Zoledronic Acid Markedly Improves Bone Mineral Density for Patients with Monoclonal Gammopathy of Undetermined Significance and Bone Loss

James R. Berenson,1,2,3 Ori Yellin,1 Ralph V. Bocca,4 Marshall Flam,5 Siu-Fun Wong,6 Olcay Batuman,7 Mehdi M. Moezi,8 Donald Woytowitz,9 Herbert Duvivier,3 Youram Nassir,3 and Regina A. Swift 3

Abstract

Purpose: Patients with monoclonal gammopathy of undetermined significance (MGUS) have increased rates of bone resorption, osteopenia, osteoporosis, and risk of fractures. This study was undertaken to determine the efficacy and safety of zoledronic acid for patients with MGUS and enhanced bone loss.

Experimental Design: In this phase II open-label study, 54 patients with MGUS and osteopenia or osteoporosis were administered zoledronic acid 4 mg i.v. at 0, 6, and 12 months. The primary efficacy end point was bone mineral density, assessed using a dual-energy X-ray absorptiometry scan in the lumbar (L)-spine done at screening and at 13 months (1 month after the final zoledronic acid infusion).

Results: At study end for all patients ($N=54$), L-spine T-scores improved by a median of $+0.27$ (range, $-0.38$ to $+3.91$), corresponding to a median increase in bone mineral density of $+15.0\%$ (range, $-18.0\%$ to $+1,140.0\%$; $P<0.0001$). Hip T-scores improved by a median of $+0.10$ (range, $-2.40$ to $+2.03$), corresponding to a median increase of $+6.0\%$ (range, $-350.0\%$ to $+165.0\%$). During the study, no new fractures, osteonecrosis of the jaw, or significant renal adverse events were reported.

Conclusions: Zoledronic acid administered i.v. at a dosage of 4 mg every 6 months for three doses total was well-tolerated and substantially improved bone mineral density for patients with MGUS and bone loss. Zoledronic acid may be effective for the prevention of new fractures in this high-risk population.
Translational Relevance

Monoclonal gammopathy of undetermined significance (MGUS) is the most common plasma cell disorder, and it may progress to multiple myeloma or a related B-cell disorder. Notably, patients with MGUS have increased rates of bone resorption, osteopenia, osteoporosis, and risk of fractures. Bisphosphonates clearly reduce skeletal complications both for patients with cancer, including multiple myeloma, and those with noncancer-related bone loss. Although monthly administration of zoledronic acid or pamidronate is effective for cancer patients, less frequent annual dosing has shown efficacy for patients without cancer. In addition, zoledronic acid administered every 3 or 6 months increases bone density among cancer patients with treatment-induced bone loss. To date, no clinical studies have evaluated the use of bisphosphonates for MGUS patients with enhanced bone loss and its associated high fracture risk. In this study, we show that i.v. administration of the bisphosphonate zoledronic acid, 4 mg every 6 months for 3 doses total, was well-tolerated and substantially improved bone mineral density for patients with MGUS and bone loss. The data presented here suggest that zoledronic acid may be effective for the prevention of new fractures in this high-risk population.

T-score of -2.5). Osteopenia is defined by a bone mineral density value between 1.0 and 2.5 SD below the mean for young female adults (i.e., a T-score between -1.0 and -2.5). Furthermore, patients with T-scores of <1.0 have been shown to have a high risk of developing new fractures. Bisphosphonates, including zoledronic acid, have shown efficacy in both improving T-scores and reducing the occurrence of new fractures for patients with low bone mineral density T-scores (17–21).

The American Society of Clinical Oncology 2007 Clinical Practice Guideline Update on the Role of Bisphosphonates in Multiple Myeloma recommends the use of zoledronic acid (4 mg i.v. over at least 15 minutes) or another bisphosphonate, pamidronate (90 mg i.v. over at least 2 hours), every 3 to 4 weeks for patients with MM who have evidence of lytic bone destruction or spinal compression fractures due to osteopenia; it may also be given to patients with osteopenia but without lytic bone disease. However, zoledronic acid was not recommended for patients with MGUS because no relevant data have yet been published on the use of bisphosphonates for patients with this condition (22). Moreover, no other agents have been formally studied to date for the treatment of osteopenia or osteoporosis associated with MGUS. The rationale for this study of zoledronic acid for patients with osteopenia or osteoporosis in the setting of MGUS is based on its known efficacy for cancer patients with or without metastatic bone disease, including MM, coupled with the knowledge that patients with MGUS have a higher prevalence of bone loss and fracture risk.

Materials and Methods

Study design. This phase II open-label single-arm study was designed to evaluate the efficacy and safety of zoledronic acid for patients with MGUS and significant loss of bone. The primary objective of this study was to determine the effect of 1 y of zoledronic acid treatment administered every 6 mo for 3 doses total on L-spine bone mineral density, as measured at baseline compared with 13 mo by dual-energy X-ray absorptiometry scan, among patients with MGUS and associated osteopenia or osteoporosis. The secondary objectives of this study were to assess the safety of zoledronic acid in this patient population and to determine the effect of zoledronic acid on bone mineral density of the total hip, (b) skeletal fractures, (c) serum monoclonal (M)-protein levels, and (d) the proportion of patients who develop MM or other related malignancies.

The trial was registered with the Multiple Myeloma Research Foundation as a Phase I/II Trial of Zometa in Patients with Monoclonal Gammopathy of Undetermined Significance (ZOMGUS-001).

Patients. Patients were eligible for study if they were at least ages 18 y and had a diagnosis of MGUS, a Karnofsky Performance Status of >60%, and osteopenia or osteoporosis (defined as a T-score of <-1) assessed by a dual-energy X-ray absorptiometry scan. A diagnosis of MGUS was based on the presence of monoclonal gammopathy detected on serum or urine electrophoresis; a monoclonal protein (M-protein) level of <3.5 g/dL (IgG) or <2.0 g/dL (IgA); Bence-Jones protein of <300 mg/24 h; bone marrow plasma cells of <10%; and no evidence of lytic lesions, anemia, hypercalcemia, or renal insufficiency related to the M-protein.

Patients were excluded if they had a life expectancy of <3 mo, an active malignancy, or known secondary causes of osteopenia or osteoporosis other than MGUS (however, patients with concomitant postmenopausal osteopenia or osteoporosis were not excluded). Patients were ineligible if they had received treatment with other agents known to affect osteoclastic activity, including calcitonin, mithramycin, and gallium nitrate; had used oral bisphosphonates or fluorides for a total of >3 mo within the last 2 y; had used i.v. bisphosphonates within the last 2 y; or were currently receiving systemic corticosteroid therapy equivalent to 10 mg or more of prednisone per day. Hormonal modulation was also cause for exclusion: disorders of the parathyroid or thyroid glands, use of selective estrogen receptor modulators such as tamoxifen or raloxifene in the preceding 3 mo, prior or current use of recombinant parathyroid hormone; any change in hormone replacement therapy in the preceding 6 mo, or prior or current use of recombinant parathyroid hormone. Laboratory values defining exclusion were serum 25-hydroxyvitamin D concentration of <15 ng/mL; serum creatinine level of >3 mg/dL; alanine aminotransferase/aspartate aminotransferase of more than thrice the upper limit of normal; total bilirubin of more than twice the upper limit of institutional laboratory normal, unless clearly related to the disease; and baseline platelet count of <50 × 10^9/L, hemoglobin of <9.0 g/dL, and absolute neutrophil count of <1.0 × 10^9/L. Patients were also excluded if they were pregnant or had comorbidities of poorly controlled hypertension, diabetes mellitus, or other serious medical or psychiatric illness that could potentially interfere with the completion of treatment according to this protocol.

Written informed consent was obtained from each participant, and the trial was conducted according to the principles of the Declaration of Helsinki. An institutional review board approved the protocol at each study site in accordance with Good Clinical Practice Guidelines.

Dosage and schedule. Zoledronic acid 4 mg was administered i.v. over 15 min on day 0 and repeated at 6 and 12 mo.

Efficacy assessments. Bone mineral density was measured by dual-energy X-ray absorptiometry scans of the L-spine and hip, whereas fractures were assessed by skeletal surveys conducted at screening and 1 mo after the final zoledronic acid infusion (i.e., at 13 mo after the first infusion). In addition, M-protein levels were assessed at baseline and at the end-of-study evaluation by serum protein electrophoresis or by electrophoresis of a 24-h urine specimen when appropriate.

The primary efficacy assessment involved the evaluable patient population. A secondary efficacy assessment included the two subsets.
of patients defined as osteoporotic/osteopenic by L-spine or hip measurements.

Safety assessment and analysis. All patients who received at least one dose of zoledronic acid were monitored for adverse events. Patients were evaluated by physical examination, and blood and urine samples were obtained for laboratory analysis, at day 0 and at month 6 and at end of study; adverse events were recorded if present at these examinations.

Statistical methods. The sample size of this study was calculated based on the primary efficacy variable, percent change from baseline in postero-anterior L-spine bone mineral density. Using a two-sided paired t test with 90% power to detect 3 percent change from baseline in bone mineral density and a significance level of 0.05, it was determined that 60 patients were necessary. Allowing for a dropout rate of 25%, an enrollment of 80 patients was planned.

The efficacy data set consisted of all eligible patients who received at least one infusion of zoledronic acid. Efficacy analyses were done by evaluating all patients in the efficacy set with imputation of missing data; patients having data for the specific end point were analyzed as the “evaluable patient” subpopulation. The imputation of missing value is end point dependent as follows: zero for both BMD measurements. In addition, analyses were done to assess whether missing data were informative, including comparison of baseline data for those with and without missing values. Safety was assessed for the safety set, consisting of all patients initiating therapy.

Results

Patient characteristics and disposition. Fifty-four patients were enrolled between July 20, 2004, and November 28, 2006. After the enrollment of the 54th patient, the study was closed due to difficulty in enrolling additional patients because of their concern about potential side effects, especially with the increasing recognition of osteonecrosis of the jaw among cancer patients treated with an i.v. administered bisphosphonate.

Baseline characteristics of the enrolled patients are summarized in Table 1. The mean patient age was 67 years. Entry criteria were met by 39 patients with L-spine T-scores of <-1 (median, -2.10; 28 patients diagnosed with osteopenia and 11 patients diagnosed with osteoporosis) and 40 patients with hip T-scores of <-1 (median, -1.80; 35 patients diagnosed with osteopenia and 5 patients diagnosed with osteoporosis). Patients qualifying by L-spine or hip T-score were not mutually exclusive; 26 patients qualified with both L-spine and hip T-scores.

Table 1. Patient demographics and baseline characteristics (N = 54)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age, years median (range)</td>
<td>67 (50 – 91)</td>
</tr>
<tr>
<td>Male/female</td>
<td>26/28</td>
</tr>
<tr>
<td>L-spine T-score, median (range)</td>
<td>-1.70 (-3.97 to +2.10)</td>
</tr>
<tr>
<td>Hip T-score, median (range)</td>
<td>-1.65 (-3.50 to +1.40)</td>
</tr>
<tr>
<td>Serum M-protein, median (range)</td>
<td>0.65 g/dL (0.00*–2.70)</td>
</tr>
<tr>
<td>Patients with osteopenia (T-score, -1.0 to -2.5)</td>
<td>28</td>
</tr>
<tr>
<td>L-spine (n = 39)</td>
<td>28</td>
</tr>
<tr>
<td>Hip (n = 40)</td>
<td>35</td>
</tr>
<tr>
<td>Patients with osteoporosis (T-score &lt; -2.5)</td>
<td>11</td>
</tr>
<tr>
<td>L-spine (n = 39)</td>
<td>11</td>
</tr>
<tr>
<td>Hip (n = 40)</td>
<td>5</td>
</tr>
</tbody>
</table>

*Detectable by immunofixation and serum protein electrophoresis but not measurable.

Fig. 1. Median T-scores at baseline and at follow-up after 13 mo of treatment with zoledronic acid 4 mg i.v. for each patient. *, 10 patients (6 women and 4 men) for whom efficacy assessments at follow-up were not available (one of the 10 patients was missing a baseline hip score measurement). Baseline median T-scores for nonevaluable patients were -1.59 for lumbar spine and -1.20 for hip. A, L-spine; B, hip.

Ten patients (6 women and 4 men; median age, 75 years), including 6 patients who discontinued, were not evalu-able for efficacy due to lack of the assessment of L-spine or hip T-scores at follow-up; 1 of the 10 patients was also missing a baseline hip score measurement. Baseline median T-scores for non-evaluable patients were -1.59 (L-spine; n = 10) and -1.20 (hip; n = 9), and these T-scores were not different than the evaluable set (Fig. 1). Likewise, demographic and baseline characteristics did not differ from the evaluable set (age, sex, and serum M-protein levels).
Changes in T-scores for evaluable patients (<i>n</i> = 44). Horizontal lines, median values for each set of data. A, median change lumbar L-spine, 0.30; median change hip, 0.19. B, median % change L-spine, 16.2%; median % change hip, 8.5%.

**Table 2.** Patient responses after 13 mo of treatment with 4 mg zoledronic acid

<table>
<thead>
<tr>
<th></th>
<th>Lumbar spine T-score</th>
<th>Hip T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;i&gt;n&lt;/i&gt;</td>
<td>54</td>
<td>54</td>
</tr>
<tr>
<td>Median change (range)</td>
<td>+0.27 (-0.38 to +3.91)</td>
<td>+0.10 (-2.40 to +2.03)</td>
</tr>
<tr>
<td>Median percent improvement (range)</td>
<td>+15.0% (-18.00% to +1,140.00%)</td>
<td>+6.0% (-350.00% to +165.00%)</td>
</tr>
<tr>
<td>&lt;i&gt;P&lt;/i&gt;</td>
<td>&lt;0.0001</td>
<td>0.1679</td>
</tr>
<tr>
<td>Evaluable patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;i&gt;n&lt;/i&gt;</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Median change (range)</td>
<td>+0.30 (-0.38 to +3.91)</td>
<td>+0.19 (-2.40 to +2.03)</td>
</tr>
<tr>
<td>Median percent improvement (range)</td>
<td>+21.8% (-18.00% to +1,140.00%)</td>
<td>+8.5% (-350.00% to +165.00%)</td>
</tr>
<tr>
<td>&lt;i&gt;P&lt;/i&gt;</td>
<td>&lt;0.0001</td>
<td>0.1684</td>
</tr>
<tr>
<td>Osteopenic/osteoporotic patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;i&gt;n&lt;/i&gt;</td>
<td>32 †</td>
<td>33 †</td>
</tr>
<tr>
<td>Median change (range)</td>
<td>+0.30 (-0.38 to +3.91)</td>
<td>+0.20 (-0.60 to +2.03)</td>
</tr>
<tr>
<td>Median percent improvement (range)</td>
<td>+16.2% (-18.00% to +134.40%)</td>
<td>+8.7% (-54.50% to +165.00%)</td>
</tr>
<tr>
<td>&lt;i&gt;P&lt;/i&gt;</td>
<td>0.0021</td>
<td>0.0020</td>
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</tbody>
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*With imputation of missing data as no change from baseline.
† Of the osteopenic/osteoporotic patients who were evaluated for L-spine, five had bone disease that progressed and four had stable bone disease (i.e., no change in T-score).
‡ Of the osteopenic/osteoporotic patients who were evaluated for hip, four had bone disease that progressed and three had stable bone disease.
Forty-eight patients completed the study. Of the six patients who discontinued, one patient withdrew consent, one died (cause of death unknown), one experienced an adverse event of arthralgia, one withdrew due to physician's request, one experienced an adverse event of bone mineral density scores in L-spine and hip. For all patients, the median L-spine T-score increased by +0.30 ($P = 0.0020$) from baseline, which represented a median increase of +15.0%. Among evaluable patients ($n = 44$), the median L-spine T-score increased by +0.30 ($P = 0.0001$), corresponding to a median increase of +21.8% (Table 2). For patients defined as osteopenic or osteoporotic ($n = 33$ groups, respectively. These T-score changes correspond to improvements of 6.0% for all patients, 8.5% for the evaluable patients, and 8.7% for the osteopenic/osteoporotic subset of patients.

Skeletal surveys done at baseline and at the end of study indicated no new fractures. No patient required any bone surgery. During the study, the M-protein level did not significantly change (baseline, $n = 50$; mean, 0.89 mg/dL; end of study, $n = 45$; mean, 0.93 mg/dL; $P = 0.627$).

Safety. Adverse events are summarized in Table 3. Fatigue ($n = 12$), arthralgias ($n = 9$), fever ($n = 7$), flu-like symptoms ($n = 6$), and myalgias ($n = 3$) occurred in a small number of patients, consistent with previous studies evaluating zoledronic acid (23).

One patient developed a serious event of arthralgia, which led to that patient's withdrawal from the study. The event resolved within a few months after the patient's dose of zoledronic acid. One death occurred; the patient was a 78-year-old woman who had discontinued the study 1 month before her death. The cause of death was not thought to be related to the study drug. No patient developed osteonecrosis of the jaw or a significant renal adverse event. One patient was diagnosed with chronic lymphocytic leukemia and another was found to have primary amyloidosis during the study, and subsequently, both patients were discontinued from the study. No other patients showed progression to myeloma or to another related B-cell disorder.

Discussion

Improvement in bone density among high-risk patients has been shown to correlate with a reduction in the occurrence of new fractures in both the malignant and benign settings (10, 17, 24). In this study, we have shown that zoledronic acid administered at a dosage of 4 mg every 6 months for 3 doses to patients with MGUS and bone loss (osteopenia or osteoporosis) notably improves bone mineral density and is safe and well-tolerated; zoledronic acid at this dose and schedule is also likely to be effective in preventing the development of new fractures for patients with MGUS and either osteopenia or osteoporosis. This is the first study to suggest a therapeutic approach that may reduce the previously identified high risk of bone loss (5) and fracture (7) in this patient population.

Because MGUS patients are asymptomatic, no specific therapy is recommended unless in the setting of a clinical trial (25). However, MGUS patients have an increased risk of progressing to MM or a related B-cell disorder at a rate of ~1% per year and, thus, must be followed indefinitely. Although it is not possible to predict with certainty which patients will progress, recent studies suggest specific characteristics that may be prognostic. These variables include the level of serum M-protein, type of M-protein (IgA and IgM are associated with increased risk), number of circulating plasma cells, and abnormal serum-free immunoglobulin–light-chain ratios (2, 26). The slow progression rate of 1% per year also makes it difficult to design clinical trials to test agents that could prevent the progression of MGUS to myeloma (2). It is not known

<table>
<thead>
<tr>
<th>Table 3. Incidence of adverse events occurring during the study ($n = 54$)</th>
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<tbody>
<tr>
<td><strong>Total number of patients with any AE (%)</strong></td>
</tr>
<tr>
<td><strong>Total number of AEs</strong></td>
</tr>
<tr>
<td><strong>Specific AEs</strong></td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Anemia</td>
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<tr>
<td>Flu-like symptoms</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Generalized hurt</td>
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<tr>
<td>Back pain</td>
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<tr>
<td>Chills</td>
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<tr>
<td>Edema</td>
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<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Dyspnea</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Myalgia</td>
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<tr>
<td>Nausea</td>
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<tr>
<td>Palpitations</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Vertigo</td>
</tr>
<tr>
<td>Bone pain, chest discomfort, diarrhea, heartburn/GERD, lightheadedness, peripheral neuropathy, pruritus/itchiness, upper respiratory infection, urinary frequency, vomiting, weakness, and weight loss</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm, abscessed tooth, amyloidosis, ankle laceration, arm discomfort, arm swelling, ataxia, Bell's palsy, bloody stool, breast mass, bronchitis, bronchopneumonia, bruising, cheek lesion, colitis, depression, dysphagia, erectile dysfunction, foot pain, gout, gum irritation, hearing loss, heel discomfort, herniation, herpes zoster, hip pain, hyperglycemia, hyperkalemia, hypatremia, hyperuricemia, hypoglycemia, hypomagnesemia, imbalance, insomnia, neck pain, occult bleeding, osteoarthritis, papilloma, renal dysfunction, shakiness, sinus infection, skin lesions, sore throat, stomach cramps, urine (decreased), and visual loss</td>
</tr>
</tbody>
</table>

Abbreviation: AE, adverse events.
whether an agent that prevents or reduces skeletal-related events for patients with MGUS might have any effect on future disease progression to MM or a related disorder. However, some studies in the laboratory and clinic show that bisphosphonates, including zoledronic acid, have antitumor effects (27–30). Although none of the patients involved in this trial progressed to MM, one patient was diagnosed with chronic lymphocytic leukemia and another patient was found to have primary amyloidosis during the study. However, this clinical trial was not powered to test whether zoledronic acid might play a role in delaying progression from MGUS to myeloma or any other serious B-cell disorder.

Among cancer patients, zoledronic acid is currently indicated for hypercalcemia of malignancy and the treatment of patients with MM and bone metastases from solid tumors, in conjunction with standard antineoplastic therapy (23). The recommended dosage for patients with MM and bone metastases is 4 mg infused i.v. over no more than 15 minutes every 3 to 4 weeks. However, less-frequent dosing has been shown to increase bone mineral density for patients with osteoporosis and to decrease cancer treatment–induced bone loss among cancer patients without metastatic bone involvement (12–15, 20, 21). Specifically, a 4 mg dose of zoledronic acid given annually increased bone mineral density for patients with postmenopausal osteoporosis (20). In another study of patients who had undergone repair of a hip fracture, a single 5-mg dose of zoledronic acid administered after the fracture markedly reduced the risk of additional fractures and improved overall survival during a median 1.9-year follow-up period (21). Among patients with cancer treatment–induced bone loss, zoledronic acid 4 mg administered every 3 months (12) or once during 12 months (13) increased bone mineral density significantly in prostate cancer patients with negative bone scans receiving androgen-deprivation therapy. Similar benefits have been observed among aromatase inhibitor-treated breast cancer patients receiving zoledronic acid every 6 months (14, 15).

The decision to evaluate a 6-month dosing interval for MGUS patients was based on the positive findings from regimens using less-frequent dosing of zoledronic acid for patients with increased bone loss without evidence of metastatic bone disease as well as the potential for an increased risk of morbidity with schedules using more frequent dosing. On this schedule of administration every 6 months at the conventional 4-mg dosage for 3 doses, zoledronic acid was well-tolerated and not associated with the occurrence of either renal toxicity or osteonecrosis of the jaw. However, the duration of this study did not permit an assessment of long-term risks for these complications.

MGUS represents a common disorder in the elderly, with 5% of individuals over age 70 years harboring this protein abnormality. Typically, patients with this condition are not treated, although they clearly show a higher risk of developing MM and related B-cell malignancies as well as bone loss with associated fractures. The present study suggests that it may be important to identify this condition and perform an assessment of bone mineral density because zoledronic acid treatment may significantly reduce the risk of fracture in MGUS patients with osteopenia or osteoporosis. Larger prospective studies are needed to confirm the promising results observed in this phase II clinical trial.

Disclosure of Potential Conflicts of Interest

J. Berenson has received grant/research support from, and has served as a consultant and member of the speakers bureau for, Novartis Pharmaceuticals. M. Moezzi has served as a member of the speakers bureau for Novartis Pharmaceuticals. D. Woytowitz is a Novartis Pharmaceuticals shareholder. R. Swift has served as a member of the speakers bureau for Novartis Pharmaceuticals. Each of the other authors states that he/she has no financial relationships to disclose.

Acknowledgments

We thank Patricia Segarini, PhD, of Helix and Lynne Lederman, PhD, for providing medical writing support on behalf of Oncotherapeutics.

References

2. Kyle RA, Rajkumar SV. Monoclonal gammapathy of undetermined signifi-
   gammapathy of undetermined significance. Ann Hem-
   atol 2008;77:57–60.
4. Pecherstorfer M, Seibel MJ, Woltegu HW, et al. Bone resorption in multiple myeloma and in monoclonal gam-
   mapathy of undetermined significance: quantifi-
   cation by urinary pyridinium cross-links of collagen.
5. Pepe J, Petucci MT, Nofroni I, et al. Lumbar bone mineral density as the major factor determining in-
   creased prevalence of vertebral fractures in monoclo-
   nal gammapathy of undetermined significance. Br J
6. Gregersen H, Jensen P, Gislum M, Jorgensen B, Sor-
   ensen HT, Norgaard M. Fracture risk in patients
   with monoclonal gammapathy of undetermined signifi-
7. Melton LJ III, Rajkumar SV, Khosla S, Achenbach SJ, Oberg AL, Kyle RA. Fracture risk in monoclo-
   nal gammapathy of undetermined significance. J Bone
8. Berenson JR, Rajdev L, Broder M. Managing bone
   complications of solid tumors. Cancer Biol Ther
   2006;5:1086–98.
   efficacy and safety of zoledronic acid compared with
   pamidronate disodium in the treatment of skeletal
   complications in patients with advanced multiple my-
   eloma or breast carcinoma: a randomized, double-
   blind, multicenter, comparative trial. Cancer 2003;98:
   1735–44.
   dronic acid reduces skeletal-related events in
   patients with osteolytic metastases. Cancer 2001;
   onic acid versus pamidronate in the treatment of skeletal
   metastases in patients with breast cancer or osteolytic
   lesions of multiple myeloma: a phase III, double-blind,
12. Katznelson L, Kent K, Srinivas S. The effects of inter-
   mittent androgen deprivation therapy (ADT) and zoled-
   ronic acid administration on bone density in patients
   with prostate cancer. J Clin Oncol (Meeting
   domized controlled trial of annual zoledronic acid to
   prevent gonadotropin-releasing hormone agonist-in-
   duced bone loss in men with prostate cancer. J Clin
   inhibits adjuvant letrozole-induced bone loss in post-
   menopausal women with early breast cancer. J Clin
15. Grant MF, Minieritsch B, Luschin-Ebengreuth G, et
   al. Zoledronic acid prevents cancer treatment-induced
   bone loss in premenopausal women receiving adju-
   vant endocrine therapy for hormone-responsive
   breast cancer: a report from the Austrian Breast and
16. WHO Scientific Group on the Assessment of Osteo-
   porosis at Primary Health Care Level. Summary Meet-
   Geneva (Switzerland): World Health Organization;
   2007.
   zoledronic acid for treatment of postmenopausal os-
   years’ experience with alendronate for osteoporosis

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Clin Cancer Res 2008;14(19) October 1, 2008 6294 www.aacrjournals.org

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