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ABSTRACT

A single 5-mg infusion of zoledronic acid restores biochemical markers of bone turnover into the reference range in the majority of patients with Paget's disease and maintains biochemical remission for at least 2 years. This effect is largely independent of pretreatment disease activity and prior bisphosphonate therapy.

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Long-Term Control of Bone Turnover in Paget’s Disease With Zoledronic Acid and Risedronate

David Hosking,1 Kenneth Lyles,2 Jacques P Brown,3 William D Fraser,4 Paul Miller,5 Manuel Diaz Curiel,6 Jean-Pierre Devogelaer,7 Michael Hooper,8 Guoqin Su,9 Ken Zelenakas,10 Judy Pak,9 Taiwo Fashola,10 Youssef Saidi,10 Erik Fink Eriksen,11 and Ian R Reid11

ABSTRACT: A single 5-mg infusion of zoledronic acid restores biochemical markers of bone turnover into the reference range in the majority of patients with Paget’s disease and maintains biochemical remission for at least 2 years. This effect is largely independent of pretreatment disease activity and prior bisphosphonate therapy.

Introduction: Zoledronic acid (ZOL) is a potent bisphosphonate that produces a rapid and complete control of the increased bone turnover of Paget’s disease. Long-term control of disease activity is an important aim of treatment in the hope that this will reduce the risk of complications such as deformity, fracture, and degenerative joint disease.

Materials and Methods: This study compares the ability of ZOL 5 mg given as a 15-minute intravenous infusion with risedronate (RIS) 30 mg daily by mouth for 60 days to maintain long-term control of bone turnover. No bisphosphonate was given during the extension study. All patients (n = 296) who achieved a therapeutic response, defined as normalization or a >75% reduction in the total alkaline phosphatase (total ALP) excess above the midpoint of the reference range, were eligible for inclusion.

Results: ZOL maintained the mean level of total ALP at the middle of the reference range, whereas those treated with risedronate showed a linear increase in total ALP from the 6-month post-treatment time-point. Both treatments resulted in a linear relationship between the 6-month nadir and 24-month total ALP. The relationship for RIS was shifted upward, showing that for a given level of post-treatment biochemical activity, bone turnover increased with time. This was in contrast to the ZOL-treated patients where total ALP generally remained unchanged over this 18-month extension period. A similar pattern of response was seen with the other bone turnover markers.

Conclusions: ZOL maintains bone turnover within the reference range over 24 months from the initiation of treatment. A reduction in the incidence and severity of long-term complications may require persistent normalization of bone turnover over many years, and this now seems a realistic possibility with ZOL.

J Bone Miner Res 2007;22:142–148. Published online on October 9, 2006; doi: 10.1359/JBMR.061001

Key words: Paget’s disease, bone turnover, remission, zoledronic acid, risedronate
INTRODUCTION

Paget’s disease is one of the best examples of a high turnover bone disease where management has been revolutionized by the introduction of increasingly potent bisphosphonates. Recent modifications to the bisphosphate R2 side-chain have resulted in greater binding affinity to hydroxypatite and increased potency in terms of inhibition of osteoclastic bone resorption. The ability to achieve optimal control of bone turnover with small amounts of bisphosphate has opened the way to intravenous administration, whereas the greater binding affinity offers the potential for sustained remission.

Zoledronic acid (ZOL) is a potent bisphosphonate that has been developed for intravenous administration. A recent comparison with oral risedronate (RIS) in the treatment of Paget’s disease showed the ability to produce a more rapid and complete control of the increased bone turnover. Long-term control of disease activity is also an important goal of treatment because of the possibility that this might reduce the risk of long-term complications such as deformity, fracture, and degenerative joint disease. Bisphosphonates are retained intact within bone during treatment but may subsequently re-exert an effect on osteoclasts when the site of deposition is remodeled. Whereas this subsequent effect on resorption will depend on potency and the amount of bisphosphate initially deposited (determined by dose administered and hydroxypatite affinity), it is also clear that the level of post-treatment bone turnover is a major influence.

It is therefore important to examine the long-term effects on bone turnover in the above trial to identify important differences between these two bisphosphonates as well as the determinants of remission and relapse.

MATERIALS AND METHODS

This report presents a pooled analysis of two independent randomized controlled trials that followed identical protocols between January 2002 and March 2004. A detailed description of the patient selection and methodology of the combined study is provided elsewhere.

All patients who achieved a therapeutic response, defined as at least a 75% reduction in the excess alkaline phosphatase (total ALP) above the midpoint of the reference range, were eligible for inclusion in an extension study. The aim was to compare the ability of ZOL 5 mg given as an 15-minute intravenous infusion with RIS 30 mg daily by mouth for 60 days in maintaining the long-term control of bone turnover. No bisphosphonate therapy was given during the extension study. Because supplementation of vitamin D to patients with Paget’s disease is indicated to prevent hypocalcemia and secondary hyperparathyroidism during treatment, the current trial recommended doses in the range of 400–1000 U/day together with calcium (1 g/day). The exact dose of vitamin D taken by patients was left to the investigators discretion provided it fell within the above range.

Fasting serum and urine for bone turnover markers were collected at each 6-month clinic visit and analyzed by Central Laboratory Services. Total ALP was measured using standard methods on Roche Hitachi 747 or 911 analyzers with a reference range of 31–110 U/liter (age < 58 years) and 35–115 U/liter (age > 58 years), together with amino terminal propeptide of type I collagen (PINP; Orion Diagnostica, Turku, Finland) as formation markers. Bone resorption was measured as serum βC-telopeptide (βCTX) of type I collagen (Roche Elecsys-βCrosslaps kit) and as urine aCTX using the method of Garnero et al.

The protocol was designed by the sponsor and reviewed by the investigators. Data management and statistical analyses were performed by the sponsor. The publication committee (Drs Hosking, Lyles, Reid, Miller, Fraser, and Brown) had full access to the data. Interpretation of the data and drafting of the paper was made by Drs Hosking and Lyles, who vouch for the accuracy and completeness of the report.

Endpoints

The extended observation period, starting 6 months after the first day of the initial therapy, is still ongoing. Patients have been continually followed up every 6 months after the end of core study at 6 months until their total ALP levels return to within 20% of baseline values. Current statistical analyses include all available data up to the cut-off date of October 21, 2005, at which point all participants had completed 18 months of extended follow-up.

The endpoints used for evaluating the long-term control of bone turnover in the extended observation period include the rate of maintaining therapeutic response, biochemical markers of bone formation (total ALP and serum PINP), and bone resorption (serum β-CTX and urine a-CTX) over time and the relationships in biochemical markers between the 6- and 24-month time-points after initial therapy.

During the extension study, serious adverse event (SAE) reports continued to be collected.

Statistical methods

The between-treatment differences in pretreatment characteristics were evaluated using an ANOVA model with study and treatment as factors for continuous variables and the Fisher exact test for categorical variables. The rate of maintaining therapeutic response was analyzed using a Cox regression model with treatment, study, and baseline total ALP as factors. For each biochemical marker, an analysis of covariance model with log ratio of postbaseline value over the 6-month value as the dependent variable and with treat-
ment, study, and log$_e$ 6-month value as explanatory variables was used to evaluate between-treatment and within-treatment differences. For each biochemical marker, the relationship between the 6- and 24-month values (in log$_e$ scale) after the initiation of treatment was evaluated using a simple linear regression model. For each treatment group, the between-treatment difference in the relationship was evaluated using the treatment by log$_e$ 6-month value interaction. Results are given as means ± SD unless otherwise specified.

RESULTS

The initial trial randomized 357 patients to ZOL or RIS plus appropriate placebo, and a total of 267 patients (90.2%) from the 296 who achieved the previously defined therapeutic response entered the extended period of observation (Fig. 1). This group is larger than that previously reported, which only included the 195 responding patients in whom total ALP values were available at 12 months after the start of the study. The pretreatment baseline characteristics of the initial study population and the subset who participated in the extension study are summarized in Table 1. There were no significant differences between this subset and the total population. There was no significant difference in baseline bone turnover (before any treatment) of the two groups of patients who subsequently entered the extended observation period (Table 1). Individual patient values for total ALP at baseline and 6 months after the initiation of treatment (start of the extended observation period) is shown in Fig. 2. Biochemical markers of bone turnover at the start of the extended observation study are shown in Table 2, where it can be seen that the mean level of bone turnover was significantly lower in the ZOL-treated patients.

The change in mean total ALP throughout the extended observation period is shown in Fig. 3. ZOL maintained the mean level of total ALP at the middle of the reference range with little increase in the scatter of values about the mean as shown by the relatively small increase in SE. This sustained response occurred over a wide range of baseline total ALP values up to 10 times the upper limit of the reference range (Fig. 2). This contrasted with the behavior of the group treated with risedronate that showed an almost linear increase in total ALP from the nadir achieved 6 months after the start of treatment (Fig. 3). The greater variability of individual responses is shown by the progressive increase in the size of the SE with time. Therapeutic response was defined in this study as normalization of total ALP or a >75% reduction in the excess baseline total ALP, and the time-course of maintaining this effect is shown by a Kaplan-Meir plot (Fig. 4). Whereas the therapeutic response was maintained in 98% of those given ZOL, only 57% of those treated with RIS maintained the therapeutic response by month 24. The post-treatment level of bone turnover is an impor-
tant determinant of the duration of remission and it is helpful to examine responses in individual patients to separate this influence from that caused by a specific property of the bisphosphonate. Both drugs showed a linear relationship (log scale) between the 6-month post-treatment total ALP and the 24-month value, although the relationship for the patients treated with RIS was displaced upward relative to ZOL (Fig. 5). Inspection of Fig. 5 shows that, for any 6-month post-treatment level of activity, the ALP had increased more over the subsequent 18 months in those treated with RIS compared with those receiving ZOL. This is indicative of an effect of ZOL in addition to its effect on bone turnover. In the ZOL-treated patients, total ALP generally remained unchanged over this 18-month period as is shown by the slope of the relationship, which was close to unity. However, a similar pattern of sustained response was also seen for the small number of RIS-treated patients who reached the lower part of the reference range after the initial treatment, although the increased tendency to relapse at higher bone turnover is clearly seen. Adjusting for the 6-month total ALP values in the Cox regression model showed that the rate of maintaining therapeutic response (as defined in the Materials and Methods section) was still statistically higher in the ZOL group than the RIS group ($p < 0.0001$). A similar pattern of response was seen with the other bone formation marker, P1NP (Table 2).

There was also a linear relationship between the post-treatment $\beta$CTX value at 6 months and that at 24 months. Both treatment groups, with a slope below unity, showed a slow increase from 6 to 24 months, but ZOL maintained a more persistent response than RIS, as shown by a slope of 0.47 compared with 0.65 (Fig. 6). Even though the between treatment difference in the relationship between 6 and 24 months was not statistically significant, most of the ZOL-

### Table 2. Bone Turnover Marker Concentration During the Extension Study

<table>
<thead>
<tr>
<th></th>
<th>Zoledronic acid</th>
<th>Risedronate</th>
<th>Risedronate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>Month 6</td>
<td>Month 24</td>
</tr>
<tr>
<td>Total ALP (U/liter)</td>
<td>121</td>
<td>76.4 ± 37.1</td>
<td>80.3 ± 55.1</td>
</tr>
<tr>
<td>PINP (µg/liter)</td>
<td>110</td>
<td>32.3 ± 23.8</td>
<td>32.6 ± 18.4</td>
</tr>
<tr>
<td>Urine $\alpha$CTX (µg/mmol creatinine)</td>
<td>105</td>
<td>270.7 ± 197.5</td>
<td>263.7 ± 171.2$^*$</td>
</tr>
<tr>
<td>Serum $\beta$CTX (nM)</td>
<td>55</td>
<td>2.6 ± 1.6</td>
<td>2.7 ± 1.5</td>
</tr>
</tbody>
</table>

All dates from start of initial study: extended observation period began at month 6. All values are mean ± SD.

$N$ = number of patients with values at both month 6 and month 24.

$^*$ Within-treatment difference between month 6 and month 24 was statistically significant ($p < 0.05$).

$^*$ Difference between ZOL and RIS was statistically significant at month 24 ($p < 0.05$).
treated patients still remained within the reference range. A similar relationship was observed for αCTX as for βCTX (Table 2).

Prior treatment did not influence the propensity to relapse after ZOL treatment in that the mean increase in total ALP from month 6 to month 24 was similar between patients who had received prior bisphosphonates (6.5 ± 30.2 U/liter) and patients who were treatment naive (1.1 ± 22.7 U/liter). However, for the risedronate group, the mean increase in total ALP from month 6 to month 24 was much higher (p < 0.01) for patients who received prior bisphosphonates (89.4 ± 109.9 U/liter) than patients who were treatment naive (27.1 ± 43.1 U/liter).

In the ZOL cohort, death was reported in 5/152 (3.3%) and SAEs in 26/152 (17.1%). In the risedronate cohort, death was reported in 3/115 (2.6%) and SAEs in 17/115 (14.8%). The most common SAEs reported were cancer and cardiovascular events consistent with the age of the population. Although osteonecrosis of the jaw was not a specific outcome, no case occurred during the 24 months of the study.

**DISCUSSION**

The previous report on this study showed that ZOL restores normal bone turnover in the majority of patients with very active Paget’s disease. This analysis extends these observations by showing that this bisphosphonate maintains bone turnover within the reference range over at least 24 months from the initiation of treatment. A number of factors are important in producing this prolonged remission.

ZOL binds strongly to hydroxyapatite so that it is more likely to be retained in bone during the remodeling cycle because of reattachment of bisphosphonate released during resorption. The potency of the drug in inhibiting osteoclastic bone resorption through an action on the key enzyme farnesyl diphosphate synthase also means that smaller amounts of the bisphosphonate are needed to maintain normal bone turnover in a focal area of Paget’s disease.

The relationship between post-treatment bone turnover and prolonged remission is well recognized but this study extends these observations. The plots of individual data points are important because they allow comparison between the two bisphosphonates at any given level of bone turnover. Inspection of Fig. 5 shows that when individual patients are matched for 6-month total ALP, those treated with RIS generally experience a greater increase in total ALP compared with those given ZOL. This “matching” for post-treatment bone turnover indicates that the more sustained control with ZOL is caused by an additional property of the drug. The most likely explanation is its greater binding to hydroxyapatite and persistence at remodeling sites. It can be seen that patients who achieved a bone turnover in the lower one half of the reference range behave similarly irrespective of whether they were treated with ZOL or RIS. This suggests that, at very low levels of turnover, there is sufficient RIS to exert control of osteoclastic activity. However, for higher values both within and outside the reference range, the escape of bone turnover from control is clearly apparent in those patients treated with RIS. This indicates either inadequate potency or insufficient residual drug at the bone surface to maintain inhibition of osteoclastic activity. In contrast, the patients treated with ZOL maintained a level of bone turnover very similar to the post-treatment nadir over the whole of the total ALP reference range and slightly beyond. This is consistent with recycling of effective amounts of bisphosphonate within the foci of Paget’s disease sufficient to maintain local control of remodeling. Bone turnover is an important determinant, along with renal function, of the amount of intravenous bisphosphonate retained within pagetic bone. Patients with high disease activity retain more bisphosphonate at very active sites, and this is consistent with the observed close correlation between change in bone turnover and bisphosphonate uptake corrected for skeletal size. This was also seen in this study where there was a close correlation, for both bisphosphonates, between the basal total ALP and the nadir value over a wide range of pretreatment disease activity.

Although the level of bone turnover 6 months after the initiation of treatment with ZOL was related to the pretreatment value, as is seen in some but not all previous studies, the propensity to relapse was independent of this influence. A similar lack of effect of baseline bone turnover on the duration of remission was also shown for olpadronate but not for less potent bisphosphonates such as tiludronate.

The duration of remission achieved with ZOL was also independent of the presence or absence of previous treatment, although this was not so obvious with RIS. In part, this is a function of the significantly lower post-treatment bone turnover achieved with ZOL, which would blunt any effect of prior treatment.

It is convenient to use serum total ALP as an indicator of treatment-induced changes in bone turnover because it is cheap, widely available, and has a low interassay variation. A similar pattern of response was seen with the other biochemical markers, which all have an in vivo CV comparable with that of total ALP of ∼10%. However,
\( \beta \text{CTX} \) showed more within-patient variation than total ALP when comparing the 6- and 24-month time-points. Degradation products of type 1 collagen include both \( \alpha \text{CTX} \), which contains an aspartyl-glycine motif derived from newly formed collagen, and \( \beta \text{CTX} \) formed from spontaneous isoaspartyl formation as the bone ages. In untreated Paget’s disease, \( \alpha \text{CTX} \) is raised proportionately more than \( \beta \text{CTX} \) but decreases to a greater extent than \( \beta \text{CTX} \) in response to bisphosphonate therapy,\(^{(22)} \) which normalizes the relative proportions of \( \alpha \) and \( \beta \text{CTX} \). This process might be incomplete by the 6-month time-point, resulting in the greater within-patient variability. There are a number of practical implications that follow from the high degree of long-term disease control that can be achieved with ZOL. Although early studies with etidronate showed a dose–response relationship with pain relief,\(^{(23)} \) subsequent comparator studies with more potent bisphosphonates such as pamidronate and alendronate showed better control of bone turnover but no statistical advantage in terms of pain relief.\(^{(18,24)} \) A factor here may not be the percentage change in bone turnover but the degree of control within the reference range. ZOL reduced bone turnover to well within the reference range and had a superior effect on bodily pain compared with RIS.\(^{(6)} \) There was a similar trend for the effect of normalization in the other bisphosphonate studies.\(^{(18,24)} \) However, reduction in the incidence and severity of long-term complications such as fracture and deformity\(^{(7)} \) may require persistent normalization of bone turnover over many years, and this now seems a realistic possibility with ZOL. There is concern that these aims might be compromised by the risk of osteonecrosis of the jaw. This is an uncommon event, and reports of this condition have primarily been in patients with advanced malignancy and skeletal metastases, but cases in patients receiving oral bisphosphonates for nononcology indications have also been described, albeit very infrequently.\(^{(25–27)} \) The ability to control Paget’s disease for a prolonged period of time with a single 5-mg infusion may also contribute to the low risk of osteonecrosis as a complication of bisphosphonate treatment. To ensure independent and consistent safety assessment of this condition during the ongoing development program of ZOL 5 mg in bone metabolic diseases, a blinded adjudication process led by a group of independent maxillofacial experts has been established to assess any reported cases in clinical trials.

The incidence of Paget’s disease is decreasing, and optimal care is probably best delivered in specialist centers even though this involves patients in more traveling. The pattern of response to ZOL with a rapid and sustained control of bone turnover makes it ideal for this type of scenario. Initial disease assessment and treatment could be done at a (distant) specialist center with longer-term monitoring in primary care using total ALP. Monitoring intervals could be assessed from the post-treatment nadir and might need to be at 6- to 12-month intervals.\(^{(19)} \) This study shows that this would be more than adequate in patients treated with ZOL. This approach would have considerable cost advantages, particularly in health care systems where there is an emphasis on moving long-term monitoring of chronic diseases from secondary to primary care.

**ACKNOWLEDGMENTS**

This study was supported by Novartis Pharmaceuticals Corp., East Hanover, NJ, USA.

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Received in original form July 31, 2006; revised form September
26, 2006; accepted October 5, 2006.