Patient preference in the management of postmenopausal osteoporosis with bisphosphonates

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Abstract: The leading treatments for postmenopausal osteoporosis are the nitrogen-containing bisphosphonates, which are required long term for optimal benefit. Oral bisphosphonates have proven efficacy in postmenopausal osteoporosis in clinical trials, but in practice the therapeutic benefits are often compromised by patients' low adherence. Nonadherence to bisphosphonate therapy negatively impacts outcomes such as fracture rate; fractures are in turn associated with decreased quality of life. The most common reason cited by patients for their nonadherence is that the strict dosing instructions for bisphosphonates are difficult to follow. One aspect of bisphosphonate administration that can be changed is dosing frequency and several studies have evaluated patient preferences for different dosing schedules. Studies have shown a preference for a weekly bisphosphonate regimen versus daily dosing and it has been demonstrated that this preference for reduced dosing frequency impacts on adherence. Ibandronate is the first nitrogen-containing oral bisphosphonate for osteoporosis that can be administered in a monthly regimen and two robust clinical studies demonstrated a strong patient preference for this monthly regimen versus a weekly regimen. It is important that physicians consider patient preference when prescribing treatment for osteoporosis to ensure that the disease is effectively managed for the long-term benefit of the patient.

Keywords: postmenopausal osteoporosis, bisphosphonates, preference, adherence, ibandronate

Introduction

Osteoporosis affects one in three postmenopausal women but the nature of this generalized, initially asymptomatic, chronic disease means that many patients are unaware that they have this disease until they experience their first fracture. Osteoporosis is characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures (WHO 2003a). Bone loss is the result of an imbalance in bone turnover, with bone resorption occurring at a faster rate than new bone formation. The resulting reduction in bone mass and accompanying damage to bone microarchitecture increases the risk of fracture. The most common form of osteoporosis, that experienced by postmenopausal women, results from reduced estrogen production following the menopause; by increasing bone resorption, estrogen deficiency disrupts the fine balance of the bone remodeling cycle. The spine (vertebral fractures), hips, and wrists (nonvertebral fractures) are the most common sites of osteoporosis-related bone fractures (ie, fractures that are out of proportion to the level of external trauma), although osteoporosis-related fractures can occur at almost any skeletal bone site.

Patients who suffer a vertebral fracture are subsequently at an increased risk of further fractures of all types, including hip fractures (Johnell et al 2001). Large

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prospective fracture studies have demonstrated an increased mortality rate following vertebral fracture. In the Study of Osteoporotic Fractures (SOF), women with at least one prevalent vertebral fracture experienced a 23% greater age-adjusted mortality rate than age-matched controls in the general population (Johnell et al 2004). In patients with postmenopausal osteoporosis in the Fracture Intervention Trial (FIT) (Melton 2000) and the European Prospective Osteoporosis Study (EPOS) (Kanis et al 2004), it was demonstrated that the presence of a vertebral fracture increases the relative risk of mortality by approximately 60%.

In addition to mortality, vertebral fractures are associated with debilitating pain (lasting several weeks or months, with chronic pain lasting for many years), kyphosis (curvature of the spine, leading to height loss, abdominal protrusion, and a hump at the top of the spine), disability, and restricted movement (Ross 1997; Center et al 1999; Lips et al 1999; Cummings and Melton 2002; Hodgson et al 2003; Jalava et al 2003; Lips 2003; Naves et al 2003). There are also psychological effects; patients may experience anxiety about their loss of independence, as well as having a fear of falls and further fractures. Nonvertebral fractures, especially hip fractures, are devastating; around half of the patients who experience a hip fracture will never be able to walk again without assistance (Johnell 1997) and as many as 30% of hip fracture patients require permanent institutional care (Lips et al 1999).

Population-based outcome modeling estimates that Caucasian women over 50 years of age have a one-in-three risk of at least one vertebral fracture and a one-in-five risk of at least one hip fracture in their remaining lifetime (Chrischilles et al 1991). The incidence of osteoporosis-related fractures increases with age, so as the population ages, the number of osteoporosis-related fractures is projected to increase dramatically (Cooper et al 1992; Melton et al 1992). Overall, 40% of women with postmenopausal osteoporosis will suffer one or more fragility fractures during their remaining lifetime (Melton et al 1992). In the year 2000, an estimated 75 million people had osteoporosis in Europe, the US, and Japan (Madhok et al 2000). During 2002, the direct impact of this disease translated to an estimated treatment cost in the US of $17.5 billion (Melton 2003), and in 2003, in the EU, the estimated total direct cost of osteoporosis-related fractures was €25 billion (IOF 2003). Due to the increasing burden of osteoporosis, there is a real need for effective treatments.

Bisphosphonates for the treatment of osteoporosis

The aim of pharmacological intervention in postmenopausal osteoporosis is to reduce the frequency of fractures and, consequently, reduce the related burden on patients and healthcare services and improve patients' quality of life. The leading treatments for postmenopausal osteoporosis are the nitrogen-containing bisphosphonates. These antiresorptive agents reduce postmenopausal bone loss by inhibiting osteoclast activity and reducing the rate of bone resorption. This shifts the balance in favor of bone formation, so that bone mass is increased (Russell and Rogers 1999). In numerous robust clinical trials, the nitrogen-containing bisphosphonates alendronate, risedronate, and ibandronate have consistently demonstrated considerable increases in bone mineral density (BMD) of the spine and hip and decreases in the biochemical markers of bone turnover together with substantial antifracture efficacy (Black et al 1996; Cummings et al 1998; Harris et al 1999; Reginster et al 2000; Chesnut et al 2004). Additionally, the bisphosphonates are the only antiresorptive agents shown in a meta-analysis to significantly reduce the risk of nonvertebral fractures (Cranney et al 2002) and, in a prospective analysis, risedronate was shown to reduce the risk of hip fracture (McClung et al 2001). All three of these bisphosphonates have favorable safety profiles, which have been shown in clinical studies to be similar to placebo. However, long-term treatment with bisphosphonates is required for optimal and sustained benefit and although oral bisphosphonates have proven efficacy in women with postmenopausal osteoporosis in clinical trials, the therapeutic benefits in clinical practice are often compromised by patients' low compliance to, and persistence with, their prescribed medication. Compliance describes the quality of intake of a given medication and considers the extent to which a dosing regimen and its associated instructions are followed. Compliance can often be quantified by a surrogate measure, the medication possession ratio, which is the number of days of available medication divided by the number of days of study follow-up. Persistence describes the length of time patients continue to take their medication, and is defined as the time from treatment initiation to treatment completion/discontinuation. Using the PHARMO Record Linkage System, which includes drug-dispensing records from community pharmacies serving more than 1 million community-dwelling patients in the Netherlands, Penning-van Beest and

colleagues (2004) showed that, overall, 1-year persistence with bisphosphonate therapy (daily or weekly) is low. Among 2124 new bisphosphonate users (alendronate daily or weekly, risedronate daily, etidronate daily), only 43% were persistent at 1 year. As few as 39% of patients may persist with weekly bisphosphonates at 1 year (Cowell et al 2005) and persistence at 2 years could be as low as 18%–23% (Harris et al 2005; Siris et al 2005).

Impact of poor therapeutic adherence

Adherence is a summary term that is determined by compliance and persistence of medication intake. Adherence is thus used to describe the extent and the quality of medication intake. Adherence to medication in postmenopausal osteoporosis is in line with the general finding of low persistence rates in other chronic diseases. Following an inspection of several reviews, the World Health Organization estimated that long-term adherence in chronic disease averages only 50% (WHO 2003b). In a recent meta-analysis of the association between adherence to drug therapy and mortality, nonadherent patients with chronic disorders had a higher mortality rate than their adherent counterparts (Simpson et al 2006). It seems that this is particularly true for diseases like postmenopausal osteoporosis that have few or no clinical symptoms, as the patient does not experience ill effects from the disease or the subsequent benefit from treatment.

In the treatment of osteoporosis, nonadherence to bisphosphonate therapy negatively impacts upon treatment outcomes, for instance poor adherence is associated with a significantly higher rate of vertebral and nonvertebral fractures (see Figure 1), which are in turn associated with a decreased quality of life (Caro et al 2004; Sebaldt et al 2004; Harris et al 2005; Siris et al 2005). The antifracture efficacy of bisphosphonates has been demonstrated in clinical studies with 2–4 years of treatment, therefore if fewer than half of patients are adhering to therapy after just 1 year, it is unlikely that the same degree of antifracture efficacy will be achieved as has been shown in clinical trials. Nonadherent bisphosphonate use also increases the risk of hospitalization associated with osteoporotic fractures (Goettsch et al 2005). Thus, as would be expected, nonadherence with bisphosphonate therapy correlates with reduced gains in BMD and lower reductions in the levels of bone turnover markers (Eastell et al 2003; Sebaldt et al 2004). As well as adversely affecting these primary treatment outcomes,

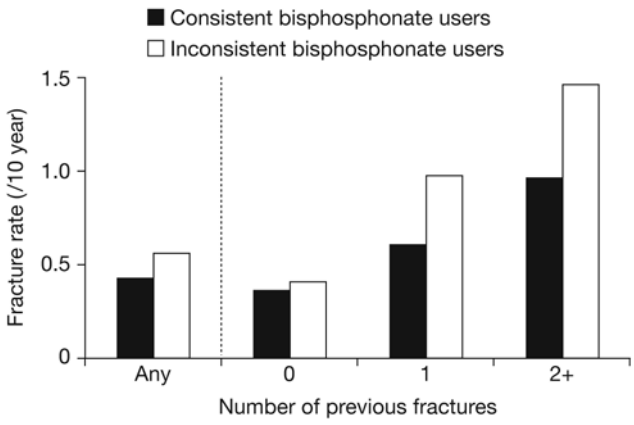

Figure 1 Fractures are increased as a result of suboptimal adherence: trend of a 33% greater fracture rate in inconsistent[a] versus consistent users (Sebaldt et al 2004).
Note: [a]Inconsistent = early discontinuation or self-reported taking of therapy <80% of the time over the follow-up interval.

nonadherence leads to an increased incidence of secondary complications associated with fractures, such as pain, nosocomial infections, and pulmonary thromboembolism, and hence to increased healthcare costs.

Understanding the causes of poor adherence

Given the impact of nonadherence to therapy on patient outcomes and healthcare resources, it is clearly important to improve adherence. However, to improve therapeutic adherence it is important to know why patients stop taking, or do not take adequate amounts of, their medication. Overall, the main reasons patients cite for not continuing to take their osteoporosis medication are the stringent dosing schedule, adverse events, not feeling that treatment is working, or not believing that they have a disease that needs treating (see Figure 2) (IOF 2005). The most common of the reasons cited above for nonadherence is that patients find the strict dosing instructions for bisphosphonates difficult to follow; fasting (overnight for at least 6 hours prior to taking the medication and 30–60 minutes after administration), and posture (staying upright for 30–60 minutes after taking the medication) requirements can be inconvenient and often not feasible in the daily routine. The strict requirements interfere not only with eating and drinking, but also with taking other medications, especially if these need to be taken with food. The next most common reason for discontinuation of therapy is that despite clinical studies reporting side-effect profiles that are similar to placebo, many patients stop taking treatment due to adverse events. The main complaints with oral bisphosphonates are

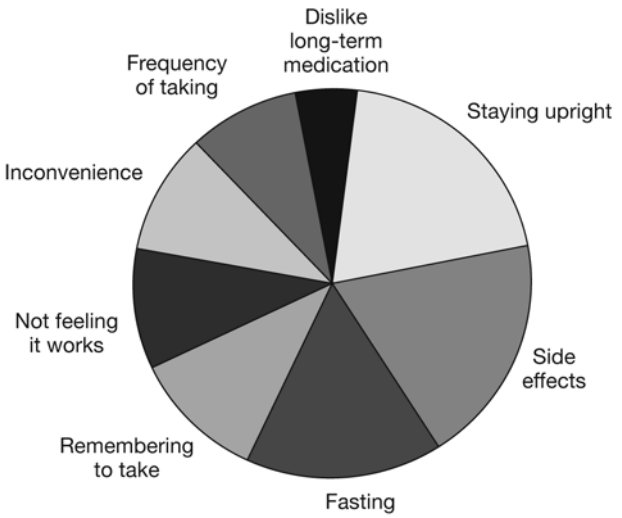

Figure 2 Reasons given by patients for not adhering to bisphosphonate therapy for osteoporosis (IOF 2005).

upper gastrointestinal irritation, dyspepsia, nausea, upper abdominal pain, vomiting, and gastroesophageal reflux. Finally, as patients often have no symptoms until they suffer a fracture, they do not feel that treatment is worth taking or do not believe they have a disease that needs treatment. This means they may consider the pill burden and inconvenience of the dosing requirements to be unnecessary. It has been suggested that, compared with other chronic diseases, adherence in osteoporosis is compromised because measures of therapeutic outcome (such as increases in BMD and reductions in the level of biochemical markers of bone turnover) are not readily available, therefore patients are unable to monitor their response to medication and thus gain feedback regarding the benefits of their medication (IOF 2005).

Many physicians believe that the main reason for patients not continuing to take their osteoporosis medication is a lack of understanding of the benefits of treatment. However, in the IOF adherence survey (IOF 2005), 71% of physicians questioned recognized that they did not know why their patients were discontinuing treatment. Almost half of the physicians surveyed believed that the best way to motivate patients to continue on treatment is to talk to them about risks and complications, however, the patients surveyed believed that it may be better to adopt a more positive approach that stresses the benefits of therapy.

Strategies to overcome the problem of nonadherence

On the whole, patients with osteoporosis want an effective and well-tolerated treatment, however, even with the proven efficacy and safety profiles of the bisphosphonates from clinical trials, patients still do not remain on treatment. Therefore other strategies are needed to improve therapeutic adherence. Improved communication between physicians and their patients may be one way to help. During the IMPACT (Improving the Measurements of Persistence on Actonel Treatment) study, patients were given verbal feedback regarding their bone turnover marker results (Delmas et al 2003). The study showed that a significant improvement in persistence was achieved if patients were given a positive message regarding their response to treatment. It has also been shown that involving patients in treatment decisions and matching them with their preferences improves patient satisfaction, adherence, perception of health, and outcomes (Lopes et al 2001; Janz et al 2004; Jahng et al 2005; Lin et al 2005). With regards to pharmacological intervention, patients have identified key product attributes as being efficacy, side effects, formulation, costs, drug interactions, dosing procedure, and dosing frequency. For the bisphosphonates, it is acknowledged that most of these attributes cannot be altered. However, one attribute that can be changed is the dosing frequency. Several studies have evaluated patient preferences for different dosing schedules and the impact this has had on therapeutic adherence.

Patient preference for an increased dosing interval: weekly dosing

The registration studies, which showed antifracture efficacy for the oral bisphosphonates, were all conducted using a daily regimen (Black et al 1996; Cummings et al 1998; Harris et al 1999; Reginster et al 2000; Chesnut et al 2004). The comparable antifracture efficacy of weekly oral bisphosphonate regimens of alendronate and risedronate with their respective daily regimens has been inferred based on equivalent increases in BMD (a validated surrogate marker for antifracture efficacy), and decreases in bone turnover markers (Schnitzer et al 2000; Brown et al 2002). The weekly regimens of alendronate and risedronate are both licensed and are widely accepted as being at least as effective as the daily regimens with the added convenience of only one tablet a week. In several studies evaluating bisphosphonate regimen preference (using alendronate or risedronate), there was a strong preference for a weekly regimen versus daily dosing (see Table 1). The weekly regimen was considered by the patients to be more

convenient, would allow them to achieve better long-term compliance, and was the regimen that most said they would be willing to take for an extended period of time, ie, would improve their adherence (Simon et al 2002; Baroutsou et al 2004; Cramer et al 2004; Kendler et al 2004; Recker et al 2004; Bartl et al 2006).

It has been demonstrated that patient preference for reduced bisphosphonate dosing frequency has impacted on therapeutic adherence. Studies that compared daily and weekly regimens found that a weekly regimen of alendronate or risedronate significantly increased rates of compliance versus a daily treatment (see Table 2) (Cramer et al 2005; Recker et al 2005; Bartl et al 2006). Patients receiving daily bisphosphonates filled prescriptions for only 33%–58% of their prescribed medication, while patients receiving a weekly regimen obtained more of their prescribed medication (46%–69%). Around half (41%–55%) of patients receiving a weekly regimen were highly compliant (at least 80% of prescribed medication taken) compared with only 23%–40% of patients taking a daily treatment. Preference for less frequently dosed bisphosphonate regimens also translates to improved therapeutic persistence (see Table 3). Analyses of a number of health databases of patients in the clinical setting show that 1-year persistence increases with weekly bisphosphonate dosing regimens by 12%–29% versus daily dosing (Ettinger et al 2004; Penning-van Beest et al 2004; Sunyecz et al 2004; Cramer et al 2005; Bartl et al 2006). However, fewer than half of patients receiving a weekly regimen persist with their therapy for 12 months so, even though adherence has been improved with weekly regimens versus daily, it is still suboptimal. Adherence, and therefore potentially quality of life, may be improved by further increasing the dosing interval, for instance from daily or weekly to monthly (Simon et al 2005).

Table 1 Patients' preference for weekly versus daily dosing of bisphosphonates

Study	Dose regimens	Outcome
Multicenter randomized crossover (n=287) (Simon et al 2002)	4 weeks of daily alendronate	86.4% preferred weekly
	1 week washout	89.0% thought weekly convenient
	4 weeks of weekly alendronate	87.5% expected weekly to improve compliance
Multicenter randomized crossover observational (n=406) (Kendler et al 2004)	4 weeks of daily alendronate	84.0% preferred weekly
	1 week washout	87.0% thought weekly convenient
	4 weeks of weekly alendronate	84.0% would receive weekly long term
Multicenter observational switchover (n=2997) (Baroutsou et al 2004)	6 months of daily calcitonin, raloxifene or bisphosphonate	99.5% preferred weekly
		99.8% thought weekly convenient
	24 weeks of weekly alendronate	99.8% willing to use weekly long term

Table 2 Studies of compliance with weekly compared with daily bisphosphonate regimens

Study	Dose regimens (n)	MPR (%)	MPR ≥80% (%)
IHCIS database (1997–2002) (Cramer et al 2005)	Daily alendronate or risedronate (2010)	58	40
	Weekly alendronate (731)	69 (p<0.0001)	55 (p<0.0001)
IMS Mediplus (Bartl et al 2006)	Daily alendronate (144)	38	19
	Weekly alendronate (144)	51	31 (p<0.05)
NDCHealth retrospective database (Recker et al 2004)	Daily alendronate or risedronate (33767)	54	~33
	Weekly alendronate or risedronate (177552)	65 (p<0.001)	~45 (p<0.001)

Abbreviations: MPR, medication possession ratio.

Table 3 Studies of persistence with weekly compared with daily bisphosphonate regimens

Study	Dose regimens (n)	Days to treatment discontinuation	Days of treatment duration
IHCIS database (1997–2002) (Cramer et al 2005)	Daily alendronate or risedronate (2010)	185	134
	Weekly alendronate (731)	227	269
IMS Mediplus(Bartl et al 2006)	Daily alendronate (144)	153	–
	Weekly alendronate (144)	212	–
NDCHealth retrospective database (Ettinger et al 2004; Sunyecz et al 2004)	Daily alendronate or risedronate (33767)	–	198
	Weekly alendronate or risedronate (177552)	–	238

Increasing the dosing interval further: monthly dosing

Ibandronate is the first nitrogen-containing oral bisphosphonate for osteoporosis that can be administered in a monthly regimen, and it is anticipated that this regimen may have a positive impact on adherence, and therefore ultimately on fracture prevention. Similarly to the other currently licensed oral bisphosphonates for postmenopausal osteoporosis, daily ibandronate has well documented clinical efficacy (Riis et al 2001; Chesnut et al 2004; Miller et al 2005). When given in an intermittent schedule (dosing interval >2 months), oral ibandronate also provides significant vertebral antifracture efficacy (relative risk reduction 50%, p=0.0006 versus placebo), which represents the first prospective demonstration of antifracture efficacy with a bisphosphonate administered less frequently than daily (Chesnut et al 2004). It is important to note that when the treatment-free interval is increased, the cumulative bisphosphonate dose must also be increased. Daily and intermittent ibandronate of the same cumulative dose provided comparable efficacy, however, similar to studies of daily and weekly bisphosphonates, a small, yet consistent, efficacy advantage was seen in favor of the daily regimen. Hence, in studies to evaluate a monthly regimen, oral doses beyond the cumulative monthly dose provided by the daily regimen were explored to compensate for the greater between-dose interval. As with the weekly regimens of alendronate and risedronate, a comparable vertebral antifracture profile for the monthly regimen of ibandronate with the daily regimen is inferred based on increases in BMD at all bone sites that are at least equivalent to those observed with the daily regimen (Miller et al 2005; Reginster et al 2006). Trial data from the MOBILE (Monthly Oral Ibandronate In Ladies) study showed that monthly ibandronate increased lumbar spine BMD and decreased markers of bone turnover and that the 150 mg monthly regimen was superior to the daily regimen (Miller et al 2005; Reginster et al 2006). After both 1 and 2 years of the study, the monthly regimen showed a good tolerability profile, similar to that of the daily regimen (Chesnut et al 2004).

Patient preference for a monthly regimen

Two robust clinical studies with almost 700 patients using patient surveys have demonstrated a strong patient preference for a monthly versus a weekly oral bisphosphonate regimen (Emkey et al 2005; Hadji et al 2006). The BALTO (Bonviva ALendronate Trial in Osteoporosis) studies evaluated patients' preference for monthly oral ibandronate or weekly oral alendronate. BALTO I (Emkey et al 2005) and BALTO II (Hadji et al 2006) comprised two separate studies of identical design; both were 6-month, randomized, multicenter, two-sequence, open-label, cross-over studies conducted in bisphosphonate-naïve or -lapsed women with postmenopausal osteoporosis as determined by the treating physician. BALTO I (n=342) was a US only study, whereas BALTO II (n=350) included centers in the USA and Europe. Postmenopausal women were randomized to receive either monthly oral ibandronate (150 mg) for 3 months followed by weekly oral alendronate (70 mg) for 12 weeks, or weekly oral alendronate (70 mg) for 12 weeks followed by monthly oral ibandronate (150 mg) for 3 months. All patients were informed that both drugs are indicated for the treatment of osteoporosis. Patient preference and opinions on convenience were assessed using a subject-completed questionnaire.

In BALTO I (Emkey et al 2005), of those women who expressed a preference (92.6% of 298 participants), the majority (71.4%) preferred the monthly ibandronate regimen to the weekly alendronate regimen (p<0.0001; see Figure 3). Similarly, in those patients expressing an opinion on convenience, the monthly regimen of ibandronate was assessed as being more convenient for patients than the weekly regimen of alendronate (74.6% vs 25.4%, respectively; p<0.0001; see Figure 4). More women reported that the monthly regimen would be easier to follow for a long time (61% vs 25%), was better suited to their lifestyle (55% vs 21%), and was easier to tolerate (17% vs 4%) than the weekly regimen. In addition, patients indicated that there

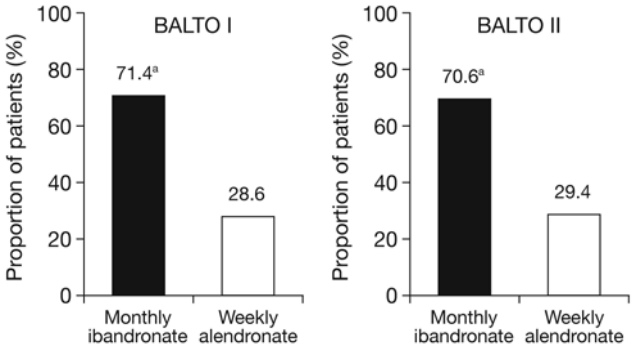

Figure 3 The majority of patients expressing a preference prefer monthly bisphosphonate treatment to weekly (Emkey et al 2005; Hadji et al 2006).
Note: Modified intent-to-treat populations = 298 (BALTO I), 321 (BALTO II); [a]Preference rate for monthly was significant in both studies (p<0.0001).

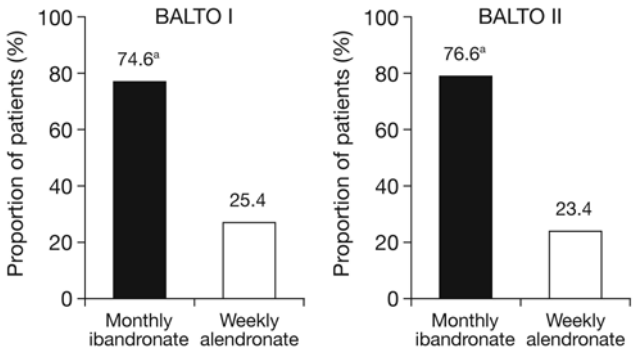

Figure 4 The majority of patients expressing an opinion perceived a monthly bisphosphonate regimen to be more convenient than a weekly regimen (Emkey et al 2005; Hadji et al 2006).
Note: Modified intent-to-treat populations = 298 (BALTO I), 321 (BALTO II); [a]Perception that the monthly regimen was more convenient than the weekly regimen was statistically significant ($p<0.0001$).

was a greater likelihood of long-term adherence and better tolerance of adverse events with the monthly regimen than the weekly regimen. The findings from BALTO I were confirmed by BALTO II. In BALTO II (Hadji et al 2006), of those patients expressing a preference (93.1%), the majority (70.6%) preferred the monthly ibandronate regimen to the weekly alendronate regimen (see Figure 3). Again the difference in preference rate between weekly alendronate and monthly ibandronate was statistically significant ($p<0.0001$). Of the patients expressing an opinion on convenience, three-quarters found the monthly regimen more convenient than the weekly regimen (76.6% vs 23.4%, respectively; see Figure 4). As in BALTO I, the most common reasons for preferring the monthly ibandronate regimen were ease of long-term adherence (81.5%) and better fit to lifestyle (75.4%).

Patient preference for a medication may encourage therapeutic adherence, but further studies are needed to determine how well preference and convenience translate into prolonged adherence. The UK PERsistence Study of Ibandronate verSus alendronaTe (PERSIST) is the first trial to investigate persistence with 6 months of a monthly bisphosphonate regimen versus a weekly bisphosphonate regimen. Patients were randomized to receive either a monthly ibandronate regimen (plus a patient support program) or a weekly alendronate regimen (Cooper et al 2006). A patient support program is available to all patients who are prescribed monthly ibandronate in the UK, however, there is no equivalent support program available to patients who are prescribed weekly alendronate. Therefore, to reflect current UK practice, only patients randomized to the ibandronate arm were enrolled into the program. The 6-month data show that compared with alendronate there was a 47% relative improvement in the proportion of patients persisting with treatment in the ibandronate/patient support program group. This compares well with the reported relative improvements in 1-year persistence of 12%–29% with weekly versus daily dosing (Ettinger et al 2004; Penning-van Beest et al 2004; Sunyecz et al 2004; Cramer et al 2005; Bartl et al 2006). Secondary endpoints, ie, proportion of patients remaining on treatment at study end and proportion of patients discontinuing from the study, were also in favor of the monthly regimen. The data from the UK PERSIST study suggest that this less frequent dosing schedule may provide improved adherence.

Conclusions

To achieve maximum treatment benefits for patients with osteoporosis, it is important that physicians discuss all options with their patients before a treatment choice is made. It has been shown that the majority of patients prefer weekly to daily therapy, although adherence with weekly regimens remains suboptimal. As adherence with daily or weekly bisphosphonates is suboptimal, patients and physicians feel there is a need for bisphosphonates with extended dosing intervals. Given the reported strong patient preference for a monthly regimen, and the impact of patient preference on adherence, it is anticipated that monthly ibandronate will offer patients an alternative convenient regimen that may improve adherence over weekly regimens and thereby enhance outcomes. The nitrogen-containing bisphosphonates are effective therapies for osteoporosis, but if patients are more likely to adhere to a monthly regimen than a daily or weekly regimen, then this may be the treatment of choice. An effective bisphosphonate that combines a good tolerability profile with a convenient dosing regimen would be beneficial for patients and it is important that physicians consider patient preference when prescribing the appropriate treatment for osteoporosis to ensure that the disease is effectively managed for the long-term benefit of the patient.

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References

Baroutsou B, Babiolakis D, Stamatiadou A, et al. 2004. Patient compliance and preference of alendronate once weekly administration in comparison with daily regimens for osteoporotic postmenopausal women. *Ann Rheum Dis*, 63(Suppl 1):455.

Bartl R, Goette S, Hadji P, et al. 2006. Persistence and compliance with daily- and weekly-administered bisphosphonates in German women with osteoporosis. *Ann Rheum Dis*, 64(Suppl 3):364.

Black DM, Cummings SR, Karpf DB, et al. 1996. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. *Lancet*, 348:1535-41.

Brown JP, Kendler DL, McClung MR, et al. 2002. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcif Tissue Int*, 71:103-11.

Caro JJ, Ishak KJ, Huybrechts KF, et al. 2004. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int*, 15:1003-8.

Center JR, Nguyen TV, Schneider D, et al. 1999. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet*, 353:878-82.

Chesnut CH, Skag A, Christiansen C, et al. 2004. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res*, 19:1241-9.

Chrischilles EA, Butler CD, Davis CS, et al. 1991. A model of lifetime osteoporosis impact. *Arch Intern Med*, 151:2026-32.

Cooper A, Drake J, Brankin E. 2006. Treatment persistence with once-monthly ibandronate and patient support vs. once-weekly alendronate: results from the PERSIST study. *Int J Clin Pract*, 60:896-905.

Cooper C, Campion G, Melton LJ III. 1992. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int*, 2:285-9.

Cowell W, Fulford-Smith A, Poultney S. 2005. Adherence with bisphosphonate treatment for osteoporosis in UK patients. *Bone*, 36(Suppl 2):S409-10.

Cramer JA, Amonkar M, Hebborn A, et al. 2004. Assessing the relationship between bisphosphonate dosing regimen and treatment adherence among post-menopausal osteoporotic women. *Arthritis Rheum*, 50(Suppl):S294.

Cramer JA, Amonkar MM, Hebborn A, et al. 2005. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin*, 21:1453-60.

Cranney A, Wells G, Willan A, et al. 2002. II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev*, 23:508-16.

Cummings SR, Black DM, Thompson DE, et al. 1998. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA*, 280:2077-82.

Cummings SR, Melton LJ. 2002. Epidemiology and outcomes of osteoporotic fractures. *Lancet*, 359:1761-7.

Delmas PD, Vrijens B, Van de Langerjit L, et al. 2003. Effect of reinforcement with bone turnover marker results on persistence with risedronate treatment in postmenopausal women with osteoporosis: improving the measurements of persistence on actonel treatment (IMPACT) study. *Calcif Tissue Int*, 72:335.

Eastell R, Garnero P, Vrijens B, et al. 2003. Influence of patient compliance with risedronate therapy on bone turnover marker and bone mineral density response: the IMPACT study. *Calcif Tissue Int*, 72:408.

Emkey R, Koltun W, Beusterien K, et al. 2005. Patient preference for once-monthly ibandronate versus once-weekly alendronate in a randomized, open-label, cross-over trial: the Bonviva Alendronate Trial in Osteoporosis (BALTO). *Curr Med Res Opin*, 21:1895-903.

Ettinger M, Gallagher R, Amonkar M, et al. 2004. Medication persistence is improved with less frequent dosing of bisphosphonates, but remains inadequate. *Arthritis Rheum*, 50(Suppl):S513.

Goettsch WG, Penning F, Erkens JE, et al. 2005. Persistent bisphosphonate usage reduces the risk of hospitalizations for osteoporotic fractures. *J Bone Miner Res*, 20(Suppl 1):S278.

Hadji P, Benhamou CL, Devas V, et al. 2006. Women with postmenopausal osteoporosis prefer once-monthly oral ibandronate to weekly oral alendronate: results of BALTO II. *Osteoporos Int*, 17(Suppl 1):S69.

Harris ST, Siris E, Abbott T, et al. 2005. Reduced osteoporotic fracture risk in patients adherence to bisphosphonate therapy. Program & Abstracts of The Endocrine Society's 87th Annual Meeting, 4-7 June 2005, pp 3-382.

Harris ST, Watts NB, Genant HK, et al. 1999. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *JAMA*, 282:1344-52.

Hodgson SF, Watts NB, Bilezikian JP, et al. 2003. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. *Endocr Pract*, 9:544-64.

IOF. 2003. Osteoporosis in the European community: action plan [online]. Accessed 1 September 2006. URL: http://www.osteofound.org/advocacy_policy/eu_policy_project/pdf/action_plan_03_e.pdf#search=%22Osteoporosis%20 in%20 the%20European% 20 community%3A%20 action%20 plan%22.

IOF. 2005. IOF adherence gap report [online]. Accessed 1 September 2006. URL: http://www.osteofound.org/publications/pdf/adherence_gap_report.pdf.

Jahng KH, Martin LR, Golin CE, et al. 2005. Preferences for medical collaboration: patient-physician congruence and patient outcomes. *Patient Educ Couns*, 57:308-14.

Jalava T, Sarna S, Pylkkanen L, et al. 2003. Association between vertebral fracture and increased mortality in osteoporotic patients. *J Bone Miner Res*, 18:1254-60.

Janz NK, Wren PA, Copeland LA, et al. 2004. Patient-physician concordance: preferences, perceptions, and factors influencing the breast cancer surgical decision. *J Clin Oncol*, 22:3091-8.

Johnell O 1997. The socioeconomic burden of fractures: today and in the 21st century. *Am J Med*, 103:20S-5S.

Johnell O, Kanis JA, Oden A, et al. 2004. Mortality after osteoporotic fractures. *Osteoporos Int*, 15:38-42.

Johnell O, Oden A, Caulin F, et al. 2001. Acute and long-term increase in fracture risk after hospitalization for vertebral fracture. *Osteoporos Int*, 12:207-14.

Kanis JA, Oden A, Johnell O, et al. 2004. Excess mortality after hospitalisation for vertebral fracture. *Osteoporos Int*, 15:108-12.

Kendler D, Kung AW, Fuleihan Gel H, et al. 2004. Patients with osteoporosis prefer once weekly to once daily dosing with alendronate. *Maturitas*, 48:243-51.

Lin P, Campbell DG, Chaney EE, et al. 2005. The influence of patient preference on depression treatment in primary care. *Ann Behav Med*, 30:164-73.

Lips P. 2003. Invest in your bones: quality of Life. Why prevent the first fracture? International Osteoporosis Foundation [online]. Accessed 1 September 2006. URL: http://www.osteofound.org/publications/pdf/quality_of_life.pdf#search=%22 Invest%20in%20your%20bones%3A%20quality%20of%20Life.%20 Why%20prevent%20the%20first%20fracture%3F%22.

Lips P, Cooper C, Agnusdei D, et al. 1999. Quality of life in patients with vertebral fractures: validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Working Party for Quality of Life of the European Foundation for Osteoporosis. *Osteoporos Int*, 10:150-60.

Lopes P, Rozenberg S, de Graaf J, et al. 2001. Aerodiol versus the transdermal route: perspectives for patient preference. *Maturitas*, 38(Suppl 1):S31-9.

Madhok R, Kerr H, Capell HA. 2000. Recent advances: rheumatology. *BMJ*, 321:882-5.

McClung MR, Geusens P, Miller PD, et al. 2001. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. *N Engl J Med*, 344:333-40.

Melton LJ III. 2000. Who has osteoporosis? A conflict between clinical and public health perspectives. *J Bone Miner Res*, 15:2309-14.

Melton LJ III. 2003. Adverse outcomes of osteoporotic fractures in the general population. *J Bone Miner Res*, 18:1139-41.

Melton LJ III, Chrischilles EA, Cooper C, et al. 1992. Perspective. How many women have osteoporosis? *J Bone Miner Res*, 7:1005-10.

Miller PD, McClung M, Macovei L, et al. 2005. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res*, 20:1315-22.

Naves B, az-Lopez JB, Gomez C, et al. 2003. The effects of vertebral fracture as a risk factor for osteoporotic fracture and mortality in a Spanish population. *Osteoporos Int*, 14:520-4.

Penning-van Beest F, Goettsch W, Erkens J, et al. 2004. Persistence with bisphosphonate therapy among post-menopausal osteoporotic women and the impact of dosing frequency. *Value Health*, 7:724.

Recker RR, Gallagher R, Amonkar AA, et al. 2004. Medication persistence is better with weekly bisphosphonates, but it remains suboptimal. *J Bone Miner Res*, 19(Suppl 1):S172.

Recker RR, Gallagher R, MacCosbe PE. 2005. Effect of dosing frequency on bisphosphonate medication adherence in a large longitudinal cohort of women. *Mayo Clin Proc*, 80:856-61.

Reginster JY, Adami S, Lakatos P, et al. 2006. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. *Ann Rheum Dis*, 65:654-61.

Reginster JY, Minne HW, Sorensen OH, et al. 2000. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int*, 11:83-91.

Riis BJ, Ise J, von Stein T, et al. 2001. Ibandronate: a comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. *J Bone Miner Res*, 16:1871-8.

Ross P. 1997. Clinical consequences of vertebral fractures. *Am J Med*, 103:30S-42S.

Russell RG, Rogers MJ. 1999. Bisphosphonates: from the laboratory to the clinic and back again. *Bone*, 25:97-106.

Schnitzer T, Bone HG, Crepaldi G, et al. 2000. Therapeutic equivalence of alendronate 70mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging (Milano)*, 12:1-12.

Sebaldt RJ, Shane L, Pham B, et al. 2004. Longer-term effectiveness outcomes of non-compliance and non-persistence with daily-regimen bisphosphonate therapy in patients with osteoporosis treated in tertiary specialist care. *Osteoporos Int*, 15(Suppl 1):S107.

Simon JA, Beusterien KM, Leidy NK, et al. 2005. Women with postmenopausal osteoporosis express a preference for once-monthly versus once-weekly bisphosphonate treatment. *Female Patient*, 30:31-6.

Simon JA, Lewiecki EM, Smith ME, et al. 2002. Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, cross-over study. *Clin Ther*, 24:1871-86.

Simpson SH, Eurich DT, Majumdar SR, et al. 2006. A meta-analysis of the association between adherence to drug therapy and mortality. *BMJ*, 333:15-18.

Siris E, Harris S, Silverman S, et al. 2005. Adherence to bisphosphonates (BPs) is associated with reduced fracture risk in women with postmenopausal osteoporosis (PMO). *Menopause*, 12:807.

Sunyecz JA, Gallagher R, Smith JC, et al. 2004. Weekly dosing with bisphosphonates has higher, but suboptimal days of therapy. 17th World Conference of Family Doctors (WONCA 2004), 13-17 October 2004.

[WHO] World Health Organization. 2003b. Adherence to long-term therapies: evidence for action. World Health Organization, 1-211.

[WHO] World Health Organization. 2003a. Prevention and management of osteoporosis. *World Health Organ Tech Rep Ser*, 921:1-164.