



ELSEVIER

Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

Maturitas 48 (2004) 243–251

MATURITAS

THE EUROPEAN
MENOPAUSE
JOURNAL

www.elsevier.com/locate/maturitas

Patients with osteoporosis prefer once weekly to once daily dosing with alendronate[☆]

David Kendler^{a,*}, Annie Wai Chee Kung^b, Ghada El-Hajj Fuleihan^c,
José Gerardo González González^d, Keavy A. Gaines^e,
Nadia Verbruggen^f, Mary E. Melton^e

^a St. Vincent's Hospital, 120-809 W 41 Avenue, Vancouver, BC, Canada V5Z 2N6

^b Queen Mary Hospital, Hong Kong, PR China

^c American University of Beirut Medical Center, Beirut, Lebanon

^d Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico

^e Merck and Co. Inc., Whitehouse Station, NJ, USA

^f Merck Sharp and Dohme Inc. (Europe), Brussels, Belgium

Received 17 July 2003; received in revised form 17 December 2003; accepted 17 December 2003

Abstract

Objectives: Once weekly dosing of alendronate has been shown to provide equivalent efficacy to once daily dosing for treatment of osteoporosis in postmenopausal women. Whether patients will prefer weekly dosing to daily dosing for a chronic condition such as osteoporosis has not been studied. The aim of this international study was to assess preference for the weekly or daily dosing regimen of alendronate among postmenopausal women with osteoporosis. **Methods:** This randomised open-label crossover study was conducted at 45 study sites in 19 countries. Four hundred and six postmenopausal women with osteoporosis were assigned randomly to treatment with either alendronate 70 mg once weekly for 4 weeks followed by alendronate 10 mg once daily for 4 weeks or vice versa. The main outcome was the responses of the participants to the Dosing Regimen Questionnaire administered at the end of the study. **Results:** Of the participants expressing a preference, 84% preferred the once weekly dosing regimen with alendronate to the once daily dosing regimen. In addition, the once weekly regimen was considered by 87% of the participants to be more convenient and was the regimen most of the participants (84%) would be more willing to take for a long period of time ($P < 0.001$ for each parameter). **Conclusions:** The majority of postmenopausal women with osteoporosis preferred the once weekly to the once daily dosing regimen of alendronate. Physicians should consider patient preference for dosing regimen when selecting the appropriate treatment for osteoporosis.

© 2004 Elsevier Ireland Ltd. All rights reserved.

Keywords: Alendronate; Weekly; Preference; Osteoporosis

[☆] This data has been presented in abstract form at the International Society of Clinical Densitometry Annual Meeting, Atlanta, GA, February 2002; the Fifth International Symposium: Clinical Advances in Osteoporosis, Honolulu, Hawaii, March 2002; The IOF World Congress on Osteoporosis, Lisbon, Portugal May 2002; the European League Against Rheumatism Annual Congress, Stockholm, Sweden, June 2002.

* Corresponding author. Tel.: +1-604-263-3644; fax: +1-604-263-3744.

E-mail address: kendler@ca.inter.net (D. Kendler).

0378-5122/\$ – see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.

doi:10.1016/j.maturitas.2003.12.012

1. Introduction

Low adherence and compliance with medications for chronic diseases is a well known problem. It has been recognized that the full benefits of medications cannot be reached at current levels of compliance. Compliance with medical therapy for chronic diseases is a complex and multifactorial problem, and requires innovative solutions. Many attempts have been made to institute interventions to improve medication compliance. These interventions have been only modestly successful at best [1]. One of the most successful interventions demonstrated to improve compliance is a simplified dosing regimen. For example, it has been shown that compliance improves as the number of doses taken each day decreases [2]. Whether even less frequent dosing regimens, such as weekly dosing, would further improve compliance for chronic therapy is not known. Few medications for a treatment of a chronic disease are available in a once weekly formulation, and therefore little information is available on patient acceptance of a medication administered once weekly.

Recently, taking advantage of pharmacokinetic properties, alendronate was developed for once weekly dosing for treatment and prevention of osteoporosis. The once weekly dosing regimen for alendronate was developed in an attempt to simplify the dosing regimen and potentially enhance compliance. Once weekly dosing with alendronate has been shown to provide equivalent efficacy to once daily dosing for treatment of osteoporosis in postmenopausal women [3]. Patients are used to establishing a daily regimen to encourage them to remember to take their medications. Whether a once weekly regimen would be easier to follow, or potentially more complicated and subject to greater inconvenience or missed doses, was unknown.

In this study, we investigated the dosing preference for alendronate given once daily or once weekly among postmenopausal women with osteoporosis in a randomized, open-label, cross-over designed, international clinical trial. The participants were given the opportunity to experience both once weekly alendronate and once daily alendronate prior to saying which they prefer, which they think is more convenient, and which they would be more willing to continue over a long period of time.

2. Methods

2.1. Protocol design

This was an open-label, randomised, crossover study of preference. This study was conducted at 45 sites across 19 countries representative of Europe, Middle East, the Americas, and Asia-Pacific. Participants were randomly assigned to treatment with either alendronate (Fosamax[®], Merck & Co. Inc., Whitehouse Station, NJ, USA) 10 mg once daily followed by treatment with alendronate 70 mg once weekly, or treatment with alendronate once weekly followed by alendronate once daily. Each dosing regimen was administered for 4 weeks, with a 1 week off therapy period between dosing regimens. After experiencing both regimens, the participants completed the Dosing Regimen Questionnaire (Fig. 1). Ethics review committee approval was obtained for each site. Informed consent was obtained from all participants prior to performance of any study-related evaluation.

2.2. Participants

Postmenopausal women with osteoporosis (as determined by the investigator) were recruited from investigators' practices and from media advertisements. Participants were naïve to therapies for osteoporosis, including bisphosphonates, calcitonin, and selective estrogen receptor modulators; hormone replacement therapy, calcium and Vitamin D were allowed. Reasons to exclude women from the study included inability to follow alendronate dosing instructions, conditions which delay esophageal emptying such as stricture or achalasia, or a history of hypocalcemia, hypoparathyroidism, osteomalacia, Paget's disease or renal osteodystrophy. Other exclusions included uncontrolled moderate or severe hypertension, new onset angina or myocardial infarction within 6 months, impaired renal function, other significant end organ diseases, or cancer. Use of nonsteroidal antiinflammatory agents, H₂ antagonists, proton pump inhibitors, or a history of gastrointestinal disorders (other than disorders of esophageal motility) were not reasons for exclusion.

DOSING REGIMEN QUESTIONNAIRE

You have just completed this study and have followed two different osteoporosis treatment routines: you have taken the osteoporosis medication once a week and you have taken it once a day. It is important to remember that the osteoporosis medications you took during these two treatment routines have the same beneficial effect for your bones. Please answer the three questions below. We encourage you to choose the answer that best describes your experience.

For each question, please check *one* box only

1. Which treatment routine do you prefer?

- I prefer the once a week treatment routine
- I prefer the once a day treatment routine
- I have no preference

2. Which treatment routine is more convenient?

- The once a week treatment routine is more convenient
- The once a day treatment routine is more convenient
- The once a week treatment routine and the once a day treatment routine are equally convenient

3. Which treatment would you be more willing to take for a long period of time?

- I would be more willing to take the once a week treatment for a long period of time
- I would be more willing to take the once a day treatment for a long period of time
- I would be equally willing to take either the once a week or the once a day treatment for a long period of time

Fig. 1. Dosing Regimen Questionnaire.

2.3. Treatment assignment and randomisation

Allocation to treatment sequence was assigned randomly using a computer-generated allocation schedule. Open-label drug was provided for 4 weeks for each regimen (4 tablets of alendronate 70 mg once weekly and 28 tablets of alendronate 10 mg once daily). For each regimen, the participants received the standard dosing instructions for alendronate. For the once weekly regimen, the participants chose 1 day of the week for the weekly dosing. Throughout the study, all participants were encouraged to take

calcium and Vitamin D supplements according to the standard of care in their communities. In addition, counseling for modification of lifestyle habits related to osteoporosis, such as exercise, smoking cessation, and fall prevention, was encouraged.

2.4. Participant followup

Participants returned for a randomisation visit for initiation of the first treatment period and again when switching to the second treatment period. All participants were phoned on the day of initiation of study

drug (or up to 3 days after, in case of intervening holiday or weekend days) in each treatment period to ensure proper compliance to dosing instructions. After experiencing both treatment regimens, participants returned for a final visit for completion of the Dosing Regimen Questionnaire and collection of information on adverse experiences.

2.5. Questionnaire development and testing

The Dosing Regimen Questionnaire was designed to include the parameters of preference, convenience, and willingness to continue taking the regimen long term. In development of the questionnaire, in-depth interviews were conducted with women previously diagnosed with osteoporosis, including those receiving alendronate and those receiving other therapies for osteoporosis. These interviews were used to modify the wording of the questions to ensure concept conveyance and clarity before the questionnaire in English was finalised. Translation of the questionnaire into local languages required at least two translations for each language, back-translations for each translation, a committee review, and pre-testing of the translated questionnaire with non-study participants in the target population of women with osteoporosis. This rigorous procedure for translations was instituted to ensure that the original meaning and intent of the questionnaire was preserved when a translation was required.

At the completion of the study, a short script was read to each participant to introduce the questionnaire and to explain that the participant is to complete the questionnaire on her own, to the best of her ability, without assistance from the investigator site staff. Participants were informed that the two treatment regimens (alendronate 70 mg once weekly and alendronate 10 mg once daily) have equal benefit to bone so that their choice of regimen was not influenced by any perception of relative efficacy. Each participant completed the questionnaire herself.

2.6. Analysis

The primary analysis was the preference of participants towards either of the two regimens. The analysis included all participants who took at least one dose from each regimen and expressed a preference based on the first question of the Dosing Regimen Questionnaire.

The Mainland–Gart test for binary response in a two-treatment, two-period crossover trial was used for this analysis [4]. The analyses of the responses to the other two questions on the questionnaire were handled in a similar fashion. As there was only one primary endpoint (preference), there was no need for a multiplicity adjustment. The sample size estimation was based on 90% power to detect a 20% difference in preference with a 2-tailed test at a 5% significance level. At least 260 participants (130 per group) were required; additional participants were enrolled to allow for those who would not complete the trial.

To assess the sequence effect of treatments, that is, to test whether the percentage of participants who preferred alendronate 70 mg once weekly was the same irrespective of the order in which the two treatment regimens have been given, the Mainland–Gart test was used, with a two-sided test at the 10% significance level. To investigate the influence of various factors on preference for dosing regimen, analyses by subgroup was performed. These analyses used a logistic model on the preference of alendronate once weekly including the factor under consideration as main effect to assess the consistency across the different subgroups. The following factors were considered: country of residence, age group (≤ 65 , >65 years), number of concomitant chronic medications (defined as a medication taken for more than 75% of the time during the study), intake of at least one concomitant medication on more than 75% of the days in the study, and number of active medical conditions at baseline.

The adverse experiences were analysed for all participants who took at least one dose of study medication for the treatment phase under consideration. Also, a comparison of the overall adverse experience reporting of the two treatment regimens was done using the McNemar's Test, which included only participants who received at least one dose of each regimen.

3. Results

3.1. Participants' characteristics

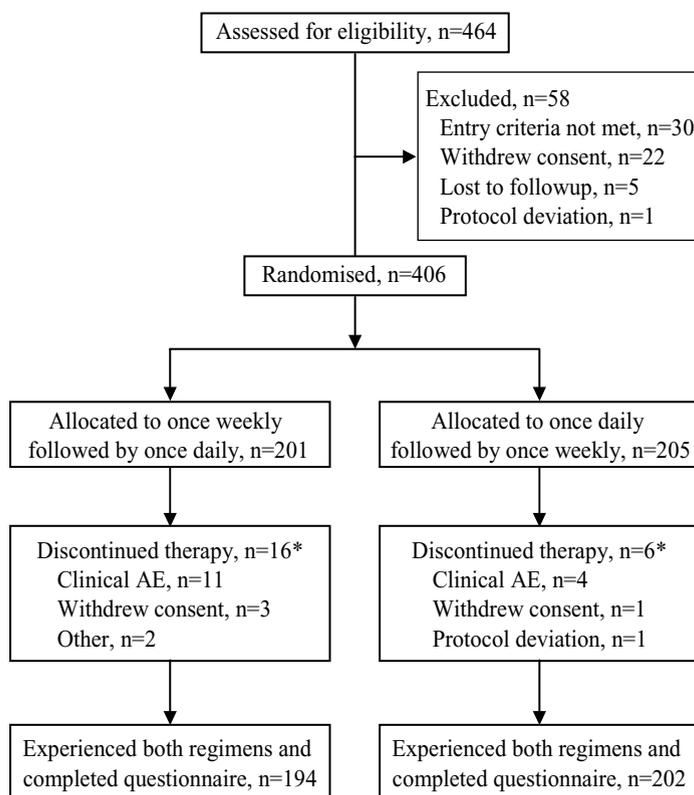
A total of 406 postmenopausal women with osteoporosis from 19 countries participated in the study. Sixty-five percent of the women reported their race as Caucasian, 22% Asian, and 8% Hispanic. Regional

Table 1
Baseline characteristics

	Alendronate once weekly then once daily (N = 201)	Alendronate once daily then once weekly (N = 205)	Total (N = 406)
Mean (S.D.) age (year)	63 (8.6)	63 (8.7)	63 (8.6)
Mean (S.D.) BMI (kg/m ²)	25.0 (4.3)	25.3 (4.4)	25.2 (4.3)
Mean (S.D.) years since last menses	16.4 (10.0)	16.8 (10.7)	16.6 (10.3)
Number (%) with family history of osteoporosis	69 (39)	72 (38)	141 (39)
Number (%) with known prior fracture	13 (6)	16 (8)	29 (7)
Number (%) with caffeine use ≥ 3 cups per day	43 (22)	51 (26)	94 (24)
Number (%) with current tobacco use	20 (10)	23 (11)	43 (11)

diversity was also achieved with 92 (23%) of the participants from North America, 57 (14%) from Central or South America, 104 (26%) from Europe, 54 (13%) from the Middle East and Africa and 99 (24%) from

the Asia-Pacific region. The baseline characteristics of the two treatment sequence groups were similar (Table 1). The most common active medical conditions reported at baseline (other than osteoporosis) were



*Patients who discontinued therapy but had experienced both regimens and completed the Dosing Regimen Questionnaire were included in the final results.

Fig. 2. Participant assessment and followup throughout the study.

hypertension (114, 28%), osteoarthritis (46, 11%), hypercholesterolemia (36, 9%) and hypothyroidism (32, 8%).

All participants randomised received at least one dose of study medication. A total of 390 (97%) participants took all 4 of their weekly tablets and 344 (86%) participants took all 28 of their daily tablets. Three hundred and ninety-six took at least one dose from each regimen and all of these completed the questionnaire. Three hundred and eighty-four participants (95%) completed the study. The most common reason for early discontinuation was a clinical adverse experience (15, 4%) (Fig. 2).

3.2. Questionnaire results

Of the 396 participants who completed the questionnaire and experienced both regimens, 364 (92%) expressed a preference for one of the two treatment regimens. Of these, 305 (84%) preferred the once weekly regimen and 59 (16%) preferred the once daily treatment regimen (Fig. 3). The preference for the once weekly regimen was statistically significant ($P < 0.001$). The preference for the once weekly regimen was similar in the two sequence groups, with 149 (84%) of those who took the once weekly regimen first expressing a preference for once weekly, and 156 (84%) of the participants who took the once daily regimen

first preferring the once weekly regimen. Therefore, no effect by sequence was seen ($P = 1.000$).

Of the 360 (91%) participants who expressed that one regimen is more convenient, 314 (87%) considered the once weekly regimen to be more convenient ($P < 0.001$). For the question asking which regimen they would be more willing to take for a long period of time, 369 (93%) indicated a choice between regimens. Of those, 311 (84%) indicated that the once weekly regimen is the one they would be more willing to take long term ($P < 0.001$).

3.3. Subgroup analyses

There was no apparent effect of any of the subgroups studied on preference for dosing regimen (Table 2). Also, responses were similar regardless of country of residence.

3.4. Adverse experiences

Of the 406 randomised participants who took at least one dose of study medication, 403 participants took at least one weekly dose and 399 took at least one daily dose. Of these participants, 99 (25%) had an adverse experience during the weekly regimen and 110 (28%) during the daily regimen. The most frequently occurring adverse experiences were in the categories

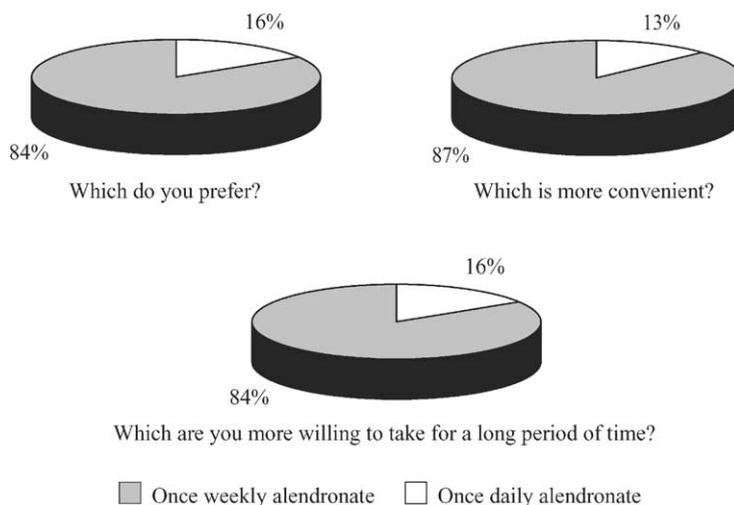


Fig. 3. Participant responses to questionnaire on parameters of preference, convenience and willingness to take long term after experiencing both alendronate once weekly and once daily regimens. $P < 0.001$ for each parameter.

Table 2
Subgroup analysis

	Total with a preference <i>N</i>	Preference for alendronate 70 mg once weekly ^a	
		<i>N</i> (%)	95% CI
Age			
≤65 years	232	189 (81)	(76, 86)
>65 years	132	116 (88)	(81, 93)
More than 75% of time with a concomitant medication			
No	49	41 (84)	(70, 93)
Yes	315	264 (84)	(79, 88)
Number of active medical conditions			
None	73	67 (92)	(83, 97)
1	75	59 (79)	(68, 87)
2	59	47 (80)	(67, 89)
3	40	34 (85)	(70, 94)
4	38	28 (74)	(57, 87)
≥5	79	70 (89)	(80, 95)
Number of concomitant chronic medications			
None	49	41 (84)	(70, 93)
At least one	315	264 (84)	(79, 88)

^a Preference for once weekly dosing with alendronate was similar regardless of subgroup tested, including country of residence (data not shown).

of body as a whole (10% and 8% for once weekly and once daily respectively) and digestive system (7% and 10%, respectively). The occurrence of adverse experiences (among participants who received at least one dose of both regimens) was not statistically different between the two treatment regimens ($P = 0.158$).

4. Discussion

In this study, we investigated the attitudes among postmenopausal women from 19 countries toward two alendronate dosing regimens, once weekly or once daily dosing, for treatment of osteoporosis. For the majority of the women, the once weekly regimen was the one they preferred, found more convenient, and would be more willing to take for a long period of time (84, 87, and 84%, respectively). Understanding patient attitudes toward various dosing regimens is an important aspect of understanding which regimens are likely to enhance compliance to therapy, especially for disorders such as osteoporosis which require long-term therapy.

A similar study of alendronate conducted in a US population demonstrated similar results to our international study [5], indicating a preference for once weekly dosing regardless of country of residence. These two studies are the first to investigate patient preference for weekly dosing as compared to daily dosing for a chronic condition. Other oral medications are dosed weekly, including chloroquine and other antimalarials [6,7], methotrexate for rheumatoid arthritis [8], cabergoline for prolactinoma [9], anti-fungals such as fluconazole [10,11], and fluoxetine for continuation therapy for depression [12]. Whether patients would also prefer weekly therapy to daily for these other medications is not known.

Information about patient preference for dosing regimens also can be obtained from anecdotal experiences and from surveys of a target patient population. However, each of these approaches has drawbacks. There are few reports of preference in dosing regimen after allowing volunteers to experience different regimens, and none that have addressed this issue for weekly dosing for osteoporosis. This trial was designed to mimic clinical practice as much as possible in the clinical trial setting. The randomised, open-label, crossover design, with 4 weeks allotted for each regimen, was chosen to allow the participants an adequate amount of time on each regimen to assess their preference. Four weeks was chosen as an adequate amount of time to assess how well the regimen is received by the participant in relation to her usual daily and weekly activities. The 4-week treatment period for each regimen was chosen to be short enough to minimize recall bias. The strength of the results of this study was confirmed by the lack of sequence effect on the results, suggesting that recall bias did not occur in this trial.

Patient preference for a therapy may also be determined by factors other than dosing regimen. Efficacy, safety, and tolerability (whether perceived or real) will also be important factors in preference for one therapy or regimen over others. In this study, attempts were made to design the trial to focus solely on the treatment regimen itself. We attempted to minimise any perceptions of differential effects on efficacy by stating to the participants, consistent with controlled clinical trial data [3], that the once weekly and the once daily regimens had similar efficacy. Also, no efficacy parameters were tested during the study. No such statements were made about tolerability and therefore perceived

tolerability, at least for some participants, may have been a factor that influenced their preference for one regimen over the other. Patient preference may also be influenced by the perceptions of the investigators and study site personnel. We believe this potential bias is minimal in this study because the study was performed prior to the availability of the once weekly alendronate regimen in the marketplace, because physicians had minimal prior experience with once weekly oral regimens for chronic conditions, and because of the initial skepticism expressed by many physicians about patients' willingness to take a weekly rather than the standard daily regimen.

To allow for adequate absorption, very specific dosing instructions are recommended for the bisphosphonates, including alendronate. These instructions may be restrictive for some, especially for daily administration. The need to follow these strict dosing instructions only once a week may have been a substantial factor in the preference for weekly over daily dosing. Whether similar preference for weekly over daily dosing would be seen for a therapy with fewer dosing restrictions cannot be determined from this study.

The participants' assessment of the dosing regimens in this study was limited to the three questions in the Dosing Regimen Questionnaire. Qualitative information about reason for the preferred regimen was not collected. In the subgroup analysis we investigated factors that may be associated with a preference for one regimen over the other, including age, country of residence, and complexity of coexisting medical care as measured by presence of concomitant medication use, number of active medical conditions (other than osteoporosis), and number of concomitant medications. In addition, we evaluated the preference in subgroups with common active medical conditions. All of the subgroups investigated not only preferred the once weekly regimen, but also had a similar preference for the once weekly regimen to that of the overall cohort. We were unable to identify any characteristics that might suggest a group of patients more likely to prefer the once daily regimen.

Compliance with medications for chronic diseases is low and methods to improve compliance have been a subject of interest for many years [1,2,13,14]. It is well established that once daily dosing as compared to more frequent dosing regimens leads to enhanced compliance [2]. Weekly iron supplementation in preg-

nant women led to higher compliance than did daily [15]. Interestingly, in our study more patients achieved 100% compliance with the once weekly regimen than with the daily regimen (97% versus 86%). Effectiveness in reducing fractures in osteoporotic patients involves not only administration of an effective therapy but also administration of a therapy that the patient is willing to take. Whether better long term compliance with treatment for osteoporosis can be achieved with regimens designed to enhance patient convenience and preference deserves additional investigation.

In determining the best therapy for a particular patient, efficacy and tolerability are important considerations. In addition, ease of use and dosing convenience are important features to consider to encourage long term compliance to therapy for chronic conditions such as osteoporosis. This study demonstrated that, compared to once daily dosing, the once weekly dosing regimen with alendronate was preferred, was more convenient, and was the regimen patients were more willing to take for a long period of time. For chronic therapy such as is required for osteoporosis, it is important for physicians to consider patient preferences in order to help optimise compliance to therapy.

Acknowledgements

We would like to thank Larry Radican and Julie Chandler for contributing their expertise to the development of the Dosing Regimen Questionnaire. We would like to acknowledge both the women participants, without whom this investigation would not have been possible, as well as the contributions of the personnel at the study sites. Funding as well as study medication, monitoring, and statistical support were provided by Merck & Co. Inc.

References

- [1] McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA* 2002;288:2868–79.
- [2] Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23:1296–310.
- [3] Schnitzer T, Bone HG, Crepaldi G, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis.

- Alendronate Once-Weekly Study Group. *Aging (Milano)* 2000;12:1–12.
- [4] Senn S. *Cross-over trials in clinical research*. Chichester: Wiley; 1993.
- [5] Simon JA, Lewiecki EM, Smith ME, Petruschke RA, Wang L, Palmisano JJ. Patient preference for once-weekly alendronate 70 mg versus once-daily alendronate 10 mg: a multicenter, randomized, open-label, crossover study. *Clin Ther* 2002;24:1871–86.
- [6] Lobel HO, Bernard KW, Williams SL, Hightower AW, Patchen LC, Campbell CC. Effectiveness and tolerance of long-term malaria prophylaxis with mefloquine. Need for a better dosing regimen. *JAMA* 1991;265:361–4.
- [7] Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993;341:848–51.
- [8] Bannwarth B, Labat L, Moride Y, Schaefferbeke T. Methotrexate in rheumatoid arthritis. An update. *Drugs* 1994;47:428–32.
- [9] Biller BM, Luciano A, Crosignani PG, et al. Guidelines for the diagnosis and treatment of hyperprolactinemia. *J Reprod Med* 1999;44:1075–84.
- [10] Nolting SK, Sanchez Carazo S, De Bouille K, Lambert JR. Oral treatment schedules for onychomycosis: a study of patient preference. *Int J Dermatol* 1998;37:454–6.
- [11] Gupta AK, Dlova N, Taborda P, et al. Once weekly fluconazole is effective in children in the treatment of *Tinea capitis*: a prospective, multicentre study. *Br J Dermatol* 2000;142:965–8.
- [12] Burke WJ, Hendricks SE, McArthur-Miller D. Weekly dosing of fluoxetine for the continuation phase of treatment of major depression: results of a placebo-controlled randomized clinical trial. *J Clin Psychopharmacol* 2000;20:423–7.
- [13] Rudd P. Clinicians and patients with hypertension: unsettled issues about compliance. *Am Heart J* 1995;130:572–9.
- [14] Eraker SA, Kirscht JP, Becker MH. Understanding and improving patient compliance. *Ann Intern Med* 1984;100:258–68.
- [15] Ridwan E, Schultink W, Dillon D, Gross R. Effects of weekly iron supplementation on pregnant Indonesian women are similar to those of daily supplementation. *Am J Clin Nutr* 1996;63:884–90.