily treatment and to maintain residual bone marker values within the premenopausal range with an intermittent regimen, and in this case with a dose-free interval of more than 2 months. If the assumption about the importance of the relation between the pattern of decrease of bone remodelling and bisphosphonate efficacy was correct, such an intermittent regimen should be able to reduce the risk

of fractures in osteoporotic women. This hypothesis was tested in BONE, a phase III clinical study with vertebral fracture as the primary end point that explored the efficacy of the daily and intermittent regimens of ibandronate described above.¹⁴

As previously reported, oral daily and intermittent ibandronate therapy significantly reduced the incidence of new vertebral fractures in osteoporotic women by 62% and 50%, respectively, after 3 years.¹⁴ This was the first demonstration of an efficacious intermittent bisphosphonate regimen in a prospective study designed specifically to examine this question. After daily ibandronate, bone resorption showed the expected response and pattern that has been associated with a reduction in fracture risk with other bisphosphonates also. Residual values after intermittent administration were higher than those obtained with daily ibandronate but remained within the premenopausal range.³⁷ The results of this study indicated that for antifracture efficacy with intermittent bisphosphonate regimens fluctuations in bone resorption are not of primary importance provided that these are not excessive and occur within the premenopausal range.

TOTAL BISPHOSPHONATE DOSE

The study described above, suggested, in addition, that for optimal efficacy a total bisphosphonate dose at least as high as the total dose of daily drug should be provided at appropriate intervals. For ibandronate this should, therefore, be 6 mg or higher a year. It also provided information for the design of therapeutic regimens with intermittent ibandronate. The reduction in fracture risk was numerically different between the two regimens, although not significantly so, with daily ibandronate showing a better response. Also, the magnitude of suppression of residual values of bone resorption and the subsequent gains in BMD were lower with the intermittent regimen than with the daily dose.^{14 37} These results are in line with conclusions derived from pharmacokinetic/pharmacodynamic modelling of the relation between various regimens with oral alendronate and long-term changes in BMD. It was reported that although weekly doses are therapeutically equivalent to daily doses for up to 10 years of treatment, less frequent administration of the same total dose is not.³⁵ These experimental and modelling findings suggested that for full equivalence to a daily regimen the prolongation of a drug-free interval with an intermittent regimen should be compensated by a higher total dose. This hypothesis was supported for ibandronate by kinetic/pharmacodynamic modelling analysis using data from clinical studies³⁶ and was subsequently tested clinically.

A randomised, double-blind, placebo-controlled pilot study explored the effect of once-monthly dosing of ibandronate on bone resorption.⁵⁷ As a result of the previously obtained clinical data with intermittent ibandronate, the modelling data and the above mentioned hypothesis, two doses were tested, 100 mg and 150 mg once a month (the total monthly dose of daily ibandronate is 75 mg). These two doses provide an annual cumulative dose of approximately 7 mg and 11 mg ibandronate, respectively. There was a dose-dependent reduction of bone resorption and the higher dose decreased bone resorption well into the premenopausal range (fig 3). In addition, the pattern of response was similar to that seen with daily ibandronate, with small fluctuations. Similar data were reported in an abstract by Geusens *et al.*⁵⁸

The hypothesis was, thus, confirmed pharmacodynamically and led to the design of a phase III study that compared once-monthly dosing with the efficacious daily regimen.⁵⁹ Results confirmed that for optimal pharmacological equivalence to the daily regimen, the monthly drug-free interval needed to be compensated by a higher total ibandronate dose, as 2.5 mg/day

Figure 3 Changes in urinary NTX after treatment of postmenopausal women with placebo or oral ibandronate 2.5 mg/day, 100 mg once a month and 150 mg once a month. Geometric means are shown. Ibandronate was given on days 1, 31 and 61 and on these days samples were obtained before the administration of the bisphosphonate. Adapted from Reginster *et al.*⁵⁷ Shaded area depicts premenopausal range (mean (SD)).⁵² BCE, bone collagen equivalent.

and 100 mg once a month induced similar and not statistically different responses.^{59–60} Moreover, response could be improved by higher doses, as 150 mg once a month was shown to produce greater suppression of bone resorption and increase in BMD,^{59–60} which may lead to greater antifracture efficacy. Bauer *et al* reported previously that greater reductions in serum bone-specific alkaline phosphatase with daily oral alendronate were associated with fewer hip and non-spine fractures, with no evidence that this relationship between change in marker and fracture risk was non-linear.⁴⁰ It may, therefore, be that greater suppression of bone turnover within the premenopausal range by bisphosphonate is required for the prevention of these fractures.

The relationship between bisphosphonate dose and dose interval was also explored in clinical studies with IV ibandronate injections. One such study examined the effect on bone turnover and BMD of 1 mg (4 mg annual systemic dose) and 2 mg (8 mg annual systemic dose) ibandronate injections given every 3 months *v* placebo.⁶¹ The 3-monthly 2 mg ibandronate dose produced greater reductions in residual values of bone resorption at 3, 6 and 12 months of treatment than the 1 mg dose. Moreover, residual bone resorption levels after 3 months were close to the premenopausal mean and remained at this level throughout continued treatment.

In tandem with these changes in bone resorption, the 2 mg dose induced significantly greater increases in mean (SD) BMD at the spine 5.0 (4.4)% *v* 2.8 (3.7)%, $p < 0.0001$ and total hip (2.9% *v* 2.2%, $p < 0.02$) after 1 year. Importantly, the reductions in bone turnover and gains in BMD observed with the 2 mg IV ibandronate regimen were comparable to those reported after 1 year with daily oral ibandronate, which has documented antifracture efficacy.

This study confirmed that the doses of ibandronate investigated earlier³¹ were suboptimal and provided additional support for the notion that a total annual systemic ibandronate dose of 6 mg or higher is essential for efficacy. However, reduction of bone resorption during the latter part of a 3-month period using an IV dose of 2 mg was not consistent across studies.^{53–61–62} Therefore, for optimal responses with IV ibandronate either the dose or the dose interval had to be further modified. This is a general principle for bisphosphonates given intravenously, the applicability of which in clinical practice will be determined by the tolerability of a single IV dose. For ibandronate, this could be achieved by keeping the dose constant and shortening the

dose interval or by increasing the dose while maintaining the administration frequency (every 3 months). Therefore, the IV doses of ibandronate selected for further study were 3 mg every 3 months and 2 mg every 2 months. These were tested against daily oral ibandronate (2.5 mg/day) in women with osteoporosis. As predicted, both regimens reduced bone resorption to a similar extent that was comparable to that induced by the daily administration of the bisphosphonate.⁶³ In addition, the intravenous regimens induced significantly higher increases in BMD.⁶³

Taken together, these data indicate that for the optimal design and efficacy of an intermittent regimen with oral or IV bisphosphonate, the dose given should be adjusted to the drug-free interval. In the case of ibandronate, an annual systemic dose of 4 mg is clearly inadequate, whereas higher doses provide better responses. For consistent reduction of bone resorption the annual systemic dose should be between 11 and 12 mg for dose-free intervals of between 1 and 3 months. Considering the differences in potency among bisphosphonates, these doses lie between a dose of 30 mg alendronate and 4 mg zoledronate that were shown in preliminary studies to induce a constant suppression of bone resorption for 1 year when given intravenously to osteoporotic patients.^{51–64} These responses conform with the differences in antiresorptive potencies of the three bisphosphonates. In addition to the sustained suppression of bone resorption, the intravenous administration of 30 mg of alendronate (7.5 mg/day for four consecutive days) induced an increase in BMD of 5% after 1 year. The corresponding cumulative oral dose of alendronate (10 mg/day over 1 year is about 24 mg (assuming absorption of 0.65%); thus, 6 mg lower. Although there is no oral zoledronate preparation for comparison, this pattern of suppression of bone resorption is expected to be associated with significant antifracture efficacy with this bisphosphonate also.

CONCLUSIONS

The ibandronate data discussed here demonstrate that first, the magnitude of reduction of the rate of bone resorption (and turnover) at the end of the drug-free interval, rather than the pattern of fluctuation in the rate of bone resorption, determine the antifracture efficacy of a bisphosphonate, provided that these fluctuations occur within the premenopausal range.

Second, the total bisphosphonate dose given with intermittent dosing regimens should be higher than the cumulative daily dose given over the same period of time. Thus, the total dose concept proposed earlier by Bauss and colleagues^{65–66} for the same bisphosphonate is applicable only under certain conditions, as described.

Finally, the intermittent administration of a bisphosphonate at the appropriate dose given by a single administration will predominantly depend on the potency and the tolerability of the bisphosphonate, which will subsequently also determine the drug-free interval. A generalisation of these conclusions to the whole bisphosphonate class has the limitation that these are based mainly on clinical data obtained with ibandronate. Subtle differences in bone binding affinities may exist among nitrogen-containing bisphosphonates that in turn may affect their distribution, retention and release from bone.^{67–68} Such differences may alter their pharmacodynamics. However, limited data with other bisphosphonates are in line with these conclusions.

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