Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget’s Disease

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ABSTRACT

BACKGROUND
The advent of bisphosphonates advanced therapy for Paget’s disease, but more effective and convenient agents are needed to increase adherence. Zoledronic acid, a bisphosphonate administered as a single intravenous infusion, might meet these needs.

METHODS
In two identical, randomized, double-blind, actively controlled trials of 6 months’ duration, we compared one 15-minute infusion of 5 mg of zoledronic acid with 60 days of oral risedronate (30 mg per day). The primary efficacy end point was the rate of therapeutic response at six months, defined as a normalization of alkaline phosphatase levels or a reduction of at least 75 percent in the total alkaline phosphatase excess. The results of the studies were pooled.

RESULTS
At six months, 96.0 percent of patients receiving zoledronic acid had a therapeutic response (169 of 176), as compared with 74.3 percent of patients receiving risedronate (127 of 171, P < 0.001). Alkaline phosphatase levels normalized in 88.6 percent of patients in the zoledronic acid group and 57.9 percent of patients in the risedronate group (P < 0.001). Zoledronic acid was associated with a shorter median time to a first therapeutic response (64 vs. 89 days, P < 0.001). Higher response rates in the zoledronic acid group were consistent across all demographic, disease-severity, and treatment-history subgroups and with changes in other bone-turnover markers. The physical-component summary score of the Medical Outcomes Study 36-item Short-Form General Health Survey, a measure of the quality of life, increased significantly from baseline at both three and six months in the zoledronic acid group and differed significantly from those in the risedronate group at three months. Pain scores improved in both groups. During post-trial follow-up (median, 190 days), 21 of 82 patients in the risedronate group had a loss of therapeutic response, as compared with 1 of 113 patients in the zoledronic acid group (P < 0.001).

CONCLUSIONS
A single infusion of zoledronic acid produces more rapid, more complete, and more sustained responses in Paget’s disease than does daily treatment with risedronate.
Paget's disease of bone is characterized by a dramatic increase in bone turnover (both formation and resorption) at one or more sites. Measurement of biochemical markers of bone turnover is used to assess disease activity and monitor the response to therapy. About 2 percent of the U.S. population older than 60 years of age have Paget's disease, as do up to 6 or 7 percent of the elderly population in Western Europe. The bone pain, skeletal deformity, pathologic fractures, secondary arthritis, neurologic complications, and deafness that may accompany this disease contribute to substantial morbidity in the older population.

Bisphosphonate therapy is the most commonly used treatment for Paget's disease, often normalizing biochemical markers of bone turnover and resulting in the replacement of chaotic woven bone with normal lamellar bone. Bisphosphonates may also reduce bone pain. Currently used oral bisphosphonates require daily oral dosing for two to six months, with patients required to fast before and after treatment because of the very low bioavailability of the drugs and to remain upright for at least 30 minutes after dosing to reduce the risk of upper gastrointestinal complications. The intravenous bisphosphonate pamidronate is also used but is inconvenient for patients because it is usually given as a series of slow intravenous infusions each lasting a few hours, requiring multiple visits. The development of convenient, more effective, and longer-acting agents might address these problems.

Of the bisphosphonates that have entered clinical trials, zoledronic acid was very effective in preclinical models. It is administered as a single 15-minute infusion and has effects on bone mineral density in postmenopausal women similar to those afforded by 12 months of oral bisphosphonate therapy. This medication offers the possibility of a substantial increase in the convenience of treatment and adherence, which together with its greater efficacy, may increase response rates and the duration of remission. We compared the effects of zoledronic acid with those of risedronate, a leading bisphosphonate in current use, on biochemical indexes of disease activity and the quality of life.

**METHODS**

Two randomized, controlled trials that followed identical protocols were carried out between January 2002 and March 2004, each including patients from North America, Europe, and Australasia. One study also included patients from South Africa. Although the trials were independent, each protocol called for pooling of the results in a joint analysis.

**PATIENTS**

A total of 357 men and women who were older than 30 years of age and had radiologically confirmed Paget's disease of bone were studied at 76 centers in 10 countries. With the exception of four patients, all had alkaline phosphatase levels that were more than twice the upper limit of normal.

Exclusion criteria included a serum 25-hydroxyvitamin D level of less than 15 ng per milliliter (37 nmol per liter); primary hyperparathyroidism; evidence of hepatic or renal disease; a history of uveitis, iritis, upper gastrointestinal disorders that might interfere with adherence to the protocol, or diabetic nephropathy or retinopathy; and use of therapy specifically for Paget's disease in the preceding 180 days.

The institutional review board of each participating center approved the protocol, and all patients gave written informed consent.

**TREATMENT**

Patients were randomly assigned in a double-blind fashion through an interactive voice-response system to receive either a 5-mg infusion of zoledronic acid over a 15-minute period followed by placebo tablets or a saline infusion followed by 30 mg of risedronate per day for 60 days. The volume of all infusions was 105 ml. All patients received 1 g of calcium per day and 400 to 1000 U of calciferol per day.

**STUDY END POINTS**

The primary end point was the proportion of patients who had a therapeutic response, defined as normalization of the alkaline phosphatase level or a reduction of at least 75 percent in the alkaline phosphatase excess (the difference from the midpoint of the reference range) at six months. Measurements were made by Covance Central Laboratory Services, with the use of Roche Hitachi analyzers (model 747 or 911). The respective midpoints and upper limits of the reference ranges are 71 and 110 U per liter in patients 58 years of age or younger and 75 and 115 U per liter in those older than 58 years.

Secondary and exploratory efficacy variables included biochemical markers of bone resorption, as reflected by serum levels of C-telopeptide of type I collagen (Elcsys \( \beta \)-CrossLaps kit, Roche) and the
ratio of urinary 𝛼C-telopeptide of type I collagen to creatinine; biochemical markers of bone formation, as reflected by the serum levels of N-terminal propeptide of type I collagen (Orion Diagnostica); and the quality of life. The quality of life was measured with use of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36), which assesses eight aspects of health status: general and mental health, physical and social functioning, physical and emotional roles, pain, and vitality; scores on each scale can range from 0 (worst) to 100 (best).

**Bone Histomorphometry**
Transiliac bone biopsies were performed while the patient was under local anesthesia after having received two courses of tetracycline. To be suitable for quantitative histomorphometry, biopsy samples had to contain both cortices with intact trabecular bone.

**Safety Assessments**
Physical examinations, hematologic tests, and serum chemical tests were performed regularly throughout the six-month study. Serum creatinine and urinary protein were measured 9 to 11 days after intravenous dosing.

**Statistical Analysis**
Each study had a statistical power of 80 percent to demonstrate the noninferiority of zoledronic acid relative to risedronate with respect to the proportion of patients who had a therapeutic response at six months. Assuming a dropout rate of approximately 10 percent per study, we estimated that 88 patients were needed in each group (176 patients total) to evaluate noninferiority. Noninferiority was established if the one-sided 97.5 percent confidence interval for the absolute difference between zoledronic acid and risedronate exceeded 16 percent. In that case, superiority was evaluated with the use of a logistic-regression model that included treatment and the baseline alkaline phosphatase level as explanatory variables.

All efficacy variables, except the time to a therapeutic response, were analyzed according to the modified intention-to-treat principle, which required patients to have a baseline and at least one post-baseline measurement of alkaline phosphatase. The time to a therapeutic response was analyzed according to the intention-to-treat principle and therefore included all randomized patients.

Missing values for the primary efficacy variable were imputed by carrying the last observation forward.

Differences between groups in secondary or exploratory efficacy variables were evaluated by means of logistic regression, analysis of covariance, or Cox regression, where appropriate. For secondary efficacy variables, a two-sided P value of 0.05 was considered to indicate statistical significance. A closed testing procedure was used to control the type I error rate of these comparisons. Comparisons within groups were made with t-tests.

Results are based on pooled data from the two studies. All parametric models included study as an explanatory variable. Data are given as means ±SD unless otherwise specified.

The protocol was designed by the sponsor and reviewed and modified by the investigators. Data management and statistical analyses were performed by the sponsor. The publications committee (Drs. Reid, Miller, Lyles, Fraser, Brown, and Hosking) had full access to and interpreted the data. Drs. Reid and Miller wrote the article and vouch for the accuracy and completeness of the reported information.

**Results**

**Patients**
A total of 182 patients were enrolled in the zoledronic acid group and 175 in the risedronate group, of whom 177 and 172 patients, respectively, received the study drug (Fig. 1). Patients' characteristics at baseline are shown in Table 1. Adherence exceeded 90 percent in 98.3 percent of patients in the risedronate group and 93.2 percent of patients in the zoledronic acid group, as determined by pill counts.

**Serum Alkaline Phosphatase**
Serum alkaline phosphatase levels (Fig. 2A) showed a more rapid and marked reduction in the zoledronic acid group than in the risedronate group. After 10 days, the rates of therapeutic response were consistently higher in the zoledronic acid group than in the risedronate group, reaching 96.0 percent and 74.3 percent respectively, at six months (P<0.001) (Fig. 2B). Response rates were similar in the two studies: 95.5 percent in the zoledronic acid group and 75.3 percent in the risedronate group in one study (P<0.001) and 96.5 percent and 73.2 percent, respectively, in the other study (P<0.001). The median time to a first therapeutic response was 64 days in the zoledronic acid group and 89 days in the...
risedronate group (P<0.001). The higher rates of response in the zoledronic acid group were independent of age, sex, baseline alkaline phosphatase level, and the presence or absence of previous therapy for Paget's disease. The rates of normalization of the alkaline phosphatase level also differed significantly between groups (P<0.001) at all times from one month onward (Fig. 2C).

**OTHER BIOCHEMICAL MARKERS OF BONE TURNOVER**

Serum levels of the N-terminal propeptide of type I collagen, another marker of osteoblast activity, showed a pattern similar to that of alkaline phosphatase, but the response tended to be greater, probably because the serum level of the N-terminal propeptide of type I collagen is a more specific index of osteoblast activity (Fig. 3A). Bone resorption, assessed in terms of the serum level of the βC-telopeptide of type I collagen (Fig. 3B) and the ratio of urinary αC-telopeptide of type I collagen to creatinine (Fig. 3C), showed greater reductions with zoledronic acid than with risedronate at all times. Consistent with the osteoclast's being the primary target of bisphosphonates, these markers responded more rapidly than the N-terminal propeptide of type I collagen or alkaline phosphatase, and the very rapid decrease in resorption in response to an intravenous bisphosphonate was also evident.

Figure 1. Randomization, Treatment, and Outcome.

The populations included in the efficacy analysis consisted of patients who received at least one dose of study medication and had a baseline and at least one post-baseline measurement of alkaline phosphatase.
### Table 1. Baseline Characteristics of the Patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Zoledronic Acid (N=182)</th>
<th>Risedronate (N=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex — no. (%)</td>
<td>124 (68.1)</td>
<td>118 (67.4)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>70.8±9.8</td>
<td>70.0±10.7</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>168 (92.3)</td>
<td>164 (93.7)</td>
</tr>
<tr>
<td>Black</td>
<td>9 (4.9)</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (2.7)</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>Weight — kg</td>
<td>77.6±14.9</td>
<td>78.6±16.0</td>
</tr>
</tbody>
</table>

Previous therapy for Paget's disease — no. (%)
- Risedronate
- Alendronate
- Other oral bisphosphonates
- Intravenous bisphosphonates
- Clodronate
- Calcitonin
- None

- Serum alkaline phosphatase — µg/liter | 428±321 | 425±312 |
- Serum N-terminal propeptide of type I collagen — µg/liter | 453±355 | 422±482 |
- Serum C-telopeptide of type I collagen — nmol/liter | 13.0±11.5 | 12.6±7.2 |
- Urinary C-telopeptide of type I collagen:creatinine — µg/mmol of creatinine | 3100±2060 | 3200±3550 |

### QUALITY OF LIFE
In the zoledronic acid group, mean scores for each of the eight components of the SF-36 trended upward at both three and six months, suggesting improvements in the quality of life, whereas the responses were more mixed in the risedronate group (Fig. 4). The zoledronic acid group had a significantly greater improvement than the risedronate group in physical functioning at three months and general health at six months. The zoledronic acid group had a significant improvement from baseline scores in the physical-component summary score at both three and six months, and these changes were significantly greater than those in the risedronate group at three months. Multivariate tests for all components of the SF-36 suggested the superiority of zoledronic acid.

### BONE BIOPSY
Transiliac bone biopsies were performed in 22 patients, 12 taking zoledronic acid and 10 taking risedronate. Eleven biopsy specimens were incom-
plete, and one included only remnants of iliac epiphysis, but these showed no abnormality on qualitative examination. Of the 10 biopsy specimens that could be evaluated, 2 came from sites of Paget's disease (from one patient in each group) and were otherwise normal, apart from increased mineralizing surface in the patient in the risedronate group. The remaining eight biopsy specimens from non-pagetic bone were similar, except that the extent of the mineralizing surface was below the reference range in the zoledronic acid group (P=0.04 for the comparison with the risedronate group). There was no evidence of adynamic bone or qualitative abnormalities of bone formation in any biopsy specimen.

ADVERSE EVENTS

No deaths occurred. The numbers of patients with adverse events (146 in the zoledronic acid group and 133 in the risedronate group) and serious adverse events (9 in the zoledronic acid group and 11 in the risedronate group) were similar in the two groups. Because there was a marked clustering of adverse events in the first three days after intravenous drug administration, the data were tabulated separately for this period (Table 2).

In the first three days, the zoledronic acid group had twice the number of adverse events as the risedronate group (P < 0.001), and these were principally the influenza-like symptoms that are known to occur in association with the intravenous use of nitrogen-containing bisphosphonates. These symptoms were mild to moderate in severity (leading to the overnight hospitalization of one patient), and most resolved within four days. Subsequently, the rates of adverse events were similar in the two groups. The frequencies of gastrointestinal and renal or urinary disorders were similar in the two groups. One patient in the risedronate group and one patient in the zoledronic acid group who had preexisting renal impairment had moderate increases in serum creatinine levels at two months and six months, respectively. The mean serum creatinine level had decreased slightly but significantly by day 10 in the zoledronic acid group, as compared with the risedronate group (−0.05±0.10 mg per deciliter [4.4±8.8 µmol per liter] vs. −0.00±0.10 mg per deciliter [0.1±8.8 µmol per liter], P<0.001). At subsequent visits, the values were similar and did not differ significantly between groups.

Figure 2. Mean (±SE) Levels of Serum Alkaline Phosphatase (Panel A) and Percentage of Patients with a Therapeutic Response (Panel B) or Normalization of Alkaline Phosphatase Levels (Panel C).

The shaded area in Panel A represents the normal range of serum alkaline phosphatase (32 to 110 U per liter) in premenopausal women.
Hypocalcemia developed in eight patients in the zoledronic acid group and was asymptomatic in six of these patients. The two patients with mild symptoms had not taken their calcium and vitamin D supplements. One patient in the risedronate group had severe symptomatic hypocalcemia, despite taking calcium and vitamin D supplements, and required hospitalization and intravenous calcium. All these events occurred during study days 3 through 13. There were decreases in serum calcium levels in both groups at day 10, but the decrease was larger in the zoledronic acid group than the risedronate group (-0.80±0.50 mg per deciliter [0.20±0.13 mmol per liter] vs. -0.32±0.50 mg per deciliter [0.08±0.13 mmol per liter], P<0.001). Calcium returned to baseline levels in both groups by six months. These changes were reflected by increases in parathyroid hormone levels in both groups at three months (16±31 pg per milliliter in the zoledronic acid group and 11±19 pg per milliliter in the risedronate group) and six months (7±15 pg per milliliter and 2±12 pg per milliliter, respectively), and the changes were significantly greater at six months in the zoledronic acid group (P=0.002).

**TRIAL EXTENSION**

Patients who met the definition of a therapeutic response were eligible to enter a trial extension. A total of 113 patients in the zoledronic acid group and 82 in the risedronate group entered an open extension of the study, during which alkaline phosphatase was measured at six-month intervals. At a median of 190 days after the end of the core study, 21 of 82 patients in the risedronate group showed a loss of therapeutic response (25.6 percent), as compared with 1 of 113 patients in the zoledronic acid group (0.9 percent), a difference of 96.5 percent (P<0.001).

**DISCUSSION**

This study demonstrates the safety and efficacy of a single-dose therapy for Paget's disease. A single infusion of 5 mg of zoledronic acid, given over a 15-minute period, produced changes in a variety of biochemical markers of disease activity that appeared to be as great as or greater than the best results achievable with conventional oral therapies, all of which require daily administration over pe-
ZOLEDRONIC ACID FOR PAGET'S DISEASE

Risedronate group at 3 mo
Risedronate group at 6 mo
Zoledronic acid group at 3 mo
Zoledronic acid group at 6 mo

% of Patients

Physical functioning
Physical role
Bodily pain
General health
Vitality
Social functioning
Emotional role
Mental health

 change from baseline score

Zoledronic

Risedronate

Acid

P<0.05 (P<0.05)
P<0.05 (P<0.05)
P<0.05 (P<0.05)
P<0.05 (P<0.05)
P<0.05 (P<0.05)
P<0.05 (P<0.05)
P<0.05 (P<0.05)
P<0.05 (P<0.05)

Change from Baseline Score

Data were analyzed by an analysis-of-covariance model with treatment, study, and baseline score as explanatory variables. Differences within groups were analyzed by a one-sample t-test. No adjustments were made for multiple comparisons. Multivariate testing (Wilks' lambda multivariate F-test) across the domains suggested the superiority of zoledronic acid (P<0.05), as did similar testing across the two summary scores (P<0.04). A five-point improvement is generally considered to be clinically significant, and the percentage of patients with at least this change at six months is shown on the right for the groups. P values on the graph indicate significant differences from baseline, and P values in parentheses indicate significant differences between groups.

For comparison, a single 5-mg dose of zoledronic acid resulted in an 80 percent decrease in alkaline phosphatase levels at six months, with normalization of this index in 89 percent of subjects, whereas six months' therapy with daily oral alendronate results in a decrease in alkaline phosphatase levels of 73 to 79 percent at six months, with normalization of this index in 48 to 63 percent of patients. Other trials of risedronate have shown a decrease in alkaline phosphatase levels of 69 to 77 percent at six months, with normalization of this index in up to 73 percent of patients. Tildronate reduces alkaline phosphatase levels by
90 to 59 percent at six months, with normalization of the level in 11 to 44 percent of patients.\textsuperscript{23-25} Ibandronate, an intravenous agent still in development, reduces alkaline phosphatase levels by 70 percent after one or two doses.\textsuperscript{16} When Paget's disease is being treated with bisphosphonates, the duration of remission is strongly determined by the bone-turnover nadir, so the greater efficacy and longer duration of effect with zoledronic acid suggest that the interval between treatments is likely to be much greater with this agent. This could yield dividends to patients in terms of convenience and may even influence the risk of long-term complications, such as degenerative joint disease.

It is encouraging that the marked biochemical effects of zoledronic acid appeared to be accompanied by significant improvements in indexes of the quality of life, including physical functioning, pain, general health, vitality, and emotional well-being. The improvements in some of these indexes in the zoledronic acid group were significantly greater than those in the risendronate group. Although there is an issue regarding the use of multiple statistical

tests on these numerous quality-of-life end points, it should be noted that all the domains showed a trend toward improvement with zoledronic acid therapy, which was not so for risendronate, suggesting that the significant results are not merely a statistical artifact. This suggests that the benefits observed in biochemical end points will ultimately result in greater clinical dividends among patients with Paget's disease, who may sometimes have substantial disability. In contrast, the currently used agents have not been demonstrated to yield significant differences between groups in quality-of-life measures in randomized, controlled trials,\textsuperscript{34,35} even though the agents used for comparison were placebo or the weak bisphosphonate etidronate.

Zoledronic acid has previously been studied in two preliminary trials involving patients with Paget's disease. In one, doses of 24 to 400 µg were administered and biochemical end points followed for two weeks.\textsuperscript{17} The highest of these doses caused reductions in hydroxyproline of almost 50 percent, though, as expected, there was no effect on alkaline phosphatase levels during this brief period. A second study\textsuperscript{18} showed a halving of bone turnover markers 90 days after an infusion of 400 µg of zoledronic acid, with lesser responses to lower doses. Our findings confirm the efficacy of zoledronic acid in patients with Paget's disease and add substantially to the available data by demonstrating that prolonged remissions can be achieved, accompanied by improvements in the quality of life.

The magnitude and time course of the effect of zoledronic acid are likely to result from its single-dose administration, the drug's high affinity for bone mineral, and its potent inhibition of the putative target of nitrogen-containing bisphosphonates, the enzyme farnesyl diphosphate synthase.\textsuperscript{19-22} The persistence of its effect makes it a particularly suitable agent for the management of Paget's disease, in which the need for frequent re-treatment is a major clinical problem. Influenza-like symptoms are common after the intravenous administration of nitrogen-containing bisphosphonates, being reported in two thirds of patients receiving pamidronate for Paget's disease.\textsuperscript{23,24}

Our findings confirm the apparent renal safety of zoledronic acid in patients with non-neoplastic bone disease,\textsuperscript{8} though it should be noted that only those with a baseline creatinine clearance greater than 30 ml per minute were eligible, consistent with current dosing recommendations for oral bisphosphonates. Asymptomatic hypocalcemia is common

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**Table 2. Timing and Range of Adverse Events.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Zoledronic Acid (N=177)</th>
<th>Risedronate (N=172)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days 1–3</td>
<td>95 (53.7)</td>
<td>43 (25.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>17 (9.6)</td>
<td>7 (4.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Myalgia</td>
<td>13 (7.3)</td>
<td>6 (3.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (7.3)</td>
<td>1 (0.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (6.8)</td>
<td>4 (2.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (6.8)</td>
<td>7 (4.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Rigors</td>
<td>12 (6.8)</td>
<td>1 (0.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (6.2)</td>
<td>3 (1.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Bone pain</td>
<td>9 (5.1)</td>
<td>2 (1.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>After study day 3</td>
<td>117 (66.1)</td>
<td>126 (73.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Pain in an arm or leg</td>
<td>12 (7.3)</td>
<td>12 (7.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (5.1)</td>
<td>19 (11.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (5.1)</td>
<td>5 (2.9)</td>
<td>0.41</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (5.1)</td>
<td>14 (8.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (4.5)</td>
<td>9 (5.2)</td>
<td>0.81</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (4.0)</td>
<td>10 (5.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (2.3)</td>
<td>12 (7.0)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Events that occurred in more than 5 percent of patients in either group are shown. Only patients who received at least one dose of study drug were included in the analysis.*
after the use of intravenous bisphosphonates in patients with Paget's disease, and seldom requires intervention, but patients with preexisting hypocalcemia or vitamin D deficiency must be treated before receiving these agents. Our results suggest that the use of calcium supplements is important in minimizing symptomatic hypocalcemia.

In conclusion, we found that a single infusion of zoledronic acid can produce rapid and sustained remissions, which appear to be accompanied by improvements in the quality of life. The long duration of remission may result in more complete control of disease activity than has previously been possible.

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REFERENCES


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