**Objective:** To evaluate the efficacy and safety of oral alendronate sodium therapy once daily in preventing glucocorticoid-induced bone loss in patients with immunobullous skin diseases treated with long-term glucocorticoid therapy.

**Design:** A 12-month randomized, double-blind, placebo-controlled trial.

**Setting:** A tertiary referral dermatology center in Singapore.

**Participants:** Patients newly diagnosed as having an immunobullous disease and deemed to require at least 6 months of systemic glucocorticoid therapy.

**Interventions:** The patients were randomized to receive either oral alendronate sodium (10 mg/d) or a matching placebo for 12 months. All patients also received concurrent calcium with vitamin D, 2 tablets daily.

**Main Outcome Measures:** Percent change in bone mineral density (BMD) at the lumbar spine and the femoral neck at 12 months.

**Results:** A total of 29 patients (alendronate [n=15], placebo [n=14]) were evaluated. The percent change in BMD in the alendronate group was +3.7% and +3.5% at the lumbar spine and the femoral neck, respectively, whereas in the placebo group, it was −1.4% and −0.7% at the lumbar spine and the femoral neck, respectively. The increase in BMD observed in the alendronate group compared with the placebo group was statistically significant at both the lumbar spine (P=.01) and the femoral neck (P=.01). There was also a statistically significant decrease in serum heat-labile alkaline phosphatase levels after 12 months (−32.6%, P<.01) in the alendronate group but not in the placebo group. Adverse events were generally minor, and the frequency of occurrence did not differ significantly between both treatment groups (P=.59).

**Conclusions:** There were statistically significant increases in BMD at both the lumbar spine (P=.01) and the femoral neck (P=.01) with alendronate therapy. It is imperative to use bisphosphonate therapy in patients with immunobullous disorders who are receiving oral corticosteroids because it largely prevents the morbidity associated with low BMD.


**The Use of Glucocorticoids is Associated with Bone Loss and an Elevated Risk of Fracture.** The bone loss is particularly noted in the early phase of treatment, when the dosage of glucocorticoid therapy is usually high and the underlying disease for which glucocorticoids are prescribed is active. Also, glucocorticoid-induced bone loss is dose related.¹ The mainstay of therapy of immunobullous skin disease continues to be long-term use of glucocorticoids with initial high doses, which may have devastating effects on bone quality and result in an increased risk of fractures.² ³ Moreover, a recent large case-control study suggested that patients with pemphigus are more likely to have osteoporosis.⁴ The use of bisphosphonates has been strongly advocated for more than a decade in guidelines for patients who are being treated with at least 7.5 mg/d of prednisone for 3 months or more.³ However, all the published trials using bisphosphonates have involved white patients with rheumatologic and respiratory diseases, for
which the dosage of glucocorticoid therapy is generally lower than that for immunobullous diseases. To date, to our knowledge, no controlled randomized studies have assessed whether early treatment with bisphosphonates in immunobullous skin disorders will offer any benefits in terms of lowering bone loss and fracture rates or fracture-related morbidity and mortality. Moreover, Asians who have low bone mineral density (BMD) and low consumption of milk products may be more susceptible to involutional osteoporosis than other populations.6 The aim of our study was to evaluate the efficacy and safety of oral alendronate therapy once daily in preventing glucocorticoid-induced bone loss in patients with immunobullous skin diseases treated with long-term glucocorticoid therapy.

TREATMENT

Daily alendronate sodium (10-mg tablet) was the prevailing form of oral biphosphonate therapy during the study period. The patients were stratified according to sex and menopausal status: men, premenopausal women, and postmenopausal women. They were then randomly divided into blocks of 6 and then into 2 treatment groups: one group received alendronate (10 mg/d) and the other group received a placebo for a total duration of 12 months. These treatments were administered at the same time that prednisolone and calcium plus vitamin D therapy was initiated. Both groups were instructed to take the medication first thing in the morning with a full glass of water, to remain in a standing or sitting position, and not to eat or drink anything for the next 30 minutes. Patients and study investigators were unaware of their designated group.

MEASUREMENTS

Baseline x-ray films of the lumbar spine (anteroposterior and lateral views) were obtained and bone mineral densitometry of the lumbar spine and femoral neck (QDR 2000 plus; Hologic) was performed within 3 weeks of the initiation of prednisolone therapy. Besides lumbar fractures, the x-ray film of the lumbar spine was also used to screen for radio-opaque renal calculi. Markers of bone metabolism (calcium, phosphate, vitamin D, and heat-labile alkaline phosphatase [hL-ALP]) and thyroxine were also measured at baseline.

FOLLOW-UP

After randomization and baseline data acquisition, follow-up visits were scheduled for BMD measurements and radiography at the 6th and 12th month of prednisolone therapy. At the end of the study period, the x-ray films were read independently of each other by experienced radiologists (S.S.S.T. and J.Y.Y.T.), and the readers were blinded as to the order of the images. The semiquantitative vertebral deformity assessment score of van Kuijk and Genant6 was used to detect any new vertebral fractures. T scores were used to diagnose osteopenia or osteoporosis in accordance with established criteria.8 Complete blood cell counts (Coulter LH750; Beckman Coulter, and Vitros 250; Ortho Diagnostics), liver function tests, and determination of hL-ALP levels were performed at baseline and repeated at the 6th and 12th month. Patients who developed anemia or dyspepsia were referred for esophagogastroduodenoscopy.
Dietary calcium intake was estimated using a standardized questionnaire administered by an investigator who was blinded to the patients’ study groups. The patients were asked about their food consumption over the preceding week, and the average calcium intake was calculated with a table of known food calcium contents. Dietary assessment was performed at baseline and again at 12 months.

ASSESSMENTS

The primary end point was the percent change in both lumbar spine and femoral neck bone densities at 12 months compared with baseline. The secondary end points were the change in hl-ALP levels at 12 months, the presence of new clinical or radiologic fractures, and any significant adverse events encountered during the study.

STATISTICAL ANALYSIS

For the primary end point of the percent change in lumbar spine and femoral neck bone densities, a 2-sample t test was performed on the mean percent change from baseline at 12 months between the alendronate and the placebo groups when normality and equal variance assumptions were satisfied; otherwise, the Mann-Whitney U test was used. Multiple regression analyses were performed, with the mean percent change from baseline as the response variable after adjustment for relevant covariates. A paired t test was used to determine any significant differences between baseline and 12-month readings within each group when normality was satisfied; otherwise, the Wilcoxon signed rank test was used.

The above analyses were also performed for the secondary end point of change in hl-ALP levels. For the secondary end points of incidence of new vertebral fractures and adverse events, \( \chi^2 \) tests were used to determine association between the 2 groups, with odds ratios presented when necessary. Logistic regression was carried out to adjust for relevant covariates. The relationship between the prednisolone dose and the change in bone density was tested using the Spearman rank correlation coefficient.

Subgroup analyses, where appropriate, were performed to determine the relative impact of the above changes in men, premenopausal women, and postmenopausal women. It was anticipated that the difference between the 2 groups would be 2.5%, with an SD of 2.5% at 12 months. The sample of 44 patients to be randomized equally to the 2 groups would have a power of 90% and a 2-sided level of 5% to achieve statistical significance.

RESULTS

PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

A total of 44 patients (25 men, 19 women) with bullous pemphigoid, cicatricial pemphigoid, pemphigus vulgaris, pemphigus foliaceus, and epidermolysis bullosa acquisita were enrolled and randomized into the alendronate (n=22) and the placebo (n=22) groups (Figure 1). The 2 study arms did not differ significantly in terms of participants’ age, sex, weight, and height (P=.34, .36, .71, and .62, respectively). Markers of bone turnover, including serum calcium, phosphate, vitamin D, and hl-ALP levels, were equal in both groups, as were other variables, such as baseline BMD, daily calcium intake, and fracture history (Table 1).

No glucocorticoid other than oral prednisolone was consumed by study participants. There were no statistically significant differences in the average daily prednisolone dose, use of adjuvant medication, or daily calcium intake between both groups at the end of the study (Table 2).

EFFICACY

Among patients treated with alendronate who completed the study (n=15), there was an increase in BMD from the baseline at both the lumbar spine and the femoral neck. The mean percent change in lumbar spine T score was +2.1% and +3.7% at 6 and 12 months, respectively, while the mean percent change in femoral neck T score was +3.4% and +3.5% at 6 and 12 months.
respectively. Alternatively, among patients treated with placebo who completed the study (n = 14), there was a decline in BMD from baseline at both the lumbar spine and the femoral neck. The mean percent change in lumbar spine T score was −0.6% and −1.4% at 6 and 12 months, respectively, while the mean percent change in femoral neck T score was −0.7% at 6 and 12 months, respectively. The increase in BMD in the alendronate group compared with the placebo group at 12 months was significant at both the lumbar spine (+3.7% vs −1.4%, P = .01) and the femoral neck (+3.5% vs −0.7%, P = .01) (Figure 2). The BMD at the femoral neck correlated with the daily prednisolone dose in both groups, although the strength of correlation was not strong (Figure 3). In the alendronate group, a greater percent increase in BMD was observed at higher daily prednisolone doses (r = 0.53, P = .04). The placebo group, in contrast, showed a greater percent decrease in BMD at higher daily prednisolone doses (r = 0.56, P = .04). We did not find any significant correlation between lumbar spine BMD and daily prednisolone dose in either group (data not shown).

Table 2. End-of-Study Comparison in the Daily Prednisolone and Dietary Calcium Intake, Adjuvant Therapy Received, and Number of New Fractures in Both Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alendronate Sodium (n=15)</th>
<th>Placebo (n=14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily prednisolone dose, mg</td>
<td>16.9 (9.7)</td>
<td>16.1 (6.8)</td>
<td>.64</td>
</tr>
<tr>
<td>Daily dietary calcium intake, mg</td>
<td>836.7 (691.0)</td>
<td>923.2 (439.8)</td>
<td>.70</td>
</tr>
<tr>
<td>New fractures</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Patients who received adjuvant therapy, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>9 (60)</td>
<td>7 (50)</td>
<td>.72</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2 (13)</td>
<td>3 (21)</td>
<td>.65</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Alendronate Sodium (n=15)</th>
<th>Placebo (n=14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily prednisolone dose, mg</td>
<td>16.9 (9.7)</td>
<td>16.1 (6.8)</td>
<td>.64</td>
</tr>
<tr>
<td>New fractures</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Overall, there were no statistically significant differences in the frequency of adverse effects between both groups (Table 3), suggesting that treatment with alendronate is safe and well tolerated. The most common adverse effects experienced were minor and included dyspepsia, headaches, musculoskeletal pain, and rashes. One patient from each group developed leukopenia; however, the cause was attributed to the concurrent use of azathioprine. Regarding serious adverse events, 1 patient from the alendronate group died during the study, and 1 patient from the placebo group was hospitalized for myocardial infarction. Neither event was considered to be related to the study.

SAFETY

Advances in pharmacotherapeutics have widened the repertoire of drugs used in dermatologic treatment. Nevertheless, systemic glucocorticoids remain the mainstay of therapy for immunobullous disorders. The benefits of glucocorticoids, however, come at the cost of numerous adverse effects, including a gradual loss of bone density. Glucocorticoids promote bone loss through multiple pathways. The result is a substantially higher fracture risk in patients receiving glucocorticoid therapy.

A meta-analysis demonstrated strong correlations between cumulative glucocorticoid dose and BMD loss as well as between daily glucocorticoid dose and risk of fracture (which may increase within 3 to 6 months of initiation of therapy). The risk is independent of underlying disease, age, and sex. A separate study suggested that daily glucocorticoid doses of at least 7.5 mg of prednisolone or the equivalent lead to a greater risk of both vertebral and nonvertebral fractures compared with daily doses of less than 2.5 mg. In our study, the patients at the end of the 1-year period received a mean daily dose of 16.5 mg (16.9 mg in the alendronate sodium group, 16.1 mg in the placebo group), which is higher than daily doses used in previous studies of between 10 and 11 mg. It is possible that the control of immunobullous disorders involves higher glucocorticoid doses compared with other diseases, highlighting the need to actively reduce fracture risk in such cases.
Bisphosphonates are considered first-line therapy for preventing glucocorticoid-induced osteoporosis.\textsuperscript{18} They inhibit osteoclastic activity, thereby reducing bone resorption and improving mineralization.\textsuperscript{19} A systematic review of controlled clinical trials involving bisphosphonates for glucocorticoid-induced osteoporosis gave a weighted mean difference of BMD between the treatment and placebo groups of 4.3% at the lumbar spine and 2.1% at the femoral neck.\textsuperscript{20} Treatment with bisphosphonates is also cost-effective in preventing osteoporotic fractures in women.\textsuperscript{21} Alendronate is an oral bisphosphonate with a good safety profile and proven efficacy. In a randomized controlled trial involving 477 patients receiving glucocorticoids, those who received alendronate sodium (10 mg/d) showed an increase in the mean BMD by 2.9% and 1.0% at the lumbar spine and the femoral neck, respectively, while those who received placebo showed a decrease in the mean BMD by 0.4% and 1.2% in the lumbar spine and the femoral neck, respectively.\textsuperscript{16} Another recent study using a once-weekly dose of 70 mg of alendronate demonstrated a similar increase in the lumbar spine BMD, with a mean increase of 2.45% in the lumbar spine and 1.16% in the trochanteric hip. In our study, we observed a higher mean increase in BMD (3.7% and 3.4% in the lumbar spine and the femoral neck, respectively) from baseline after 12 months in patients who were receiving alendronate. These results were unexpected since our patient population used higher doses of glucocorticoids than in previous studies, and the baseline BMD in both the lumbar spine and the femoral neck was at a low T score to start with. A possible explanation is that these earlier studies included patients with other comorbidities that affect osteoporosis, such as rheumatoid arthritis, lupus, inflammatory bowel disease, diabetes, and chronic obstructive pulmonary disease. However, the low baseline BMD in our patient population before oral glucocorticoid therapy was initiated supports the finding of a marked association between osteoporosis and pemphigus in a recent study.\textsuperscript{4} Further studies in larger cohorts should investigate the BMD in immunobullous diseases. An alternative explanation is that Asians and whites respond differently to bisphosphonates. A study comparing the response to 2 years of alendronate treatment in early postmenopausal Asian and white women did not find any difference in increase in BMD or urinary N-telopeptide collagen cross-linkage.\textsuperscript{22} However, to our knowledge, racial differences in a cohort of patients receiving glucocorticoid therapy have not yet been investigated and might be a target for further research.

It is not unexpected that higher daily prednisolone doses resulted in a greater percentage of bone loss in the

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Adverse Event & Alendronate Sodium (n=22) & Placebo (n=22) & P Value \\
\hline
None & 13 (59) & 9 (41) & \\
Dyspepsia & 4 (18) & 2 (9) & \\
Headache & 1 (4) & 1 (4) & \\
Musculoskeletal pain & 1 (4) & 3 (14) & .59 \\
Constipation & 0 & 1 (4) & \\
Rash & 1 (4) & 1 (4) & \\
Other & 2 (9) & 5 (23) & \\
\hline
\end{tabular}
\caption{Comparison of Rate of Adverse Events Experienced in Both Groups}
\end{table}
placebo group. However, interestingly, of the patients who received alendronate, those who consumed higher daily prednisolone doses recorded a better percentage of increase in BMD. This finding seemingly suggests that alendronate’s effects become more pronounced at greater glucocorticoid doses.

Biochemical markers of bone turnover have been adopted as predictors of BMD and are also useful in monitoring alendronate treatment. Bone-specific ALP (BSAP) refers to isozymes of ALP that originate from osteoblasts. In patients receiving glucocorticoid therapy, treatment with alendronate is associated with a reduction in BSAP. Our laboratory does not quantify BSAP directly but may estimate it by determining the heat stability of ALP (bone-specific isozymes are hl). Using hl-ALP as a surrogate marker in place of BSAP, we observed a similar decrease with alendronate treatment. In our study, patients treated with alendronate showed a statistically significant decrease of 32.6% in mean hl-ALP after 12 months (P < .01), which was not seen in the placebo group.

Recently, Furukawa et al also studied the prevention of glucocorticoid-induced osteoporosis with bisphosphonates in patients with various skin diseases (not limited to autoimmune bullous dermatoses). Compared with our study, the differences include the use of etidronate instead of alendronate and the use of biochemical markers (urinary deoxypyridinoline and serum bone-specific ALP) rather than BMD as the primary outcome measure. The authors reported a decrease in urinary deoxypyridinoline levels after treatment with etidronate; however, they did not find any difference in bone ALP levels. In contrast, our study demonstrated a decrease in hl-ALP levels after treatment with alendronate, which could be explained by alendronate’s greater efficacy on bone remodeling compared with etidronate.

Calcium plus vitamin D alone may also confer modest protection in bone demineralization. Previous authors have reported maintenance of BMD in their patients who were receiving glucocorticoids with the concurrent use of calcium plus vitamin D at doses comparable to those in our study. Our patients in the placebo group continued to receive prophylactic calcium plus vitamin D therapy and still sustained a loss of BMD of −1.4% at the lumbar spine and −0.7% at the femoral neck from baseline at the end of the study. While the differences appear modest, they were sufficient for 2 new patients to be classified as osteopenic and 1 as osteoporotic. Over a longer follow-up period, the impact of this decrease in BMD may become clinically apparent.

Prophylaxis against glucocorticoid-induced osteoporosis had been reported to be underused among practicing dermatologists in the United States. Education and awareness are needed among practicing dermatologists to take an active role in the screening, prevention, and management of glucocorticoid-induced osteoporosis. The current study provides significant evidence of the importance of performing measures of bone protection and screening for patients with immunobullous diseases who are receiving glucocorticoids.

Alendronate therapy was generally well tolerated among the patients with immunobullous diseases. These results were similar to the safety and tolerability profiles reported in larger studies. As expected, the rare adverse effects associated with the use of bisphosphonates, such as osteonecrosis of the jaw, atypical fractures, and severe bone and musculoskeletal pain, that had recently prompted a labeling change by the Food and Drug Administration (FDA) were not reported among any of our patients. Nonetheless, dermatologists should inform their patients who are receiving glucocorticoid therapy about these rare complications and exclude these entities during their follow-up. The current recommended dosage of alendronate is 70 mg once a week, which may help to reduce adverse effects. It should be administered in the morning with a full 6- to 8-oz glass of water at least 30 minutes before eating, drinking beverages, or taking other drugs. It should not be taken in the supine position. For premenopausal women, a discussion on potential teratogenicity of bisphosphonates is necessary, as animal studies have demonstrated fetal growth retardation, hypocalcemia, and skeletal malformation (alendronate is designated FDA pregnancy category C). The risk in human pregnancy remains uncertain in the absence of large controlled studies; however, to our knowledge, preconception and early pregnancy exposure have not resulted in congenital abnormalities. Other FDA-approved bisphosphonates for the treatment of osteoporosis include risedronate sodium (5 mg/d, 35 mg/wk, or 150 mg/mo), intravenous zoledronic acid (5 mg every 1 or 2 years), and ibandronate sodium (2.5 mg/d, 150 mg/mo, or 3 mg intravenously every 3 months). The use of risedronate substantially improved BMD and reduced fracture risk in patients with glucocorticoid-induced osteoporosis compared with placebo.

Zoledronic acid demonstrated noninferiority to risedronate in another study with respect to these outcomes. Ibandronate therapy was not recommended for glucocorticoid-induced osteoporosis by the American College of Rheumatology owing to limited data.

We acknowledge a high dropout rate of 30% in both groups, mostly as a result of patients who were unavailable for follow-up. However, their numbers were comparable in both groups, and the baseline characteristics of those who dropped out were not statistically different from those who completed the study (data not shown). We do not believe that the dropout rate affected the overall results.

In conclusion, this study demonstrated a statistically significant increase in BMD with alendronate therapy. We believe that it is imperative to use bisphosphonates in patients with immunobullous disorders who are receiving oral corticosteroids because we found that they significantly prevented the morbidity associated with low BMD in this group.

Accepted for Publication: September 7, 2011.
Correspondence: Shang-Ian Tee, MRCP, National Skin Centre, 1 Mandalay Rd, Singapore 308205 (sitee@nsc.gov.sg).
Improving the Care of Our Patients Who Are Receiving Glucocorticoid Therapy

The study by Tee et al,1 which was first published online last November in the Archives, convincingly shows that the use of bisphosphonates in patients who are receiving long-term steroid therapy for bullous diseases can reduce steroid-induced osteoporosis. This is equally true for nonbullous diseases, as has been demonstrated in many placebo-controlled randomized trials reported in the medical literature. Numerous studies have also demonstrated poor bisphosphonate implementation in populations at risk for glucocorticoid-induced osteoporosis.

Many dermatologists prescribe glucocorticoids but not bisphosphonates; therefore, additional familiarity with bisphosphonate therapy is important to optimize patient care. Based on the available evidence, bisphosphonates should be part of the therapeutic regimen when prednisone therapy above a dose of 7.5 mg/d is initiated for treatment lasting 3 months or more.2 Women of child-bearing potential, in any man older than 50 years or in a postmenopausal premenopausal women with a prevalent fragility fracture.

Bisphosphonates are not without problems. Caution is needed with patients in end-stage renal failure, but moderate renal failure with a creatinine clearance greater than 30 mL/min is not a contraindication. The most common initial problem is that bisphosphonates may irritate the esophagus. Bisphosphonates need to be taken with a full glass of water, and the patient should not lie down for at least 30 minutes afterward. Even if the patients follow this advice, some of them do not tolerate the drug and need to receive intravenous bisphosphonate therapy.

Rarely, the use of bisphosphonates causes jaw osteonecrosis, which is more frequent in patients who have significant oral disease requiring tooth extractions and use of dentures or multiple myeloma or in those who receive the more potent, longer-acting intravenous bisphosphonates. Patients who begin bisphosphonate therapy should have a thorough dental evaluation, perform oral hygiene and routine dental prophylaxis, and have invasive dental procedures completed before starting therapy 4 to 6 weeks later. While the Food and Drug Administration has issued a warning about the occurrence of rare subtrochanteric and diaphyseal femur fractures during treatment with bisphosphonates, it has not issued a guideline that would change therapy. The risk of osteoporosis and subsequent fractures is much higher than the rare atypical long-bone fractures.

In summary, based on current evidence, treatment with bisphosphonates and adequate calcium and vitamin D supplementation therapy should be initiated in any man older than 50 years or in a postmenopausal patient who is either beginning or receiving doses greater than 7.5 mg of prednisone equivalent daily for an anticipated duration of 3 months or more. High-risk patients would have a lower steroid dose threshold for intervention. Men younger than 50 years and premenopausal women with a prevalent fragility fracture also require intervention.2

Joerg Albrecht, MD
Victoria P. Werth, MD

Author Affiliations: Division of Dermatology, Department of Medicine, John Stroger Jr Hospital of Cook County, Chicago, Illinois (Dr Albrecht); and Departments of Dermatology, Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania (Dr Werth), and Hospital of the University of Pennsylvania, Perelman Cen-