Cross-sectional Study of Bisphosphonate Use in Dermatology Patients Receiving Long-term Oral Corticosteroid Therapy

Rosemarie H. Liu, MD; Joerg Albrecht, MD; Victoria P. Werth, MD

Objective: To examine whether patients had received bisphosphonates at the beginning of planned long-term glucocorticoid therapy, which is recommended by the guidelines from the American College of Rheumatology to prevent glucocorticoid-induced osteoporosis, prior to referral to a tertiary dermatology clinic.

Design: Cross-sectional study.

Setting: Tertiary referral center.

Patients: We reviewed 35 patients from an established cohort of patients referred with chronic skin diseases that require prolonged glucocorticoid use.

Main Outcome Measure: The use of osteoporosis prophylaxis was determined by medical chart review and communication with patients.

Results: Of 35 patients, 28 (80%) were not receiving any bisphosphonates at referral. These patients began glucocorticoid therapy 17 months (median, 6 months; range, 1-102 months) prior to referral. The proportion of patients treated with bisphosphonates in our cohort did not change after the guidelines of the American College of Rheumatology were published.

Conclusions: For patients of non-child-bearing potential with dermatological diseases in which prolonged oral corticosteroid treatment is anticipated, bisphosphonates should be prescribed concomitantly with the initiation of glucocorticoid therapy.

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LUCOCORTICOIDs have a wide range of applications in multiple disciplines of medicine. In dermatology, their prolonged use is a mainstay of therapy for severe diseases such as pemphigus vulgaris, dermatomyositis, and bullous pemphigoid. The administration of oral corticosteroids for other diseases such as cutaneous lupus erythematosus depends on the practitioner. Independent of the reason for their use, all patients receiving long-term glucocorticoid treatment have an increased risk of developing osteoporosis, a debilitating and occasionally life-threatening adverse effect of this potentially life-saving treatment. Bone mineral density (BMD) declines with daily oral glucocorticoid doses of prednisolone (or an equivalent drug) greater than 5 mg but has been shown to decline at doses even as low as 2.5 mg.1 The largest reductions in bone mass occur in the first 6 months of treatment, with a rapid increase of risk of fracture within the first 3 months of glucocorticoid therapy.1,2 In glucocorticoid-induced osteoporosis (GIOP), the risk of fractures exceeds the risk of reduced BMD. Thus, for a given BMD, the risk of fracture may be greater in GIOP than in postmenopausal osteoporosis.4 The magnitude of this problem has been demonstrated by cross-sectional studies, which suggest that most patients receiving long-term glucocorticoid therapy have low BMD and that more than one fourth sustain osteoporotic fractures.5 Early prevention of osteoporosis with appropriate prophylaxis is therefore essential.

See also page 82

To address the management of GIOP, the American College of Rheumatology (ACR) guidelines recommend bisphosphonate therapy for all patients beginning long-term oral corticosteroid therapy with prednisone at a dose greater than 5 mg/d.6 Meanwhile, a suggested guideline for osteoporosis prophylaxis in the Veterans Affairs population sets the prednisone dose of at least 7.5 mg/d as the threshold for bisphosphonate therapy.7 For our study, we examined patients who were receiving at least a 10-mg/d dose of prednisone.
Many studies have demonstrated that glucocorticoid-induced apoptosis of osteoblasts (bone-forming cells) and prevent glucocorticoid-induced apoptosis of osteoclasts (bone-resorbing cells) and prevent spine and nonvertebral fractures.11-16 Alendronate so-

...evidence that supplementation with calcium and vi-

data to the guidelines for prevention of GIOP by the ACR, which were published July 2001.8 To allow for the guidelines to be dispersed, we compared the proportion of patients treated with bisphosphonates before January 2002 and after that date. The data were then formatted into tables with Excel (Microsoft Corp, Red-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
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</tr>
<tr>
<td>Female</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Male</td>
<td>14 (40)</td>
</tr>
<tr>
<td>Total</td>
<td>35 (100)</td>
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<tr>
<td>Race, No. (%)</td>
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</tr>
<tr>
<td>White</td>
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<tr>
<td>Asian</td>
<td>3 (9)</td>
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<td>Black</td>
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<tr>
<td>Hispanic</td>
<td>1 (3)</td>
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<tr>
<td>Age, y</td>
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<tr>
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<td>Highest daily dose of prednisone* on file, mg</td>
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<tr>
<td>Mean</td>
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<tr>
<td>Median</td>
<td>50</td>
</tr>
<tr>
<td>Range</td>
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<tr>
<td>Duration of continuous oral prednisone use prior to referral, mo†</td>
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<tr>
<td>Mean</td>
<td>17</td>
</tr>
<tr>
<td>Median</td>
<td>6</td>
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<tr>
<td>Range</td>
<td>1-102</td>
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<tr>
<td>Indication for corticosteroid use, No. (%)</td>
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<tr>
<td>Pemphigus vulgaris</td>
<td>28 (80)</td>
</tr>
<tr>
<td>SLE/LLE</td>
<td>2 (6)</td>
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<tr>
<td>Dermatomyositis</td>
<td>2 (6)</td>
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<tr>
<td>Sjogren syndrome/SLE</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SCLE</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Arthritis with interstitial granulomatous dermatitis</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Not receiving bisphosphonate therapy prior to referral, No. (%)</td>
<td>28 (80)</td>
</tr>
</tbody>
</table>

Abbreviations: DLE, discoid lupus erythematosus; SCLE, subacute cutaneous lupus erythematosus; SLE, systemic lupus erythematosus.

*Prednisone or equivalent.
†Based on 33 patients; 1 premenopausal woman refused bisphosphonate therapy and 1 patient had began bisphosphonate therapy prior to corticosteroid treatment because of osteoporosis.

Bisphosphonates are pyrophosphate analogues that adhere to hydroxyapatite in bone, thereby serving as potent antiresorptive agents.9 At the cellular level, they inhibit osteoclasts (bone-resorbing cells) and prevent glucocorticoid-induced apoptosis of osteoblasts (bone-forming cells).10 Many studies have demonstrated that bisphosphonates increase BMD and decrease the risk of fracture in elderly women with at least 1 risk factor for fractures.8

Bisphosphonates also increase bone density at the radius, tomodent, and extend the interval to BMD measurement.

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# METHODS

## STUDY POPULATION

In this cross-sectional study set in a tertiary referral center, eligible patients included men and women with a chronic dermatological disease requiring treatment with at least a 10-mg/d dose of prednisone (or equivalent) for a minimum of 1 month prior to their referral. A 10-mg/d dose minimum of prednisone was established because it is generally recognized as a high dosage for which appropriate bone prophylaxis would be expected. The patients were referred to the corresponding author's clinic at the Hospital of the University of Pennsylvania after October 1995, which was the FDA approval date of the first bisphosphonate for osteoporosis, and were mostly seen in December 2004 and identified in the clinic. “Long-term” glucocorticoid treatment was defined as 1 month or longer in this study because all patients had a primary diagnosis for which prolonged corticosteroid use (>3 months' duration) should have been anticipated (Table). There were no exclusion criteria.

## DATA COLLECTION

Data regarding the use of oral glucocorticoid and osteoporosis prophylaxis were obtained from patients during their clinic visit at the Hospital of the University of Pennsylvania and by reviewing the patients' medical records. Several patients were contacted by telephone for information not found in their medical records. The data collected included the following: patient demographics (sex, race, and age); primary diagnosis; comorbid conditions; medications; corticosteroid dose on initial visit (if any); highest corticosteroid dose prior to initial visit; length of corticosteroid use prior to initial visit; length from initiation of corticosteroid use to referral; and T score values for lumbar spine, total hip, and femoral neck. Follow-up dual energy x-ray absorptiometry (DEXA) results were obtained if available. If the exact date of the primary diagnosis was not known, the onset of the disease was assumed to be June of that year. If the date of diagnosis occurred prior to October 1995, the time to referral was calculated from that date, which was the approval date of bisphosphonates for prophylaxis for GIOP. We also summarized the data in relation to the publication of the guidelines for prevention of GIOP by the ACR, which were published July 2001.6 To allow for the guidelines to be dispersed, we compared the proportion of patients treated with bisphosphonates before January 2002 and after that date. The data were then formatted into tables with Excel (Microsoft Corp, Redmond, Wash).

## BONE DENSITY MEASUREMENTS

We categorized the patients according to the classification of BMD by the World Health Organization (WHO). Normal BMD was defined as a T score of -1 or greater, osteopenia as a T score
between −1 and −2.5, and osteoporosis as a T score of −2.5 or less.17 When the T score for lumbar spine L1-L4 was not available, the L2-L4 value was used.

RESULTS

A total of 35 patients met the inclusion criteria. The demographic characteristics of the study population are summarized in the Table. Of the 35 patients, 28 (80%) were not taking any bisphosphonate prior to their referral and 7 (20%) received a bisphosphonate prior to referral (6 received it specifically for GIOP prophylaxis and 1 received it from her internist for previously diagnosed non–glucocorticoid-related osteoporosis).

One 29-year-old premenopausal patient refused bisphosphonate therapy because of her desire to conceive. Although she received calcium and vitamin D supplements, she became severely osteopenic after 19 months on this therapy. One patient had a debilitating vertebral fracture within 4 to 5 months of starting prednisone therapy prior to appropriate osteoporosis prevention.

In our population the publication of the ACR guidelines6 on management of GIOP (published in July 2001) did not have any influence on the prescription of bisphosphonates. Prior to January 2002, 6 (75%; 95% confidence interval, 45% to >100%) of the patients were not treated with bisphosphonates. In the group that was referred after that date, 22 (81%; 95% confidence interval 66% to 96%) were not treated with bisphosphonates.

The results from DEXA were obtained from 18 of the 35 patients and evaluated according to the WHO guidelines. These scans were obtained an average of 13 months after corticosteroid treatment had been initiated. At the time of the first available DEXA scan, 7 patients still had T score values within normal range, 8 were osteopenic, and 3 were osteoporotic. Follow-up DEXA results were available for only 3 patients, all of whom began bisphosphonate therapy within 6 months of beginning glucocorticoid therapy. In 1 patient, the T score for both lumbar spine and hip improved after 13 months of treatment with bisphosphonates. The other 2 patients displayed mixed results when T scores after 6 and 29 months of glucocorticoid therapy (for the second patient) and after 4 and 81 months (for the third patient) were compared. The second and third patients’ T scores of the lumbar spine improved from −0.90 to −0.70 and from −2.21 to −1.50, respectively. Their T scores of the hip worsened slightly from 0.40 to 0.20 and from −1.41 to −1.72, respectively.

COMMENT

This small cross-sectional study was conducted to evaluate whether patients receiving long-term corticosteroid therapy also received appropriate osteoporosis prophylaxis. In our sample, most dermatology patients (28 of 35 [80%]) receiving long-term glucocorticoid treatment did not receive osteoporosis prophylaxis with bisphosphonates after a median of 6 months of receiving high-dose corticosteroid therapy. These findings are consistent with those from studies in other medical specialties in which bisphosphonates were rarely prescribed.18-21 In a British study by Hart and Green,19 bisphosphonates were prescribed at a rate of 21.6% for patients who qualified for GIOP prophylaxis. Two other studies from the United States showed that bisphosphonates were received by only 4% and 8% of patients, respectively, prior to the revision of the ACR guidelines.20,21

The low rate of bisphosphonate use prior to referral and prolonged time interval until initiation of prophylaxis are disappointing because bisphosphonates are agreed to be the most efficacious agents known to prevent GIOP. This may be due to variations in knowledge about GIOP among different physician specialties.22 A recent study by Buckley et al23 showed that GIOP prophylaxis and BMD testing were strongly associated and that patients were more likely to have received preventive treatment and have bone density assessed if they received follow-up from a rheumatologist or generalist.

Although the data on DEXA scan results for the patients are incomplete, the results from first available DEXA scans demonstrate the critical need for prompt initiation of bisphosphonate therapy. At the most extreme, 1 patient had a vertebral fracture within 4 to 5 months of starting glucocorticoid therapy but before prophylaxis was implemented.

INTERVENTIONS TO INCREASE ADHERENCE TO TREATMENT GUIDELINES

Multifaceted interventions have since been developed to improve the management of GIOP in patients who receive long-term glucocorticoid therapy.29,30 The results have so far been mixed. Solomon et al22 designed a 3-part intervention that was specifically targeted toward practicing rheumatologists. The intervention failed to result in any differences in treatment or bone densitometry use even after a 6-month follow-up period. Unlike the study by Solomon et al,22 a comprehensive educational program involving general practitioners and community pharmacies was implemented in Tasmania, Australia, and led to greater use of osteoporosis preventive therapies.23 Bisphosphonate use, for example, increased from 6% before intervention to 24% after intervention.

USE OF BISPHOSPHONATES

Although dermatology-specific guidelines have been proposed by Yosipovitch et al26 for patients receiving high-dose, long-term glucocorticoid therapy, they do not define a minimum corticosteroid dose required for prophylaxis with bisphosphonates. In contrast, the ACR guidelines for the prevention and treatment of GIOP include threshold doses for glucocorticoids and can be applied in dermatology.6 Patients with diseases such as pemphigus vulgaris, which require prolonged courses of glucocorticoids, should promptly begin bone prophylaxis with a bisphosphonate at the time glucocorticoid therapy is initiated. A baseline BMD should also be obtained, as advised in the US Surgeon General’s report on the nation’s bone health and by the ACR.6,27 Two oral bisphosphonates are currently licensed for the prevention and/or treatment of GIOP, each of which is available in a once-weekly formulation to en-
hance patient compliance (70-mg tablet by mouth once weekly for alendronate and 35-mg tablet by mouth once weekly for risodronate).9,28

Bisphosphonates are generally well tolerated by patients.20 However, they should be used with caution in premenopausal patients because they have a prolonged half-life and carry the potential risk of producing fetal skeletal abnormalities.20,30 Treatment with bisphosphonates should be continued throughout the duration of glucocorticoid therapy because bone loss continues to occur.1 There are no consensus guidelines on the timing of follow-up DEXAs; therefore, they should be ordered when clinically indicated. However, on completion of corticosteroid treatment, another bone density assessment should be conducted.31 Subsequent treatment of patients would then be similar to non-glucocorticoid users.

LIMITATIONS

The study was relatively small and conducted at a tertiary referral center on a special population of patients with complex skin diseases. All patients received at least twice the minimum dose of oral corticosteroids that is considered by ACR criteria to be the threshold for osteoporosis prophylaxis with bisphosphonates. In addition, all patients shared diagnoses that are associated with prolonged corticosteroid therapies. Therefore, we believe that the study most likely overestimated the extent of osteoporosis prophylaxis in the dermatology community. Most patients receiving long-term corticosteroid therapy are likely to receive lower dosages of corticosteroids in a less predictable fashion; it is thus more likely that they do not receive adequate prophylaxis. This study did not, however, estimate the degree of compliance with the ACR guidelines. The study revealed a general lack of discussion of the issue of osteoporosis prophylaxis with these patients. Only 1 patient had an identifiable contraindication to bisphosphonates, while for the other patients no reference to the need for the financial burden or the refusal of bisphosphonate treatment could be found. Therefore, it is not possible to assess the importance of cost constraints on the prescription of bisphosphonates in our patient population, and it is possible that a minority of patients may not have filled written prescriptions of bisphosphonates. We also cannot comment on the degree of patient compliance with prescribed bisphosphonates in this cross-sectional study.

Although prophylaxis with bisphosphonates was likely overestimated, the DEXA findings may have underestimated the likelihood of pathological findings. A proportion of the study population consisted of postmenopausal women who may have had abnormal DEXA results prior to glucocorticoid therapy. Selection bias may have also led to DEXA scans in populations primarily with clinical signs or additional risk factors.

CONCLUSIONS

The deleterious effects of glucocorticoids on bone have been well characterized and are largely preventable by the use of bisphosphonates. Despite their proven ben-efits, our study demonstrated a dramatic underuse of bisphosphonates by our referral physicians, which was not influenced by the publication of the ACR guidelines.6 Unless there is a specific contraindication, bisphosphonates should be prescribed concomitantly with the initiation of corticosteroid therapy in diseases for which long-term glucocorticoid use is anticipated as part of the standard of care.

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Author Contributions: Acquisition of data: Liu. Analysis and interpretation of data: Liu, Albrecht, and Werth. Drafting of the manuscript: Liu and Albrecht. Critical revision of the manuscript for important intellectual content: Liu, Albrecht, and Werth. Public responsibility for the whole content: Liu, Albrecht, and Werth.

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REFERENCES


News and Notes

The Certifying Examination of the American Board of Dermatology (ABD) will be held at the Crowne Plaza Hotel, Chicago O’Hare, in Rosemont, Ill, on August 13 and 14, 2006. The deadline for receipt of applications is March 1, 2006. The recertification examination of the ABD will be administered online from May 1 to June 15, 2006. The deadline for receipt of applications for the recertification examination is December 15, 2005. The examination for subspecialty certification in Dermatopathology will be administered September 19, 2006, at the testing center of the American Board of Pathology in Tampa, Fla. The deadline for receipt of applications is May 1, 2006. (Dermatologists must submit applications to the ABD and pathologists to the American Board of Pathology.) The examination for subspecialty certification in Pediatric Dermatology will be administered October 23, 2006. Location to be determined. The In-Training Examination for Dermatology residents (administered online at dermatology residency training centers in the United States and Canada) will be held on April 6, 2006. Deadline for receipt of applications is February 1, 2006. For further information about these examinations, contact Antoinette F. Hood, MD, American Board of Dermatology, Henry Ford Health System, One Ford Place, Detroit, MI 48202-3450 (phone: 313-874-1088; fax: 313-872-3221; e-mail: abderm@hfhs.org), or check the ABD Web site at www.abderm.org.