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PAPER

Vitamin D and bisphosphonate therapy in systemic lupus erythematosus patients who receive glucocorticoids: are we offering the best care?

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Objective: This study aimed to evaluate management practices for glucocorticoid (GC)-induced osteoporosis (GIOP) in systemic lupus erythematosus (SLE) patients using 2017 American College of Rheumatology guidelines as a gold standard. **Methods:** We conducted a retrospective cohort study using a clinical database from the years 2011 to 2016. SLE cases with >90 days continuous prednisone use at doses of ≥7.51 mg daily were identified. Osteoporosis risk factors were assessed via chart review. The Fracture Risk Assessment (FRAX) score was estimated for patients > 40 years of age. Vitamin D, bisphosphonate prescriptions, and osteoporotic (OP) fractures were ascertained through chart review. A classification tree was used to identify the key patient-related predictors of bisphosphonate prescription. **Results:** A total of 203 SLE patients met the inclusion criteria. The recommended dose of vitamin D supplement was prescribed to 58.9% of patients < 40 years of age and 61.5% of patients ≥ 40 years of age. Among patients aged ≥ 40 years, 25% were prescribed bisphosphonates compared to 36% who met indications for bisphosphonates per the ACR guidelines. Another 10% were prescribed a bisphosphonate, despite not having indication per the ACR guidelines, which was considered as overtreatment. Among patients aged ≥ 40 years, older age and a higher FRAX score for major OP fracture and hip fracture predicted bisphosphonate prescription. In a classification tree analysis, patients with FRAX scores (for major OP fracture) of ≥ 23.5% predicted bisphosphonate prescription in this SLE population. Among patients who had OP fractures in the follow-up period, nine (6.50%) were inpatients receiving appropriate GIOP care versus 12 (13.6%) who were inpatients not receiving ACR-appropriate care ($p = 0.098$). **Conclusions:** In clinical practice, fewer SLE patients with or at risk for GIOP are prescribed vitamin D and bisphosphonates than recommended by the 2017 ACR guidelines. Also, in this study, another 10% were prescribed a bisphosphonate, despite not having an indication per the ACR guidelines. Patients were most likely to receive a bisphosphonate prescription if they had a major OP FRAX score of > 23.5%. *Lupus* (2020) **29,** 263–272.

Key words: Glucocorticoids; SLE; glucocorticoid-induced osteoporosis; bisphosphonates; vitamin D; Fracture Risk Assessment score

Introduction

Glucocorticoid (GC) therapy is frequently used for the treatment of disease flares and complications in systemic lupus erythematosus (SLE). Long-term follow-up of SLE cohorts shows that up to 88% of patients are treated with GC, with as many as 57–86% receiving continuous treatment.[1–3] A major concern about long-term GC use in SLE is risk for GC-induced osteoporosis (GIOP). Studies have shown nearly a fivefold increase in fractures in women with SLE in comparison to the general population, and studies have suggested that older age at diagnosis of SLE and longer duration of GC

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are independent predictors of fracture risk.[4] Two prospective studies have demonstrated that bone loss occurs predominantly in SLE patients treated with at least 7.5 mg prednisone per day, whereas use of a lower daily prednisone dose is not associated with bone loss.[5,6] If GC treatment is terminated, bone mineral density increases, and fracture risk declines.[7–9] Hence, high doses of GC ($\geq$7.5 mg/day) and prolonged GC use are important risk factors for bone loss and fractures in patients with SLE. If continued treatment with GC is indicated, calcium and vitamin D supplementation are recommended by the American College of Rheumatology (ACR) for all patients for prevention of GIOP, in addition to life-style measures (exercise, reducing alcohol consumption, and smoking cessation).[10] There is also evidence to support the use of bisphosphonates for the prevention and treatment of GIOP in high-risk populations. Several randomized controlled trials have examined the efficacy of bisphosphonates on rates of GC-associated bone loss and risk of radiographic vertebral fractures.[11,12] These trials studied heterogeneous patient populations, including between 5% and 15% of patients with SLE. Positive effects on bone density, particularly at the spine, were seen with bisphosphonate therapy, and this response was consistent across underlying diseases. These studies established the efficacy of bisphosphonates in preventing GIOP, especially when started early during high-dose GC use. Beyond bone health, one recent study by Ohmura et al. showed that combined treatment with bisphosphonates and vitamin D may have a role in preventing atherosclerosis in patients with SLE.[13] It has also been shown that disease activity and autoantibody production in SLE may be aggravated by vitamin D insufficiency.[14] This speaks to additional benefits of vitamin D and bisphosphonates in patients with SLE.

Despite these data, there is a care gap in the prevention and treatment of GIOP among SLE patients. In an Italian study of SLE patients, 48% were receiving vitamin D drops, and 24% were receiving vitamin D and calcium tablets, while 14% received no supplementation.[15] In another study of 64 SLE patients conducted in the UK, just 29.7% were prescribed a bisphosphonate, despite 71.9% being on oral GC.[16] In another study conducted in Canada, only 50% of providers had prescribed bisphosphonates for patients with SLE taking steroids for prolonged periods.[17] Hence, these studies show that vitamin D and bisphosphonates are underused for the prevention and treatment of GIOP in SLE patients. However, this was not compared to existing society guidelines.

The ACR first published its guidelines on GIOP in 1996[18] in order to standardize GIOP management, and it recently updated its guidelines for GIOP management in 2017.[19] By using the 2017 ACR guidelines as a gold standard, our study evaluated the current standard of care being provided for GIOP management for SLE patients in a pragmatic setting. Our study aimed not only to identify the gaps in GIOP prevention and treatment for SLE patients but also to examine patients' characteristics associated with appropriate GIOP management.

Methods

Study design and inclusion criteria

We conducted a retrospective cohort study of patients with SLE receiving care within the Fairview Health System (including the University of Minnesota Medical Center), a large nonprofit, integrated health system that serves 2.5 million patients across Minnesota.

We identified patients in the Fairview clinical database who met the following criteria for inclusion in our study: aged $\geq$18 years and had received care at a Fairview clinical site for a minimum of one year between January 1, 2011, and August 1, 2016; had at least two clinical encounters for SLE during that time frame; and were high-risk GC users, defined as patients who were prescribed a daily dose of at least 7.51 mg of prednisone for $\geq$90 continuous days. We manually reviewed patients' electronic medical records to extract demographic information, dose and duration of prednisone use, and other past medical and social history, including prior history of fracture, and history of rheumatoid arthritis (RA) and bone mineral density (BMD). GC use was ascertained from provider orders and subsequent records indicating whether patients continued or stopped GC use. Beyond the initial 90 days of GC use, continuous use was defined as no gaps longer than one month between prescriptions. If there were multiple intermittent episodes of high-dose GC use per patient, the first available episode was included in our analyses. Body mass index (BMI), height, and weight were measured at the outpatient visit closest to GC start date.

OP fracture risk assessment

Because the ACR GIOP guidelines differ by age, we considered patients <40 years of age and those ≥ 40 years of age separately in our analyses.

For the older patient group, 10-year fracture probability was assessed using the University of Sheffield online fracture risk calculator (FRAX; https://www.sheffield.ac.uk/FRAX/tool.jsp) based on patient medical information from charts at the time of starting high-dose GC therapy. Since information on BMD was not available for all patients, for consistency, the FRAX score was calculated without BMD for all patients. For the younger patient group, fracture risk was assessed by the presence of established osteoporosis risk factors: low body weight, history of hypogonadism, secondary hyperparathyroidism, thyroid disease, history of fracture in self or family, history of heavy alcohol use (three or more units a day), or history of current or past smoking documented per patient medical records at the time of starting high-dose GC therapy.

Outcome measures related to the management of GIOP

Our key outcomes of interest were the use of supplemental vitamin D, dose of vitamin D, serum levels of vitamin D within six months of starting high-dose GC, bisphosphonate prescription during the first six months of high-dose GC therapy, and osteoporotic (OP) fracture during the follow-up period. We examined order history and reviewed patient charts to determine use of vitamin D by prescription or patient self-report, vitamin D dose, serum vitamin D level ordered, and nearest serum vitamin D results within six months of high-dose GC use. We also collected data on bisphosphonate use (both oral and intravenous) within six months of high-dose GC therapy, dose and duration of bisphosphonates, and any contraindications to their use (atypical femur fracture, chronic or acute kidney disease with glomerular filtration rate ≤ 30 mL/min, hypocalcemia, allergy, or osteonecrosis of jaw). We also obtained information on prescription for bisphosphonate alternatives, for example teriparatide, denosumab, raloxifene, or salmon calcitonin.

Two clinicians independently ascertained the indication for bisphosphonates through chart review using the 2017 ACR guidelines as a gold standard. For patients aged ≥ 40 years, fracture risk was considered at least moderate if any of the following criteria were met: (a) pre-BMD FRAX score (GC adjusted) for major OP fracture was $\geq 10\%$; (b) pre-BMD FRAX score (GC adjusted) for hip fracture was $\geq 1\%$; (c) the patient had a history of prior OP fracture(s); (d) for men aged ≥ 50 years and post-menopausal women, the hip or spine T score was ≤ -2.5 on the nearest available DEXA scan; or (e) the patient was on a very high dose of GC (≥ 30 mg per day and a cumulative dose of > 5 g in the past year). For patients aged < 40 years, fracture risk was considered at least moderate if the patient (a) had a prior history of fracture(s), (b) had a Z-score of ≤ -3 at the hip or spine, (c) experienced rapid bone loss ($\geq 10\%$ at the hip or spine over one year), or (d) was using a very high dose of GC (≥ 30 mg/day and a cumulative dose of > 5 g in the past year).[19]

We further ascertained incident OP fractures during the follow-up period. The data on OP fractures were obtained through manual chart review. The follow-up period started six months after the index date and continued until 2017, the patient's death, or loss to follow-up, whichever occurred first. We defined an OP fracture as vertebral, hip, wrist-forearm, humeral, femoral, rib, pelvic, clavicular, scapular, sternal, or tibial and fibular fractures occurring with no history of trauma or minimal trauma (e.g., falling from standing height).[20] We excluded incidentally found healed fractures. We compared the incidence of OP fractures between patients that were started on appropriate GIOP care within six months of the index date based on ACR guidelines versus those who were not deemed to be on appropriate GIOP care. This accounted for both being on vitamin D supplements and bisphosphonates if indicated within six months of initiating high-dose GC therapy.

Statistical analyses

Descriptive statistics, including medians and quartiles for continuous variables and counts and percentages for categorical variables, were computed by age group. Continuous variables were compared using the Wilcoxon/Mann–Whitney rank sum test. Categorical variables were compared using Fischer's exact test. Bar plots were created using median values for continuous variables and percentages for categorical variables. Error bars on the bar plots were computed using the first and third quartile for continuous variables and 95% exact confidence intervals using the method of Clopper and Pearson.[21] Further, a multivariable classification tree analysis was used to identify the key patient-related factors associated with bisphosphonate prescription for patients aged ≥ 40 years. The Gini impurity was used for splitting. A minimum terminal leaf was required to have ≥ 10 people. Variables included in the classification tree were age, sex, race, GC use duration and average daily dose, BMI, smoking history, number of

inpatient/outpatient visits, medication count, and a FRAX score for major OP fracture (for patients aged ≥ 40 years). Ethics approval for this study was through Fairview Research Administration.

Results

Sample characteristics

Of the 654 patients with SLE identified in the clinical database, 203 were assessed as having high-risk GC use and were included in our analyses (Figure 1). Demographic and clinical characteristics of this sample are summarized in Table 1 by two age groups: 18–39 years old ($n = 73$; 36%) and ≥ 40 years ($n = 130$; 64%). In both groups, patients were predominantly female and white. In the younger age group, the median daily dose of prednisone was 15 mg/day (IQR 10.0–20.9 mg/day), and the median duration of prednisone usage was 219 days during the study period (IQR 150–409 days). In the older age group, the median daily dose of prednisone was 12.5 mg/day (IQR 10.0–18.9 mg/day), and the median duration of prednisone usage was 252 days (IQR 165–518 days) during the study period. Older patients had a higher mean BMI and were more likely to be current smokers than younger patients were, whereas younger patients had more health service encounters during the six months before and after starting GC. Groups were similar in their history of endocrine disorders, RA, family history of fractures, and medication count. The median FRAX 10-year probability of major OP fracture for those aged ≥40 years was 7.8 (IQR 4.2–14.5), and the median FRAX score of hip fracture was 0.6 (IQR 0.2–2.0).

Vitamin D supplementation

As shown in Table 2, 58.9% (43/73) of patients < 40 years old and 61.5% (80/130) of patients ≥ 40 years old were prescribed the recommended dose of vitamin D (≥800 IU/day). A small percentage in each group (5.5–10%) were prescribed a lower dose of vitamin D. Nearly a quarter (23.3%) of younger patients and 13.8% of older patients had no record of any vitamin D supplementation. The remainder in each group were missing the specific

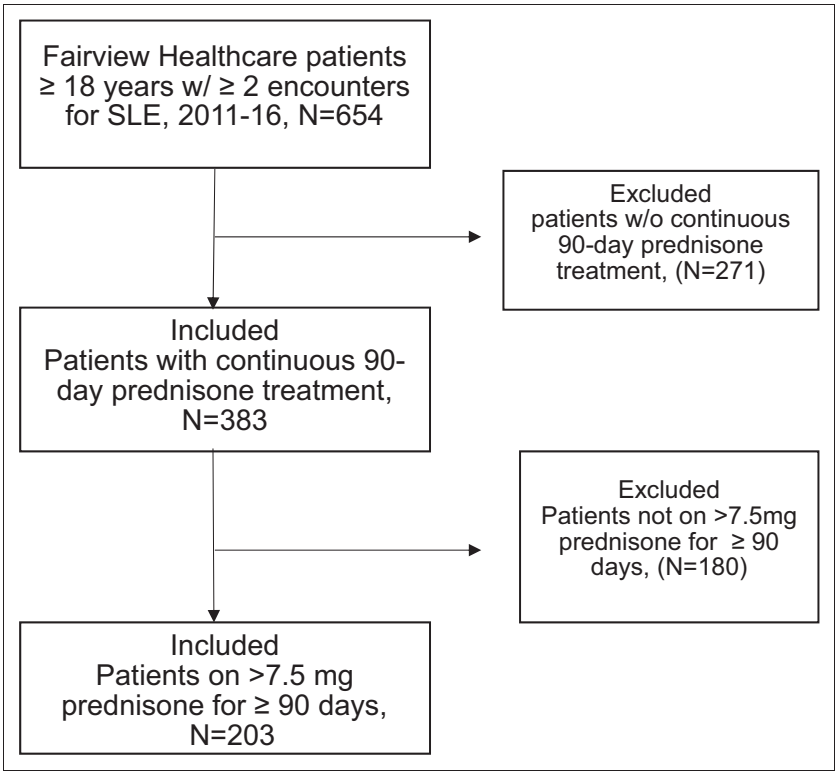

Figure 1 Study flow diagram. A total of 654 patients receiving long-term care for system lupus erythematosus (SLE) and any glucocorticoids (GC) were identified upon electronic data inquiry. Of these, 383 patients met the criteria for ≥90 days of GC use. After a manual chart review for accuracy, 203 SLE patients who received at least 7.51 mg of prednisone or equivalent daily dose for at least 90 days continuously were included in the analyses.

Table 1 Demographic and clinical characteristics of SLE patients receiving long-term high-dose GC by age group

	Aged < 40 years	*Aged ≥ 40 years*	p-*Value*
N	73	130	
Index age (years), median (Q1, Q3)	31.2 (24.5, 34.3)	54.3 (48.2, 63.1)	<0.001
Female, *n* (%)	69 (94.5)	105 (80.8)	0.007
Race, *n* (%)			0.005
White	46 (63.0)	96 (78.7)	
Black or African American	12 (16.4)	20 (16.4)	
Asian	14 (19.2)	6 (4.9)	
Multiple	1 (1.4)	0 (0)	
BMI (kg/m^2), median (Q1, Q3)	24.1 (21,7, 29.2)	28.2 (24, 34.2)	<0.001
Prednisone[a] (mg/d), median (Q1, Q3)	15 (10, 20.9)	12.5 (10, 18.9)	0.336
Duration (days), median (Q1, Q3)	219 (150, 409)	252 (165, 518)	0.182
Patient history of fracture, *n* (%)	6 (8.5)	21 (16.9)	0.131
Smoking history, *n* (%)			0.010
Current	3 (4.1)	17 (13.2)	
Past	16 (21.9)	43 (33.3)	
None	54 (74.0)	69 (53.5)	
Heavy alcohol use (3 + drinks/day), *n* (%)	1 (1.4)	0 (0.0)	0.361
History of endocrine disorders,[b] *n* (%)	16 (21.9)	33 (25.4)	0.613
History of rheumatoid arthritis	14 (19.2)	40 (30.8)	0.097
Family history of osteoporosis or fracture, *n* (%)	4 (5.6)	8 (6.3)	>0.99
FRAX score,[c] median (Q1, Q3)	–	7.8 (4.15, 14.5)	
FRAX score,[d] median (Q1, Q3)		0.6 (0.2, 2.0)	
Service encounters,[e] median (Q1, Q3)	5 (2, 9)	3 (1, 6.75)	0.008
Medication count,[f] median (Q1, Q3)	6 (4, 9)	5 (0.25, 9)	0.104
OP fracture in follow-up period, *n* (%)	1 (1.3)	20 (13.5)	<0.001

[a]Average daily dose.
[b]Thyroid disease, hyperparathyroidism, or hypogonadism.
[c]Major OP fracture.
[d]Hip fracture.
[e]Inpatient and outpatient ± 6 months of starting GC.
[f]At the time of starting GC.
SLE: systemic lupus erythematosus; GC: glucocorticoids; BMI: body mass index; FRAX: Fracture Risk Assessment; OP: osteoporotic.

Table 2 Vitamin D and bisphosphonate use among SLE patients receiving long-term high-dose GC by age group

	Aged < 40 years	*Aged ≥ 40 years*	p-*Value*
N (%)	73 (36.0)	130 (64.0)	
Serum vitamin D level ordered,[a] *n* (%)	28 (38.4)	33 (25.4)	0.058
Nearest serum vitamin D result within 6 months, μg/L, median (Q1, Q3)	21 (18, 29.5)	27.5 (19.8, 33.5)	0.338
Vitamin D supplement use, *n* (%)	56 (76.7)	112 (86.2)	0.120
Vitamin D supplement use by dose, *n* (%)			0.300
<800	4 (5.5)	13 (10.0)	
800+	43 (58.9)	80 (61.5)	
Missing dose	9 (12.3)	19 (14.6)	
No documented vitamin D use	17 (23.3)	18 (13.8)	
Bisphosphonate use within 6 months, *n* (%)	1 (1.4)	32 (24.6)	<0.001
Bisphosphonate recommended[b] and prescribed (%)	0 (0)	19 (14.6)	
Bisphosphonate recommended and not prescribed (%)	0 (0)	28 (21.5)	
Bisphosphonate alternatives prescribed[c] (%)	0 (0)	3 (2.3)	

[a]Vitamin D level ordered within 6 months before or after starting of high-dose GC therapy.
[b]Considered to meet American College of Rheumatology guidelines by trained chart reviewer.
[c]Bisphosphonate alternatives include teriparatide, denosumab, raloxifene, or salmon calcitonin.

dose. Serum vitamin D levels were ordered within six months before or after starting high-dose GC in 38.4% (28/73) of younger patients (median level = 21.0 μg/L, IQR 18.0–29.5 μg/L) and 25.4% (33/130) of older patients (median level = 27.5 μg/L, IQR 19.8–33.5 μg/L).

Bisphosphonate therapy

Based on retrospective risk stratification, none of the 73 patients < 40 years of age were considered candidates for bisphosphonates per the ACR guidelines. Nonetheless, one (1.4%) patient was prescribed bisphosphonate. For the 130 patients ≥ 40 years of age, bisphosphonate therapy was indicated for 47 (36.2%) patients, but only 19 (14.6%) were prescribed one. Another 13 (10.0%) patients were prescribed a bisphosphonate, despite not having an indication per the ACR guidelines, considered as overtreatment. Three (2.3%) patients in the older age group were prescribed bisphosphonate alternatives (teriparatide, denosumab, raloxifene, or salmon calcitonin).

For patients in the older age group, we performed additional analyses to ascertain predictors of receiving oral or intravenous bisphosphonate prescription. As shown in Figure 2, compared to patients who were not prescribed bisphosphonates, those with a prescription were older (median age = 62.3, IQR 50.9–65.6 vs. 53.1, IQR 47.4–62.2; $p = 0.012$), and more patients with prescription had higher FRAX scores for both major OP (60.0% vs. 35.5%; $p = 0.017$) and hip fracture (57.1% vs. 32.7%; $p = 0.016$). Here, a high FRAX score for major OP fracture was defined as ≥ 10%, and a high FRAX score for hip fracture was defined as ≥ 1% based on ACR criteria of moderate fracture risk.[19]

We then performed a multivariable classification tree analysis that included age, sex, race, GC use duration and average daily dose, BMI, smoking history, number of inpatient/outpatient visits, medication count, and FRAX score for major OP fracture. This analysis identified a single node, based on a patient's FRAX score for major OP fracture that discriminated the decision to prescribe or not prescribe a bisphosphonate. Specifically, among patients whose FRAX score was ≥ 23.5, 75% were prescribed a bisphosphonate; in contrast, only 19% of patients with a FRAX score of < 23.5 were prescribed a bisphosphonate (Figure 3).

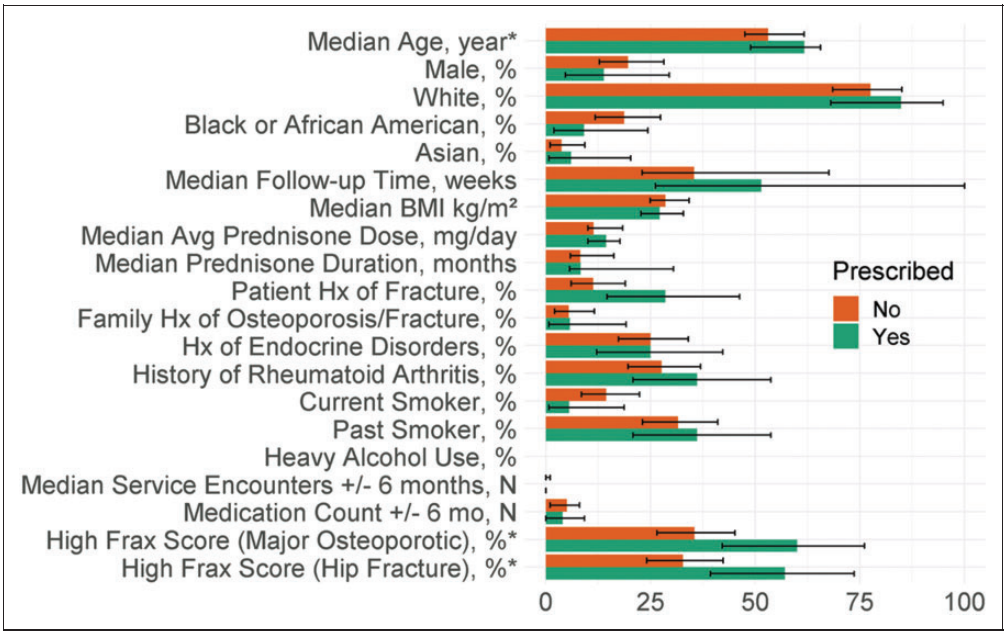

Figure 2 Factors associated with bisphosphonate prescription in SLE patients on long-term GC therapy aged ≥40 years. Patient-related factors associated with bisphosphonate prescription in SLE patients aged ≥ 40 years. Color bars correspond to absolute median values for continuous variables and percentages for categorical variables. Error bars on the bar plot were computed using the first and third quartile for continuous variables and 95% exact confidence intervals using the method of Clopper and Pearson. *$p = 0.05$. Among patients aged ≥40 years, key factors associated with the decision to prescribe bisphosphonate were older age and a high FRAX score for major osteoporotic (OP) fracture and hip fracture. Here, "high FRAX score" is defined as a FRAX score for major OP fracture of ≥10% and a FRAX score for hip fracture of ≥ 1% based on the American College of Rheumatology criteria of moderate to high fracture risk. BMI: body mass index; Hx: history: Hx of endocrine disorders: history of hyperparathyroidism, hypogonadism, and thyroid disease; FRAX: Fracture Risk Assessment.

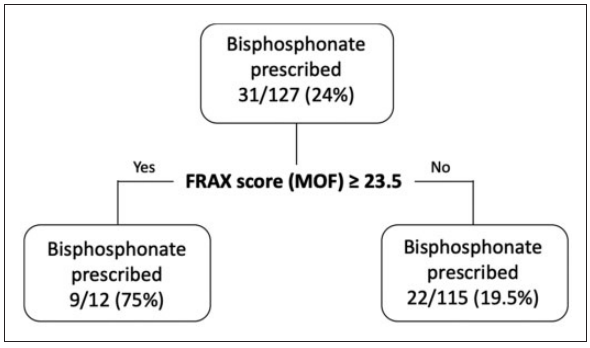

Figure 3 Multivariable classification tree analyses of patient-related factors associated with bisphosphonate prescription in SLE patients aged ≥ 40 years. Among patients aged ≥ 40 years, a FRAX score for major OP fracture of ≥ 23.5 was the distinguishing factor associated with bisphosphonate prescription. Among patients who had a FRAX score of ≥ 23.5, 75% were prescribed bisphosphonate compared to patients with a FRAX score of < 23.5 where only 19.5% were prescribed bisphosphonate. FRAX (MOF): Fracture Risk Assessment score for major OP fracture.

Lastly, we identified 21 patients with incident OP fractures during the follow-up period. Among them, 20 were aged ≥ 40 years. Although we observed a trend toward fewer OP fractures among patients receiving appropriate GIOP care per the ACR guidelines (9 (6.50%) fractures in the ACR-appropriate group vs. 12 (13.6%) fractures in the ACR-inappropriate group), the difference did not reach statistical significance ($p = 0.098$).

Discussion

Accepting 2017 ACR GIOP prevention and treatment guidelines as the gold standard, this study identifies several areas of needed practice improvement for the prevention and treatment of GIOP SLE patients. While many patients meeting the guidelines were not prescribed vitamin D and bisphosphonate, other patients not meeting the indications for bisphosphonates were prescribed one. This emphasizes the importance of being vigilant about who meets the criteria for bisphosphonates and who does not. The majority of patients who were prescribed bisphosphonates had a FRAX score for major OP fracture ≥ 23.5, exceeding the ACR guideline threshold of 10%.

Insufficient vitamin D intake and low serum levels of vitamin D have been associated with worse bone health outcomes in SLE patients.[22] Several studies have shown a high prevalence of vitamin D insufficiency in SLE.[23–28] SLE patients are more prone to vitamin D insufficiency or deficiency due to factors such as sun avoidance, chronic renal insufficiency, use of anti-malarial agents, and development of antivitamin D antibodies.[28] The ACR recommends evaluating patients at risk for osteoporosis for vitamin D deficiency and correcting vitamin D nutritional status.[19] For patients with SLE, other studies have also suggested that supplementation should be aimed to a 25(OH) vitamin D level of 40 ng/mL due to its impact on the reduction of proteinuria, higher complement level, and improvement in global disease activity in SLE.[29,30] Although the mean serum vitamin D level in our study cohort was higher than the recommended level in the ACR guidelines, the mean vitamin D level was still < 40 ng/mL, and a significant proportion of both younger and older patients had no record of any vitamin D supplementation, which reflects a gap in care.

Several previous studies reported suboptimal use of bisphosphonates in SLE patients.[31–33] The indications for bisphosphonates were ascertained from GC dose, BMD, T scores, or history of fragility fractures. However, the FRAX score, one of the components for risk stratification outlined in the ACR guidelines, was not included as an indication for bisphosphonate therapy in these studies. FRAX integrates clinical risk factors for osteoporosis, which in addition to age and sex contributes to fracture risk independently of BMD.[34] Several clinical factors associated with a fracture risk integrated by FRAX score is greater than what can be accounted for by BMD alone.[35] In our study, roughly 40% of patients with a pre-BMD FRAX-based indication received bisphosphonates. It is also worth noting that our multivariable decision tree analysis identified a FRAX score for major OP fracture ≥ 23.5% as the key discriminator for bisphosphonate prescription. This suggests that interventions to improve bisphosphonate use for the prevention and treatment of GIOP should focus on patients at with a 10–20% 10-year FRAX probability of major OP fracture.

Interestingly, 10% of patients were prescribed a bisphosphonate, despite not meeting ACR guideline criteria. It may be that risk factors or decision making behind bisphosphonate prescription were not completely captured by the chart review, but this also could reflect an issue with overtreatment. This is concerning due to the known side effects of bisphosphonates. In particular, osteonecrosis of the jaw and atypical femoral fractures (AFF), although rare, are serious potential harms of longer-term treatment with bisphosphonates.[36] Evidence has found that increasing the duration of bisphosphonate use is associated with increasing incidence of

atypical femoral fractures.[37] Although the guideline has clear indications for initiation of bisphosphonate therapy, safe duration of therapy is not specified. This could pose another barrier to adherence in recommendations, especially for younger SLE patients who might have ongoing GIOP risk factors for extended duration.

We identified several patient characteristics associated with bisphosphonate prescribing in our SLE sample, including older age and higher FRAX scores for both major OP and hip fracture. The findings in regards to age are comparable to previous studies.[31,38,39] Although in previous studies male patients were less likely to receive appropriate GIOP prevention and treatment,[38,40–42] this was not translated in our study as getting less prescription. The factors contributing to lower rate of therapeutic intervention for the younger population could be explained by uncertainties regarding absolute risk for fracture in the younger age group, reliance on DEXA (bone densitometry) scans,[43] and a lack of fracture risk assessment tools for patients < 40 years of age. Also for premenopausal women, who are included in younger age group, the guidelines recommend caution in the use of bisphosphonates due to teratogenic risks, which can be a barrier.[44]

Several studies have identified other barriers for improving GIOP care. In one provider questionnaire study, the most frequently identified barriers were lack of knowledge regarding indications of bisphosphonate therapy, limited clinic time, nonadherence to treatment plan by patients, difficulty in scheduling DEXA scans, and insufficient insurance coverage of anti-OP drugs.[45] A recent meta-analysis evaluated a variety of quality improvement strategies to improve osteoporosis screening (BMD/DXA testing) and/or treatment (pharmacotherapy) initiation rates.[46] This study showed that fracture liaison service/case management interventions and multifaceted interventions targeting both providers and patients could significantly increase osteoporosis treatment outcomes in patient populations with recent or prior fracture.[46] Ongoing educational programs for patients and providers, as well as computer-based reminders based on latest GIOP guidelines, could be promising interventions to apply in the future to improve adherence. A Dutch study found that feedback by pharmacists to prescribers of patients eligible for GIOP preventive treatment did not increase the prescribing of bisphosphonates in the total study population, but a significant increase was seen in men and in the elderly aged > 70 years.[47] Thus, combining computer-based reminders and pharmacist reinforcement to providers could be a potential solution. In a previous study, a multifaceted approach (faxed physician reminders combined with patient education) resulted in increase rates of appropriate osteoporosis treatment in older people seen in the emergency room after a wrist fracture.[48] Another intervention could include redesigning aspects of the health-care system and the addition of new management processes (e.g., nurse managed case management), which may help improve GIOP management in high-risk patients. Similar concepts have been studied in the past in patients with recent OP fracture by Harrington et al. and were found to be effective in increasing osteoporosis treatment.[49]

Our study has several strengths, including a large sample size with SLE patients from various clinical settings (academic and community). The use of the 2017 ACR GIOP guideline as a gold standard enabled us to identify gaps in care that need to be addressed to meet the most current recommendations. We also applied a full manual chart review to improve accuracy.

Our study was limited by the nature of observational studies in which cause and effect cannot be determined. Further, this retrospective cohort study relied on chart completeness for all variables. Due to this, factors such as family history of OP fracture and personal history of OP fracture could have been misclassified or missed due to a lack of documentation. The number of patients with an indication for bisphosphonates may also have been underestimated due to limited bone density evaluations available in patients < 40 years old, and not accounting for SLE disease activity, which itself can lead to osteoporosis due to a chronic inflammatory state. Perhaps GIOP guidelines should be adapted to SLE patients to factor in disease activity in the future. Although we have included data on OP fractures during the follow-up period, the study was not powered to evaluate the impact of adherence to the ACR GIOP guideline on OP fractures, indicating an ongoing need for larger and prospective studies to assess the effectiveness of guideline-based care for GIOP.

In summary, although GIOP in SLE is a well-known complication, we found that routine clinical care for the prevention and treatment of GIOP in our large patient sample during the time period of study did not meet the standards set by the ACR in 2017. To bring care up to the 2017 ACR recommendations, vitamin D supplements and bisphosphonates should be prescribed more often to appropriate candidates and not prescribed to patients who do not meet appropriate criteria. Further characterization of provider barriers,

systems-based interventions, and safe duration of anti-resorptive therapy to improve GIOP care in SLE patients are necessary.

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Supplemental Material

Supplemental material for this article is available online.

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