Osteoporos Int (2013) 24:253–262
DOI 10.1007/s00198-012-2179-3

ORIGINAL ARTICLE

A meta-analysis characterizing the dose–response relationships for three oral nitrogen-containing bisphosphonates in postmenopausal women

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Received: 26 July 2012 / Accepted: 28 September 2012 / Published online: 26 October 2012

Abstract
Summary A meta-analysis of spine BMD dose–response relationships for alendronate, risedronate, and ibandronate was performed. Data from all three oral bisphosphonates conform to a log–linear relationship between dose and change in spine BMD relative to placebo at 1 year, with an incremental gain of about 1 % for each doubling of dose.
Introduction Animal data suggesting differences in potency and differences in approved oral dosage strengths for alendronate, risedronate, and ibandronate in the treatment of osteoporosis raise questions about their dose–response relationships and relative potencies in humans.
Methods A meta-analysis of dose–response relationships for spine BMD increases for these three bisphosphonates was performed using data from 21 placebo-controlled trials that collectively included over 13,000 patients on active treatment and over 8,000 on placebo.
Results For alendronate over the range of 1 to 20 mg/day, there was a strong log–linear relationship between dose and the increase in spine BMD relative to placebo at 1 year (R^2 = 0.994 using sample-weighted means). For each doubling in alendronate dose, there was an incremental gain of about 1 % in spine BMD. On the same scale, risedronate and ibandronate are approximately equipotent to alendronate on a weight-for-weight basis. The increases in BMD efficacy with each doubling of dose are parallel for all three nitrogen-containing bisphosphonates (NCBPs).
Conclusions All three NCBPs are approximately equipotent and exhibit a log–linear relationship between dose and the increase in spine BMD. Differences in efficacy between the available oral bisphosphonate regimens appear to be a function of dose rather than inherent differences in therapeutic potential.

Keywords Alendronate · Dose response · Ibandronate · Meta-analysis · Risedronate

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Introduction

Three oral nitrogen-containing bisphosphonates (NCBPs), alendronate, risedronate, and ibandronate, are used widely worldwide for the treatment and prevention of osteoporosis in postmenopausal women. Early animal studies suggested differences in potency between these NCBPs. For example, in 1991, Mühlbauer and colleagues published a rat study suggesting that ibandronate was about twice as potent as risedronate and ten times more potent than alendronate [1]. In addition, the approved daily doses for treatment of postmenopausal osteoporosis are lower for ibandronate (2.5 mg) and risedronate (5 mg) than for alendronate (10 mg). Similarly, the approved weekly dose for risedronate (35 mg) and monthly doses for risedronate and ibandronate (both 150 mg) each provide the same cumulative dose as 5 mg per day, whereas the weekly dose of alendronate for treatment of osteoporosis (70 mg) provides the same cumulative dose as 10 mg/day. Although alendronate 5 mg daily and 35 mg weekly are approved for prevention of osteoporosis, proportionally by far the greatest use of alendronate is of the 70 mg weekly formulation. These differences in reported animal data and approved dosage strengths suggest possible differences in potency between different oral NCBPs in humans. However, the Mühlbauer rat study used the subcutaneous rather than oral route of administration [1]. In contrast, a study by Green and colleagues suggested that, even in rats, if the bisphosphonates are administered orally, rather than subcutaneously, the potencies of these three NCBPs

appear to be similar [2]. Furthermore, it is known that relative potencies of different drugs may vary between species, and thus, the rat studies may have little relevance to the question of the relative potencies of oral bisphosphonates in postmenopausal women.

The current meta-analysis was performed to better characterize the dose–response relationships and to compare relative potencies of each of the three oral NCBPs from placebo-controlled studies of treatment or prevention of osteoporosis in postmenopausal women.

Materials and methods

A search was conducted to identify all published placebo-controlled studies of oral alendronate, risedronate, or ibandronate for treatment and/or prevention of postmenopausal osteoporosis that met the study criteria. Only studies that presented percent changes in spine BMD for each dose of the NCBP studied and placebo at 1 year were considered. In cases where the 1-year spine BMD data were presented only graphically, every attempt was made to accurately measure the differences from placebo at 1 year scaled from the published figures. Studies complicated by other factors affecting bone, such as corticosteroid use or malignancy, such as the studies by Eastell et al. and Delmas et al. using risedronate, were excluded [3, 4]. Also, a study of alendronate which required morning post-dose fasting for 2 h was excluded, since such dosing is associated with substantially higher oral bioavailability relative to morning dosing 30 to 60 min before breakfast [5, 6]. However. studies with dosing of risedronate 2 h after a meal with water only for the interval of plus/minus 2 h around dosing were included, as absorption of risedronate using such dosing has been reported to be similar to that with dosing 30 to 60 min before breakfast [7]. Calcium and/or vitamin D supplements were allowed as long as they were used equally across groups. In one study which compared calcium alone with either alendronate plus calcium or alendronate alone, only the two groups that received calcium were considered in the analysis [8].

The increases in spine BMD relative to placebo after 1 year of treatment were extracted from the published reports of 12 placebo-controlled studies of alendronate, which included a total of 5,643 patients on placebo and 7,090 on alendronate [8–19]. Similar data were obtained from six placebo-controlled studies of risedronate, which collectively included 1,672 on placebo and 3,354 on risedronate [19–24], and five placebo-controlled studies of ibandronate, which collectively included approximately 1,328 on placebo and 2,834 on ibandronate [25–29]. Spine BMD was selected as the parameter of primary interest as this is the most consistently reported and responsive site and is associated with good precision. The response at 1 year was selected because far greater increases in BMD occur during the first year compared to those in subsequent years and placebo-controlled data for the 1-year time point were reported more consistently than for later time points. For example, only two of the 12 alendronate studies provided 3-year results for one or more groups that remained on the same dose of alendronate for the entire 3 years. In addition, differential rates of study discontinuation between studies have a more profound effect at later study time points due to carrying forward of data used in intention-to-treat analyses.

One of the alendronate studies used weekly dosing with alendronate 70 mg [19]. One risedronate study compared dosing with 5 mg daily continuously with this dose for only the first 2 weeks of each month, which provides an average daily dose of 2.3 mg [20]. Two of the ibandronate studies used the same intermittent dosing regimen in which ibandronate was given as 20 mg on alternate days for 12 doses at the beginning of each calendar quarter [26, 27]. The 240 mg per quarter thus administered provided the cumulative equivalent to a daily dose of 2.63 mg. One ibandronate study used monthly dosing at 150 mg versus placebo, which provided the cumulative equivalent to a daily dose of 5 mg/day [29]. Since there is no evidence that either intermittent or monthly dosing are any less effective for the same total dose as continuous daily dosing [22], the intermittent, weekly, and monthly dosing groups for all three NCBPs were included in these analyses using the equivalent daily oral doses.

Regression analyses of the alendronate data were performed using Excel 2007 (Microsoft). The approaches used to assess dose response and relative potency are further described in conjunction with the study results.

Results

Alendronate dose response

Summary details of the 12 alendronate placebo-controlled studies and the increase in spine BMD for each active treatment group relative to placebo are provided in Table 1. Nine of the twelve were osteoporosis treatment studies. The precise definition of the osteoporosis populations in terms of BMD and prevalent vertebral fracture status varied markedly among these treatment studies. Two studies were in osteoporosis prevention populations [14, 15] and one had no BMD entry criteria, although the study reported that over half of the patients had osteoporosis at baseline [16]. In three of the 12 studies, patients were instructed to remain fasting for at least 1 h after each dose [9, 10, 14], whereas the remainder required continued fasting for only 30 min after dosing. Five studies included multiple doses of alendronate [9, 10, 12, 14, 15]. In all 12 studies, alendronate was administered after an overnight fast. Statistical analysis of

Table 1 Summary of alendronate studies

Alendronate (ALN) studies				
Study first author, year, and reference	Subject definition	Dosing instructions	Doses (and *N* per group)	Spine BMD at 1 year vs. placebo
Adami, 1995 [9]	PM women age 40–59 with spine BMD T-score<−2.0	Water only at least 1 h before breakfast	Placebo (67)	–
			ALN 10 mg (65)	4.9 %
			ALN 20 mg (67)	6.0 %
Liberman, 1995 [10]	PM women age 45–80 with spine BMD T-score≤−2.5	Water only at least 1 h before breakfast	Placebo (397)	–
			ALN 5 mg (202)	4.6 %
			ALN 10 mg (196)	5.7 %
			ALN 20 mg (199)	6.2 %
Black, 1996 [11]	PM women age 55–81 with femoral neck BMD ≤0.68 g/cm^2 (Hologic) and ≥1 prevalent vertebral fracture	Water only at least 1/2 h before breakfast	Placebo (1,005)	–
			ALN 5 mg (1,022)	3.4 %
Bone, 1997 [12]	PM women age 60–85 with spine BMD T-score≤−2.0	Water only at least 1/2 hour before breakfast	Placebo (91)	–
			ALN 1 mg (86)	0.9 %
			ALN 2.5 mg (89)	2.2 %
			ALN 5 mg (93)	4.2 %
Cummings, 1998 [13]	PM women age 55–81 with femoral neck BMD ≤0.68 g/cm^2 (Hologic) and no prevalent vertebral fracture	Water only at least 1/2 h before breakfast	Placebo (2,218)	–
			ALN 5 mg (2,214)	3.6 %
McClung, 1998 [14]	PM women age 40–59 with spine BMD T-score>−2.0	Water only at least 1 h before breakfast	Placebo (90)	–
			ALN 1 mg (92)	1.9 %
			ALN 5 mg (88)	4.7 %
			ALN 10 mg (88)	5.2 %
			ALN 20 mg (89)	5.5 %
Hosking, 1998 [15]	PM women age 45–59 without prior diagnosis of osteoporosis	Water only at least 1/2 h before breakfast	Placebo (461)	–
			ALN 2.5 mg (452)	3.1 %
			ALN 5 mg (445)	3.8 %
Greenspan, 1998 [16]	Healthy PM women age ≥65	Water only at least 1/2 h before breakfast	Placebo (60)	–
			ALN 5 mg (60)	3.6 %
Pols, 1999 [17]	PM women age under 86 with spine BMD T-score≤−2.0	Water only at least 1/2 h before breakfast	Placebo (958)	–
			ALN 10 mg (950)	4.9 %
Bone, 2000 [18]	PM women age 42–82 with spine BMD <0.862 g/cm2 (Hologic)	Water only at least 1/2 h before breakfast	Placebo (50)	–
			ALN 10 mg (92)	4.5 %
Hosking, 2003 [19]	PM women age 60–90 with spine or hip BMD T-score≤−2.5 or both ≤−2.0	Water only at least 1/2 h before breakfast (ALN only)	Placebo (108)	–
			ALN 70 mg/week (219)	4.7 %
Bonnick 2007 [8]	PM women age >45 with spine BMD T-score≤−2.0	Water only at least 1/2 h before breakfast	Placebo (138)	–
			ALN 10 mg (282)	3.5 %

PM postmenopausal

BMD was predominantly by a "modified intention-to-treat" approach in which only patients with BMD at baseline and at least one follow-up visit were included in the analyses.

The changes in spine BMD relative to placebo at 1 year as a function of dose (on a log scale) are plotted for each alendronate study in Fig. 1. Across these studies, there appears to be a log–linear dose–response relationship over the range of 1 to 20 mg. There is no suggestion that any substantial difference in dose response exists between the two osteoporosis prevention studies [14, 15] and the other studies. Responses at any given dose appeared to be slightly greater on average in the three studies in which continued

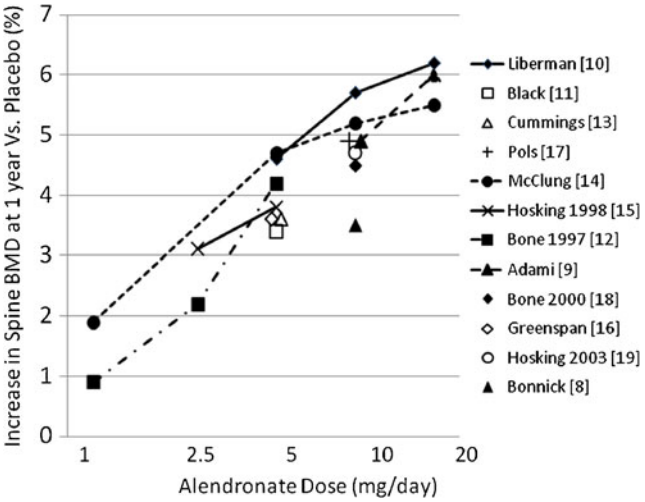

Fig. 1 Mean increase in spine BMD at 1 year vs. placebo in 12 alendronate studies. See Table 1 for study details

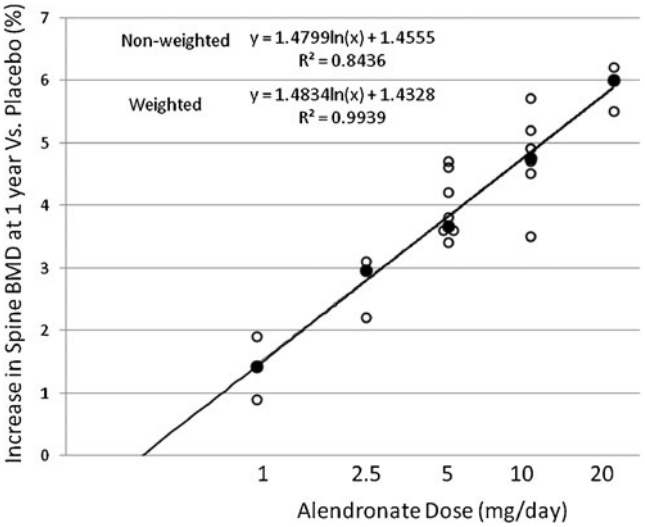

Fig. 2 Mean increase in spine BMD at 1 year vs. placebo across all alendronate studies. *Open circles* represent the same data points from the individual studies depicted in Fig. 1. *Filled circles* represent the sample-size-weighted means for each dosage strength. The log–linear regression lines (which are virtually superimposed) and corresponding formulae and correlation coefficients are shown both for the data from the individual studies and for the weighted means for each dosage strength

fasting for 1 h following dosing was required [9, 10, 14] compared to the remaining studies that required continued fasting for only 30 min after dosing.

Thus, in spite of minor differences in dosing instructions and the heterogeneity in the patient populations included in the different studies, it seems reasonable to combine all of the data points from all of the alendronate studies to provide an overall estimate of the dose–response relationship for alendronate across these study populations. Although sample size in the alendronate groups varied by study, in all 12 studies, there were a minimum of 65 patients in each alendronate dose group and thus the point estimates for response are likely to be reasonably precise in all studies. However, as an alternative approach, Table 2 shows the combined sample size for the total experience with alendronate at each of the five doses studied and the corresponding mean increases in spine BMD relative to placebo weighted for sample size of each alendronate dose group in each study.

Figure 2 shows the log–linear regression plot of the alendronate studies using these two different approaches. In the individual-studies approach, the data points from the individual studies were regressed without regard to differences in sample size between study/dose groups. This resulted in a strong positive correlation (R^2=0.844), which in itself supports the homogeneity of response despite the marked differences in population characteristics and variations in post-dose fasting periods across the studies. In the weighted-means approach, the mean spine BMD increases weighted for the alendronate-dose-group sample size in each study were used to more precisely estimate the average response at each dosage strength. This resulted in an even stronger correlation with an R^2 of 0.994. The best fit log–linear regression lines for the two approaches are virtually superimposed (both are plotted in Fig. 2). The slopes of both regression lines each correspond to a 1.03 % increase in spine BMD for each doubling of dose. On the basis of the extremely tight correlation of the weighted-mean approach, this regression line was used for comparison to the other NCBPs studied.

In order to see if a similar relationship exists for other BMD measurement sites, an analysis of increase in trochanter BMD relative to placebo as a function of log dose was also conducted. The plot (not shown) showed a similar progressive increase in BMD response to that seen at the spine and using the individual studies approach the resulting R^2 was 0.710, which is only slightly lower than that for the spine (0.844).

Table 2 Mean increases in BMD relative to placebo after 1 year of alendronate treatment weighted for sample size per group within each alendronate study

Dose (mg)	Total sample size	Weighted mean increase in spine BMD (%)
1	178	1.42
2.5	541	2.95
5	4,124	3.66
10	1,892	4.75
20	355	5.99

Risedronate dose response

Six placebo-controlled risedronate studies met the criteria for inclusion (Table 3). Four of the studies required patients to have osteoporosis as defined either by prevalent vertebral

Table 3 Summary of risedronate studies

Risedronate (RIS) studies				
Study	Subject definition	Dosing instructions	Doses (and *N* per group)	Spine BMD at 1 year vs. placebo
Mortensen, 1998 [20]	Women 6–60 months after menopause with normal BMD	2 h after dinner with water only 2 h pre- and post-dosing	Placebo (36)	–
			RIS 5 mg 2 weeks/month (38)	2.9
			RIS 5 mg (37)	4.1
Harris, 1999 [21]	PM women age <86 with ≥1 prevalent vertebral fracture	Water only 30–60 min before breakfast	Placebo (815)	–
			RIS 2.5 mg (811)	2.0 %
			RIS 5 mg (813)	3.0 %
Reginster, 2000 [22]	PM women age <86 with ≥2 prevalent vertebral fractures	Water only 30–60 min before breakfast	Placebo (407)	–
			RIS 2.5 mg (408)	3.1 %
			RIS 5 mg (407)	3.8 %
Fogelman, 2000 [23]	PM women age <81 with BMD T-score≤−2.0	Water only 30–60 min before breakfast	Placebo (180)	–
			RIS 2.5 mg (184)	2.0 %
			RIS 5 mg (177)	3.3 %
Hosking, 2003 [19]	PM women age 60–90 with spine or hip BMD T-score≤−2.5 or both ≤−2.0	2 h after main meal of the day with water only 2 h pre- and post-dosing	Placebo (108)	–
			RIS 5 mg (222)	2.7 %
Hooper, 2006 [24]	PM women age within 3 years of menopause with spine BMD T-score>−2.5	Water only 30–60 min before breakfast	Placebo (126)	–
			RIS 2.5 mg (128)	1.9 %
			RIS 5 mg (129)	2.8 %

PM postmenopausal

fracture(s) or low BMD [19–24]. In two studies, patients received their risedronate 2 h after a meal [19, 20] while in the remaining trials patients were instructed to continue fasting for 30 to 60 min after morning dosing [21–24]. Four studies provided experience with risedronate at both 2.5 and 5 mg, one with only 5 mg and one with 5 mg either continuously or for only the first 2 weeks of each month.

Figure 3 overlays the data from the six risedronate studies on top of the alendronate weighted mean regression line. The point estimates from the Mortensen and Reginster studies (open squares and closed circles) fall almost precisely on the alendronate regression line [20, 22], whereas those from the other studies [19, 21, 23, 24] each fell approximately 1 % below that line. In all five studies with two active risedronate groups, the increase in spine BMD at 5 mg was approximately 1 % greater than that seen at 2.5 mg (or an average of 2.3 mg in the monthly intermittent group), and thus, the slope of the dose–response curve between those two doses is consistent with that seen for alendronate (about 1 % for each doubling of dose) across the entire dose range studied. The sample-size-weighted means for from the five risedronate studies with more than one risedronate groups were 2.3 and 3. 3 % at the 2.3/2.5 and 5 mg doses, respectively, and thus, the slope (a mean increase of approximately 1 % with a doubling of dose from 2.5 to 5 mg/day) is consistent with that for alendronate over the entire dose range from 1 to 20 mg.

Ibandronate dose response

The five ibandronate studies that met the analysis criteria are summarized in Table 4 [25–29]. The three osteoporosis treatment studies instructed patients to continue fasting for

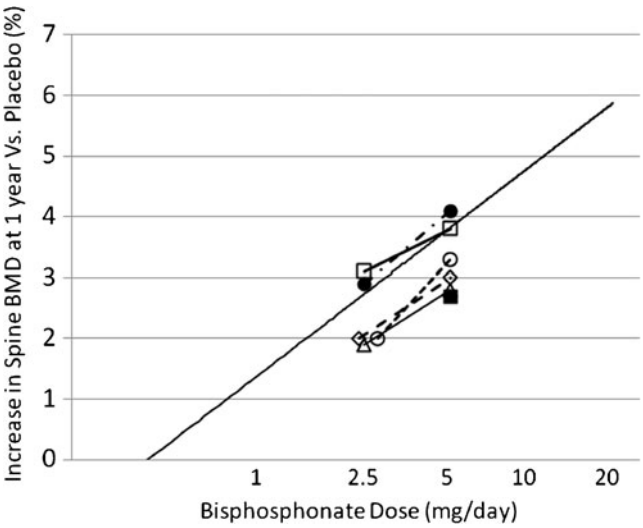

Fig. 3 Mean increase in spine BMD at 1 year vs. placebo in the six risedronate studies (see Table 3 for details). Hosking [19], *closed square*; Mortensen [20], *closed circles*; Harris [21], *open diamonds*; Reginster [22], *open squares*; Fogelman [23], *open circles*; Hooper [24], *open triangles*. These data are overlayed on top of the alendronate sample-size-weighted mean regression line shown in Fig. 2

Table 4 Summary of ibandronate studies

Ibandronate (IBN) studies				
Study	Subject definition	Dosing instructions	Doses (and *N* per group)	Spine BMD at 1 year vs. placebo
Ravn, 1996 [25]	Women >10 years past menopause, age less than 75 and forearm BMD T-score<−1.5	Water only at least 1 h before breakfast	Placebo (30)	–
			IBN 0.25 mg (30)	0.7 %
			IBN 0.5 mg (30)	1.8 %
			IBN 1 mg (30)	3.2 %
			IBN 2.5 mg (30)	4.0 %
			IBN 5 mg (30)	3.1 %
Riis, 2001 [26]	PM women age 55–76 with spine and/or femoral neck BMD T-score<−2.5	Water only at least 1 h before breakfast	IBN placebo (81)	–
			IBN 2.5 mg (81)	3.3 %
			IBN 2.63 mg[a] (78)	3.3 %
Chesnut, 2004 [27]	Age 55–80, T-score −2 to −5 in ≥1 vertebra and 1–4 prevalent fractures	Water only at least 1 h before breakfast	Placebo (975)	–
			IBN 2.5 mg (977)	3.5 %
			IBN 2.63mg[a] (977)	2.9 %
McClung, 2004 [28]	PM women with spine BMD T-score>−2.5	Water only at least 1/2 h before breakfast	Placebo (162)	–
			IBN 0.5 mg (162)	0.5 %
			IBN 1 mg (166)	0.8 %
			IBN 2.5 mg (163)	2.6 %
BA18492 [29]	PM age 45–60 with spine BMD T-score<−1.0 and > −2.5	Water only at least 1 h before breakfast monthly	Placebo	–
			IBN 5 mg[b]	4.1 %
			Total study *N*=160	

PM postmenopausal

[a] Daily dose equivalent for intermittent dosing regimen

[b] Daily dose equivalent for monthly 150 mg dosing regimen (see "Materials and methods")

1 h after morning dosing [25–27], whereas in the prevention study by McClung and colleagues patients were required to wait only 30 min after dosing before eating [28]. The precise dosing instructions for the study labeled BA18492 is not provided on the Roche website (it is not otherwise published), but since it was conducted with monthly ibandronate, it seems likely that patients were asked to adhere to the labeled instructions, which require a 1-h post-dose fast.

Figure 4 is similar to Fig. 3 for risedronate, but instead overlays the data from the five ibandronate studies on top of the alendronate sample-size-weighted mean regression line. The data from the Ravn study (open circles) for the lower four doses, but not the 5 mg dose, fall above the alendronate regression line [21]. The lower value for 5 mg might be explained in part by the high (40 %) drop-out rate seen in the 5 mg group. Note that the Ravn study included only 30 patients per treatment arm at baseline, whereas the other studies were considerably larger and in aggregate contained data from over 3,800 patients.

The data from the Riis, Chesnut, McClung, and BA18492 studies (open squares, open triangles, open diamonds, and filled square, respectively) each fell close to the alendronate regression line [26–28]. The two groups that received ibandronate 20 mg on alternate days for 12 doses repeated every 3 months (averaging 2.63 mg/day) had increases in

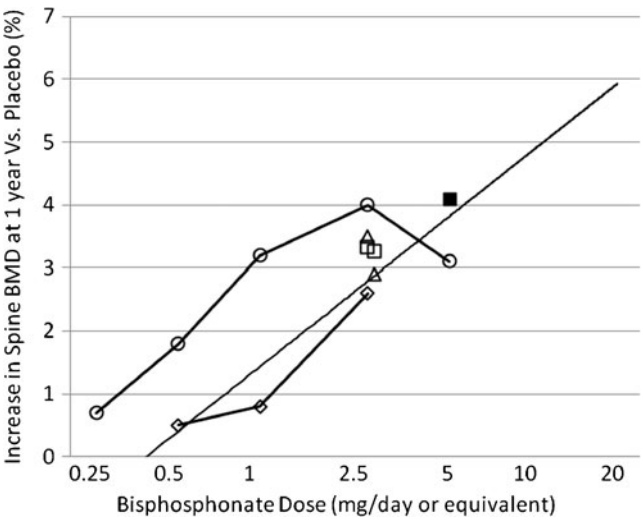

Fig. 4 Mean increase in spine BMD at 1 year vs. placebo in the five ibandronate studies (see Table 4 for details). Ravn [21], *open circles*; Riis [22], *open squares*; Chesnut [23], *open triangles*; McClung [21], *open diamonds*; BA18492 [21], *filled square*. These data are overlayed on top of the alendronate weighted mean regression line

BMD that were similar to those seen with continuous daily ibandronate 2.5 mg/day. Although only two of the studies contained multiple doses of ibandronate, the overall slope of the curves in those studies and across all five studies appears to be similar to that for alendronate and risedronate.

Discussion

Several alendronate osteoporosis studies included more than one dose of alendronate, and individually, those studies provided useful data that helped inform the selection of the alendronate doses that became approved for treatment and prevention of osteoporosis [9, 10, 12, 14, 15]. Cranney and colleagues performed a meta-analysis across all available alendronate studies [30]. These authors grouped doses of 10 mg and higher as having comparable efficacy on spine BMD in what they referred to as a "parsimonious analysis," but clearly distinguished that 5 mg had lower efficacy than those higher doses. They did not consider doses below 5 mg on the grounds that they were not used clinically. The results of this "lumping" analytical approach might suggest that alendronate 10 mg is at the top of the dose–response curve. In contrast, the present meta-analysis sought to examine the potential for a continuous dose–response relationship for alendronate using regression analysis across the entire range of doses studied from 1 through 20 mg. Note that alendronate 40 mg daily was included in a study by Chesnut that was not considered in the current analysis, as patients in that study were required to remain fasting for 2 h after dosing [5]. In that study, there appeared to be a flat dose–response curve with 5 mg having similar efficacy to all higher doses. This may have been due to the greater absorption of alendronate associated with the prolonged post-dose fasting period [6] and perhaps also the relatively small sample size of around 30 patients per group. Also, in that study, the 40 mg daily regimen was associated with a higher discontinuation rate due to upper gastrointestinal adverse events.

Among the individual alendronate studies, there is a suggestion that efficacy was slightly greater in studies that required continued fasting for 1 h relative to those that required only 30 min post-dose fasting. It is known that continued fasting for 2 h after dosing provides greater bioavailability than shorter intervals and that consuming NCBPs with or shortly after a meal results in negligible bioavailability, so it is not surprising that fasting for 1 h would permit more NCBP to be absorbed than fasting for only 30 min [6, 7]. This finding is consistent with a study of 30- versus 60-min post-dose fasting for ibandronate by Tanko and colleagues, which reported significantly lower increases in BMD at 48 weeks with the shorter fasting period [31].

The present study provides no evidence that the top of the dose–response curve has been reached at any of the doses of alendronate in the range of 1–20 mg. The fact that the sample-size-weighted correlation coefficient for alendronate is so close to unity (R^2=0.994) allows a formulistic expression of the relationship between increasing alendronate dose and increasing 1-year spine BMD that has not previously been described. Expressed simply, for each doubling of alendronate dose, there was an incremental increase in spine BMD of about 1 %. Whether this relationship would hold at doses above 20 mg cannot be assumed from these data, and it seems likely that at some putative higher dose where suppression of bone turnover would be almost complete that further increases in dose could not continue to increase BMD in the same log–linear fashion.

For all three of the NCBPs, there was approximately a 1 % greater increase in 1-year spine BMD for each doubling of dose. Contrary to the results from studies in rats [1, 2], risedronate appears to be no more potent, and in some studies less potent, than alendronate at equivalent milligram doses when given orally to humans. This is consistent with data from the published meta-analyses of risedronate and alendronate [30, 32, 33]. In the 2003 study by Hosking and colleagues, alendronate 70 mg weekly increased spine BMD at 1 year by 2 % more than risedronate 5 mg daily [19]. Two large studies have confirmed that the increases in BMD at multiple sites are smaller with risedronate 35 mg weekly compared to alendronate 70 mg weekly both at 12 and 24 months [34–37]. Together with the data from the current analysis, those studies confirm that oral risedronate is no more potent, and may even be slightly less potent, than alendronate in postmenopausal women.

Similarly, from the comparisons performed in the current study, ibandronate appears to be either equipotent or only marginally more potent than alendronate. The 1-h post-dose fasting requirement in the majority of the ibandronate studies, in contrast to only 30 min in the majority of the alendronate studies, may account for the observed slightly greater efficacy of ibandronate at equivalent milligram doses in some studies. A direct head-to-head study osteoporotic postmenopausal women by Miller and colleagues further supports the approximate equipotency of alendronate and ibandronate [38]. In that study, osteoporotic postmenopausal women were randomized to receive either alendronate 70 mg weekly or ibandronate 150 mg monthly. At month 12, the BMD increases were 5.8 and 5.1 %, respectively. The 95 % confidence intervals for the difference (0.23; 1.13) did not overlap zero, indicating that alendronate 70 mg weekly was significantly more effective at increasing spine BMD than ibandronate 150 mg monthly. The point estimate for the difference in efficacy (0.73 %) is consistent with the expected lower efficacy of ibandronate due to the fact that the average daily dose equivalent (5 mg) was half that in the weekly alendronate group (10 mg). Therefore, the data from that study are consistent with the conclusion from the current study that oral ibandronate is approximately equipotent to alendronate in humans.

There are several caveats to consider for the current study. The molecular weights of alendronate, risedronate, and ibandronate differ. Also, alendronate weight is calculated on the basis of the free acid, risedronate weight is calculated on the basis of the anhydrous sodium salt, and that of ibandronate on the monosodium monohydrate form (molecular weights of 249.1, 305.1, and 359.24, respectively), so there are corresponding differences in the moles of drug per unit weight. However, to clinicians, this makes little difference as those are simply the ways that dosages are expressed by their respective manufacturers.

Differences in study population and precise dosing instructions, as well as drop-out rates, between studies may have had some influence on the observed increases in spine BMD relative to placebo. However, the relative homogeneity of the responses to alendronate that occurred despite marked differences in these variables between studies suggests that these factors have only a small influence on BMD efficacy relative to placebo.

Another limitation is that the studies of risedronate studied only a narrow range of doses (2.3/2.5 and 5 mg/day), and the maximum daily dose equivalent studied for ibandronate was also 5 mg/day. It is unclear whether higher daily dose equivalents of these NCBPs would have been associated with greater efficacy to parallel that seen with alendronate at the higher doses studied. The animal data suggest that this is likely, since maximal efficacy at high doses of all three NCBPs appears to be similar [1, 2]. However, this remains to be tested in humans.

Also, the current study was not designed to identify which dose of each drug is optimal for treatment of osteoporosis. There appears to be some advantage to having greater increases in BMD, as these have been shown to translate into greater efficacy especially with regard to reducing the incidence of non-vertebral fractures [39]. However, a consistent relationship between greater BMD increases and greater reductions in vertebral fractures has not been demonstrated. Furthermore, there is a balance to be had, since too much suppression of bone turnover for too long may be associated with atypical fractures. Nonetheless, prescribing clinicians may wish to consider the relative potencies and dosage strengths of the available oral NCBPs as one factor that may guide them in their choice of the NCBP regimen best suited for their individual patients.

In conclusion, the current meta-analysis suggests that there are similar log–linear spine BMD dose–response relationships for oral alendronate, risedronate, and ibandronate in postmenopausal women and that for each doubling in dose the efficacy is increased by approximately 1 % for all three bisphosphonates. In addition, all three NCBPs are approximately equipotent. Based on these data, it seems that the choice of dosages used in routine clinical practice for each of these three bisphosphonates was a not a function of finding the top of their respective dose–response curves or clear evidence of differences in potency in humans. Rather, it seems that assumptions made on relative potencies from animal studies, and the resulting dose decisions made during early clinical development, influenced the doses taken into later studies and, ultimately, the clinical doses that are used today. This suggests that the differences in efficacy that exist between the available oral bisphosphonate regimens are simply a function of dose rather than inherent differences in therapeutic potential.

Conflicts of interest None.

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