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Long-Term Predictions of the Therapeutic Equivalence of Daily and Less Than Daily Alendronate Dosing*

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ABSTRACT

Less than daily alendronate dosing has been identified as an attractive alternative to daily dosing for patients and physicians. A recent 2-year study found bone mineral density (BMD) changes caused by weekly alendronate dosing therapeutically equivalent to that caused by daily dosing. There are no methods that can be used to predict how long therapeutic equivalence will be maintained after the first 2 years of treatment. In addition, it is unclear if dosing less frequently than weekly also might be therapeutically equivalent to daily dosing. In this study we use a computer simulation to develop predictions of the therapeutic equivalence of daily and less than daily dosing over time periods as long as a decade. The computer simulation uses a cell-based computer model of bone remodeling and a quantitative description of alendronate pharmacokinetics/pharmacodynamics (PK/PD). The analyses suggest that less than daily dosing regimens do not increase BMD as much as daily dosing. However, model predictions suggest that dosing as frequent as weekly still may be therapeutically equivalent to daily dosing over periods as long as 10 years. In addition, the simulations predict dosing less frequently than weekly may be therapeutically equivalent to daily dosing within the first year of treatment but may not be therapeutically equivalent after 10 years. Hypotheses based on these simulations may be useful for determining which dosing regimen may be most attractive for clinical trials. (J Bone Miner Res 2002;17:1662–1666)

Key words: bone remodeling, alendronate, osteoporosis, bone mineral density, drug dosing

INTRODUCTION

DAILY ALENDRONATE treatment has been shown to increase areal bone mineral density (BMD) and reduce fracture risk in patients with osteoporosis.[1] However, this manner of administering alendronate is associated with a number of dosing requirements that include fasting and limitations on activity for a one-half hour after the dose is administered.[2] When administered daily, the dosing requirements can be a substantial burden, especially when combined with the requirements of other drugs used by the elderly population. Less frequent dosing (less than daily) would simplify the treatment process and may improve patient compliance.[2] A recent 2 year study found the BMD increases caused by weekly and twice-weekly dosing regimens therapeutically equivalent to those caused by daily treatment.[3,4] It is not known how the results of daily and less than daily dosing would compare over longer periods of time (10 years). If weekly dosing is therapeutically equivalent to daily dosing over long time periods, there is the possibility that even less frequent treatments (twice monthly or monthly) also might be therapeutically equivalent to daily treatment.

Predicting the long-term results of a new alendronate dosing strategy is difficult because clinical results depend on the pharmacokinetics of alendronate (PK; the distribu-

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tion and elimination of the drug in the body), the pharmacodynamics of alendronate (PD; the relationship between drug concentration and physiological response), and the relationship between alendronate's primary effect (a change in bone-remodeling activity) and changes in BMD. A quantitative method that combines the PK/PD data with a description of alendronate's effects on bone remodeling and BMD could be used to predict the benefits of less frequent treatment strategies over short or long time periods and help provide new hypotheses regarding the relative effectiveness of different dosing strategies. Recently, we established a computational method of relating the changes in bone-remodeling activity caused by alendronate to changes in BMD.[5] The computer model used was only capable of simulating daily dosing because it did not detail the PK/PD of alendronate. However, if combined with existing quantitative data describing the pharmacokinetics and pharmacodynamics of alendronate,[6] our model of bone remodeling could be used to predict the long-term effects and therapeutic equivalence of less than daily dosing.

In this analysis we develop a simple PK/PD model of alendronate and integrate it with a simulation of bone remodeling to predict the therapeutic equivalence of less than daily and daily alendronate dosing regimens. Predictions are made over short-term (1 year) and long-term (10 year) periods of treatment. New hypotheses regarding the therapeutic equivalence of daily and less than daily alendronate treatments are developed based on these predictions.

MATERIALS AND METHODS

A description of the computer model used to simulate daily alendronate treatment has been presented previously[5,7] and will be discussed briefly here. The model describes the activity of basic multicellular units (BMUs) in a manner based on that used by Hazelwood and colleagues.[8,9] BMUs are organized groups of osteoclasts and osteoblasts that are responsible for bone resorption and formation at remodeling sites. The model calculates the rate of appearance of BMUs and the volume of bone resorbed and formed by all active BMUs in a volume of cancellous bone. The output from the computer model includes bone volume fraction and degree of mineralization (ash fraction). The bone volume fraction and degree of mineralization can be used to calculate total mineral content in a simulated bone sample and thereby determine BMD. Predicted changes in BMD are compared with those found clinically in the lumbar spine. Numerical parameters used in the model are derived from bone histomorphometry measurements in humans. Daily alendronate treatment is simulated by reducing the origination frequency (birthrate) of new BMUs by the same factor that has been observed clinically (an 87% reduction in BMU origination frequency for 10 mg/day of alendronate).[10] The decrease in BMU origination frequency results in increased BMD due to a reduction in the remodeling space (the resorption cavities formed during bone remodeling) and an increase in the degree of mineralization of the bone tissue.[5]

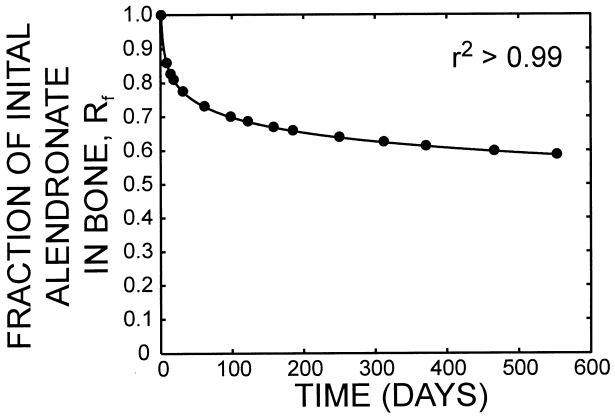

FIG. 1. Changes in alendronate concentration in bone are described. Data points are taken from clinical measurements[11] and are normalized by the amount of each dose remaining in the body 2 days after administration (assumed here to represent the total portion sequestered in the bone). The solid line represents Eq. (1) and is highly predictive of the rate of alendronate elimination over this time period ($r^2 > 0.99$).

In the current analysis the simulation of bone remodeling is combined with a simple PK/PD model. Because studies have suggested that the physiological response is related directly to the concentration of alendronate present in the bone tissue,[6] the PK/PD model is dominated by the characteristics of alendronate that influence drug concentration in the bone. Studies of alendronate absorption suggest that the fraction of an oral dose that is absorbed into bone tissue is not influenced by the size of the dose and that the rate of absorption of alendronate into the bone is very fast when compared with the remodeling process.[6] Based on these pharmacokinetic and pharmacodynamic characteristics of alendronate, we assume that the maximum BMU response (R_{max}, the change in BMU activity caused by daily treatment) is based on the cumulative dose of the drug rather than the size of each individual dose. This simplification implies that with regard to absorption into the bone, there is little difference between daily and less than daily regimens of the same cumulative dose. Therefore, the differences between daily and less than daily dosing are considered to be dependent on the rate of alendronate elimination from the bone. A knowledge of the rate of alendronate elimination is therefore essential to the model.

Alendronate elimination occurs in the model at an exponentially decreasing rate where 66% of the total dose remains 6 months after treatment is stopped.[11] A logarithmic function is used to express both the fraction of each alendronate dose that remains sequestered in the bone after administration and the response (R_f) that remains t days afterward:

$$R_f = 1 - m \times \ln(t + 1), \quad (1)$$

where m is a constant equal to 0.065 that is determined by fitting the equation to clinical data (Fig. 1).

The cumulative dose simulated in this study is the equivalent of a 10-mg/day oral dose (i.e., 10 mg/day oral, 70

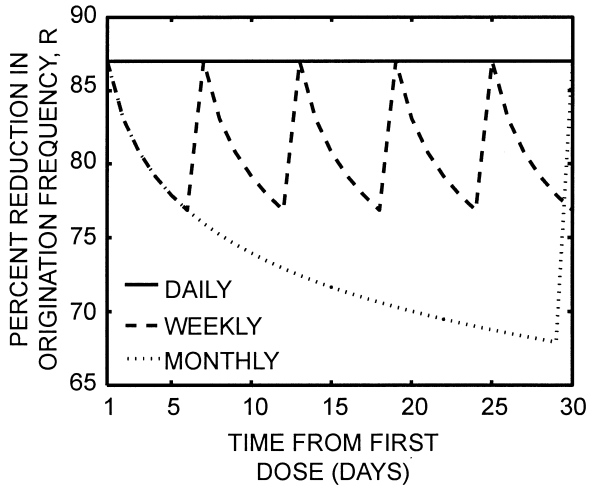

FIG. 2. The percent reduction in BMU origination frequency is presented for daily, weekly, and monthly alendronate treatment regimen. The same maximum response is used for each regimen because they all use the same cumulative dose. Time steps of 1 day are used.

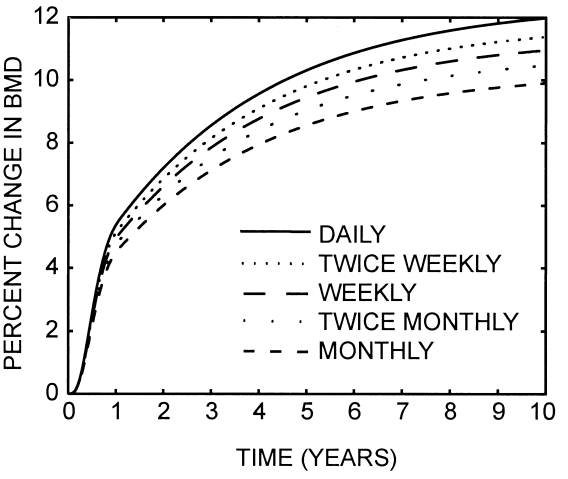

FIG. 3. The predicted changes in BMD in response to alendronate are depicted. Each line represents a different frequency of alendronate administration.

mg/week oral, etc.). The change in BMU origination frequency associated with this dosage clinically (87% reduction from pretreatment levels)[10] is used as the value for R_{max}. For less than daily dosing, the total response to alendronate (R) is reduced from the value of R_{max} at the same rate that alendronate is eliminated from the body between doses [see Eq. (1)]. The total percent decrease in origination frequency caused by alendronate can be expressed as a function of the number of days t since the last treatment:

$$R = R_{max} \times R_f = R_{max} \times (1 - m \times \ln(t + 1)), \qquad (2)$$

where R is the percent decrease in origination frequency, R_{max} is the response for daily dosing (determined by the cumulative dose), and R_f is the fraction of the response that remains after treatment ends [see Eq. (1)]. The percent decrease in origination frequency caused by daily and less than daily regimens over time can be compared (Fig. 2).

Daily, twice weekly, weekly, twice monthly, and monthly dosing regimens of the same cumulative dose are simulated. Computer simulations are performed on an SGI O2 workstation (Silicon Graphics Inc., Mountain View, CA, USA). Simulation results are presented in terms of the percent changes in BMD and therapeutic equivalence to daily treatment. Therapeutic equivalence is determined in a manner similar to that used by Schnitzer et al. [3]: a dosing regimen is considered therapeutically equivalent to daily if the percent BMD increase is within 1.5% (relative to the pretreatment level) of that predicted for daily dosing. Dosing regimens are compared after 1 year (short term) and 10 years (long-term) of simulated treatment assuming that no influences other than alendronate are actively changing the bone-remodeling process.

TABLE 1. THE PREDICTED CHANGES IN BMD FOR EACH OF THE DOSING REGIMENS

Treatment	*Predicted BMD increase after 1 year*	*Predicted BMD increase after 10 years*
Daily	5.37%	11.98%
Twice weekly	5.12%	11.38%
Weekly	4.94%	10.96%
Twice monthly	4.73%	10.47%
Monthly	4.49%	9.90%

RESULTS

The predicted increase in BMD was reduced when the treatment was administered less frequently (Fig. 3). The BMD change caused by daily treatment was 5.37% after 1 year and 11.98% after 10 years. The differences between daily and less than daily treatment methods became more pronounced with time. After 1 year the increase caused by daily treatment was predicted to be 0.88% greater than that predicted for monthly treatment but after 10 years the difference was 2.08% (Table 1). After 1 simulated year the difference in predicted BMD increase between less than daily dosing and daily dosing is predicted to be $<1.5\%$ (relative to pretreatment), suggesting that any of the less than daily dosing regimens simulated may be therapeutically equivalent to daily dosing. However, after 10 years of simulated treatment, the twice weekly and weekly regimens were predicted to be therapeutically equivalent to daily dosing and twice monthly and monthly dosing were not.

DISCUSSION

The objective of this analysis was to compare the BMD increases predicted from daily and less than daily alendro-

nate administration. Simulations of less than daily alendronate treatment suggest that the improvements in BMD are reduced as the frequency of dosage is reduced, even if the total cumulative dose of alendronate is maintained constant. Although less than daily treatment was not predicted to increase BMD as much as daily treatment, some less than daily treatments could be considered therapeutically equivalent to daily treatments. Based on the definition of therapeutic equivalence used in our study, twice weekly and weekly dosing were predicted to be therapeutically equivalent to daily dosing during the first 10 years of treatment.

It is important to address the limitations of the predictive model when assessing the results. First, the predictions are based on an implementation of the bone-remodeling model developed previously.[5] Although we refer the reader to the original publication for a thorough discussion of the limitations of that model, it is important to note that it is based on bone histology measurements and therefore takes on the assumptions used in dynamic bone histomorphometry. In addition, the simulation only takes into account the changes in the remodeling process caused by alendronate and does not consider cellular processes that may account for changes in the remodeling process (osteoclast or osteocyte apoptosis)[12] or modifications to mineral structure or crystallinity caused by the drug (although overall degree of mineralization is considered).

The predictions based on this model are useful for comparing different treatment regimens used in a general population but are not meant to describe the changes in BMD in an individual. In addition, some of the simulations performed in this analysis considered the possibility of very large doses of alendronate (the equivalent of a 300-mg or 150-mg oral dose for monthly or twice monthly dosing). Such large oral doses are not considered appropriate for use in humans. However, because the pharmacodynamics of our model are based on total alendronate sequestered in the bone, the predictions also would be consistent with any other method of administration (such as intravenous injection) that deposits the same amount of alendronate into the bone per dose.

In comparing antiresorptive drug treatments, greater increases in lumbar spine BMD have been shown to cause larger reductions in vertebral fracture risk.[13] This implies that dosing methods that generate larger increases in BMD (such as daily) may provide greater reductions in fracture incidence than other dosing methods (such as less than daily). However, a significant portion of the reduction in fracture risk caused by alendronate is not explained by BMD.[14] The unexplained portion of fracture risk reduction could reflect the reduction in stress riser prevalence associated with decreasing the surface prevalence of remodeling sites, or it could reflect other changes in microarchitecture or tissue properties that influence biomechanics. Without a good description of the unexplained portion, numerical predictions of fracture risk based on BMD during alendronate treatment may be limited.

The predictions made in this model are consistent with clinical studies that found the increases in BMD from twice weekly and weekly treatment to be 5.2 ± 0.3% and 5.1 ± 0.3% (mean ± 2 SE) after 1 year and 7.0 ± 0.4% and 6.8 ± 0.4% after 2 years.[3,4] The changes predicted in this study (5.12% and 4.94% at 1 year and 6.86% and 6.61% at 2 years) are within the 95% CIs of the clinical data, showing that the computer predictions are similar to those seen clinically. No other clinical studies of less than daily alendronate dosing for the same cumulative dose are available in the literature for comparison.

Our predictions suggest that, according to BMD increases, twice weekly and weekly alendronate dosing may be therapeutically equivalent to daily dosing, supporting the conclusions of recent clinical studies.[3,4] In addition, our predictions suggest that twice weekly and weekly alendronate dosing will continue to be therapeutically equivalent to daily dosing for as long as 10 years after the start of treatment. However, we also predict that administration of alendronate at monthly or twice monthly frequencies may appear therapeutically equivalent to daily dosing after 1 year but may not after 10 years. Therefore, we suggest that using the current definition of therapeutic equivalence, the length of an equivalence study may be a factor that can influence whether or not two treatment methods are considered equivalent. Consequently, future equivalence studies of bisphosphonates (and possibly other drugs influencing bone metabolism) should either use a definition of therapeutic equivalence relative to daily dosing or specify the time associated with equivalency conclusions.

The model used in this analysis was based on alendronate and did not explicitly address other bisphosphonates. The results would apply to other bisphosphonates that have similar PK/PD properties to alendronate. In particular, other bisphosphonates that cause similar changes in bone remodeling and display similar rates of elimination as alendronate may show results consistent with our predictions. We expect the differences between dosing methods to be greater for a bisphosphonate that has a larger influence on the remodeling process (a larger R_f) and smaller for a bisphosphonate with a slower rate of elimination. As opposed to all other bisphosphonates developed for clinical use, etidronate uniquely modifies the mineralization process that may lead to frank undermineralization and osteomalacia.[15] For this reason, our results may not apply to that agent.

Less frequent treatment methods are attractive to clinicians because they often result in increased patient compliance and a resulting improvement in treatment outcome. Clinical studies of new less frequent treatment methods for osteoporosis drugs often are long and require large commitments of resources. Identifying those treatment methods that are most likely to give the desired result could give researchers more confidence when developing clinical studies. In this analysis we have identified twice weekly and weekly alendronate treatments as those most likely to have similar benefits to daily treatment after a 10 years of administration. Although further validation would be needed to use this model to predict BMD changes in individual patients, it is useful for comparing different treatment methods and could be an important tool during the development of large clinical studies of a variety of pharmaceuticals that affect bone metabolism.

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