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Are glucocorticoid-induced osteoporosis recommendations sufficient to determine antiosteoporotic treatment for patients with rheumatoid arthritis?

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Background/Aims: We investigated differences in identifying candidates for antiosteoporotic treatment in rheumatoid arthritis (RA) patients according to two available clinical guidelines.

Methods: We prospectively enrolled 100 female patients aged 50 years or older with RA who visited Hanyang University Hospital for periodic examinations between April 2011 and August 2011. We applied the glucocorticoid-induced osteoporosis (GIOP) recommendations and the National Osteoporosis Foundation (NOF) guidelines to RA patients and examined agreement between the guidelines for identifying candidates for antiosteoporotic treatment. We also analyzed the impact of screening vertebral fractures (VFs) in determining the treatment of osteoporosis in RA patients.

Results: The 57 patients taking glucocorticoids were classified into high-risk (n = 23), medium-risk (n = 16), and low-risk (n = 18) groups according to the GIOP recommendations. Based on the NOF guidelines, 36 of 57 patients were candidates for antiosteoporotic treatment and the agreement between two guidelines was high (κ = 0.76). Two of the 18 patients in the low-risk group and 19 of 43 patients not eligible per the GIOP recommendations were classified as candidates for antiosteoporotic treatment by the NOF guidelines.

Conclusions: In determining antiosteoporotic treatment for RA patients, using only the GIOP recommendations is insufficient. Application of the NOF guidelines in patients not eligible for or classified into the low-risk group per the GIOP recommendations and screening for VFs may be helpful in deciding on antiosteoporotic treatment in RA patients.

Keywords: Glucocorticoids; Osteoporosis; Arthritis, rheumatoid; Guideline

INTRODUCTION

Osteoporosis is a common complication in rheumatoid arthritis (RA) patients [1]. In a recent large case-control study, the risk of fractures was found to be ~1.5 times higher in RA patients than in healthy controls [2]. Although a low bone mineral density (BMD) value is strongly associated with the risk of fracture, other risk factors such as age, history of a prior fragility fracture, and glucocorticoid use are independent

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contributors to the risk of fracture [3]. Although awareness of glucocorticoid-induced osteoporosis (GIOP) by healthcare professionals has increased in recent years, it remains underdiagnosed and undertreated [4,5]. Thus, the National Osteoporosis Foundation (NOF) incorporated the 10-year absolute probability of fracture, calculated according to the Fracture Risk Assessment (FRAX) tool into their guidelines for the treatment of osteoporosis and included glucocorticoid use and RA as clinical risk factors [6]. However, the role of primary prevention in high-risk patients may not be emphasized sufficiently because of the lack of specific guidelines for GIOP. Thus, the recent guidelines from the American College of Rheumatology (ACR) incorporated a FRAX-based approach to FRAX in glucocorticoid-treated patients and are currently in use [7,8]. As the GIOP recommendations were mostly recognized as guidelines for primary prevention, they could be applied to patients currently taking, as well as initiating, glucocorticoids. Despite emerging new GIOP recommendations, however, an approach to osteoporosis treatment for RA patients may be met with some confusion because these recommendations are not applicable to RA patients not using glucocorticoids. In view of the therapeutic objective of osteoporosis treatment and the prevention of the fractures in RA patients, GIOP recommendations for primary prevention and NOF guidelines for secondary prevention based on characteristics of patients and the use of glucocorticoids should be compared. Thus, in this study, we compared two antiosteoporotic treatment guidelines for RA patients to evaluate whether the GIOP recommendations are sufficient for identifying candidates for antiosteoporotic treatment in RA patients. Furthermore, we evaluated the impact of screening for vertebral fractures (VFs), which is recommended in both guidelines, but rarely done, in determining antiosteoporotic treatments for these patients.

METHODS

Study population

We enrolled prospectively 100 female patients with RA who visited Hanyang University Hospital for periodic examinations between April 2011 and August 2011. Patients aged 50 or older and who fulfilled the ACR 1987 revised classification criteria for RA were included. All patients provided written informed consent under an Institutional Review Board-approved protocol. Participants completed questionnaires via interviews about demographics (age, height, and weight) and medical history (disease duration, smoking status, alcohol use, self-reported history of fracture, and parental history of hip fracture). These variables were used to calculate the FRAX score for each patient. Disease duration was defined as the time elapsed between onset, or first disease-related symptom, and enrollment.

Risk assessment for osteoporotic fractures

GIOP recommendations

We used the ACR 2010 recommendations for GIOP for patients taking glucocorticoids [7]. In postmenopausal women and men aged ≥ 50 years with a history of glucocorticoid use, GIOP risk is classified as low (< 10%), medium (10% to 20%), or high (> 20%) 10-year probability of a major osteoporotic fracture using the FRAX tool. The 10-year probabilities of a major osteoporotic fracture and of a hip fracture were calculated using the FRAX tool (http://www.shef.ac.uk/FRAX) with femoral neck BMD. Among the low- and medium-risk postmenopausal glucocorticoid-treated women, those with anticipated glucocorticoid usage duration of ≥ 3 months or those on current glucocorticoid therapy for at least 3 months were indicated for osteoporosis treatment. In the high-risk postmenopausal glucocorticoid-treated patients, all patients were indicated for osteoporosis treatment.

NOF guidelines

NOF guidelines were applied to all patients enrolled in the study to compare them with the GIOP recommendations. According to the NOF guidelines, treatment is recommended for individuals meeting any of the following criteria: 1) history of hip or VF; 2) T-score ≤ –2.5 at the femoral neck or spine; 3) –1.0 < T-score < –2.5 and a 10-year probability of a hip fracture ≥ 3% (determined with FRAX); or 4) –1.0 < T-score < –2.5 and a 10-year probability of a major fracture ≥ 20% (determined with FRAX).

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Assessment of VFs

All enrolled patients underwent lateral plain radiographs of the thoracolumbar spine. All radiographs were analyzed by two experienced radiologists. Discrepancies between radiologists with regard to the presence of fracture were resolved by consensus. From the two radiologists, a qualitative fracture evaluation was performed to decide whether the vertebral body had a fracture and a semiquantitative fracture evaluation was made to classify the severity of vertebral deformity [9].

Statistical analysis

All analyses were performed with the SPSS version 19.0 (IBM Co., Armonk, NY, USA). We used Student *t* test and the chi-square test to compare baseline characteristics of patients who were and were not using glucocorticoids. Cohen's kappa (κ) was used to estimate the degree of consensus between the NOF guidelines and GIOP recommendations in identifying candidates for antiosteoporotic treatment. The prevalence of VFs in RA patients was investigated and the impact of screening for VFs on deciding antiosteoporotic treatment for RA patients was analyzed descriptively.

RESULTS

Clinical characteristics of the subjects are presented in Table 1. At baseline, subjects had a mean age of 61.2 years with a median (range) disease duration of 6.5 years (range, 0.2 to 22.4). The subjects' age, height, weight, and body mass index were not significantly different between the groups. The daily dosage of glucocorticoids among the enrolled patients was 2.8 ± 1.3 mg/day, and the duration of glucocorticoid therapy was 56.7 ± 64.7 months. Disease activity, measured with disease activity score 28 (DAS28), was higher in the glucocorticoid users than the nonusers (3.5 ± 0.1 vs. 2.9 ± 1.0; $p = 0.03$). Patients with a prior history of fracture were more common in patients taking glucocorticoids than those not taking them (40.4% vs. 20.9%; $p = 0.03$). The probabilities of major osteoporotic fractures (17.4 ± 10.3 and 8.8 ± 3.9) and hip fractures (7.3 ± 7.3 and 2.5 ± 2.1) using the FRAX tool were also higher in the glucocorticoid users than nonusers ($p < 0.01$). According to the commonly used World Health Organization definition of BMDs for the lumbar spine and femur neck, the prevalence of osteoporosis was higher in those taking glucocorticoids (40.4%) than in those not taking them (32.6%), based on lumbar-spine BMD, but the difference was not statistically significant ($p = 0.42$) (Table 1). The distribution of RA patients to whom the GIOP recommendations and NOF guidelines were applied is shown in Tables 2 and 3. GIOP recommendations were applied to 57 patients who were currently taking glucocorticoids. Among these patients, the agreement rate between the two guidelines for antiosteoporotic treatment was high ($\kappa = 0.76$) (Table 2). They were classified into high-risk (n = 23, 40%), medium-risk (n = 16, 28%), and low-risk (n = 18, 32%) groups, according to the GIOP recommendations. All 23 patients classified as high-risk required treatment according to the NOF guidelines, but four of the 16 patients classified as medium-risk, based on the GIOP recommendations, did not require treatment per the NOF guidelines. In contrast, two of the 18 patients classified as low-risk, based on the GIOP recommendations, were indicated to receive antiosteoporotic treatment by the NOF guidelines (Table 2).

Table 3 shows the changes in the prevalence of candidates for antiosteoporotic treatment by applying each guideline and screening for VFs. When we used only the GIOP recommendations for RA patients, 39 patients (39%) were indicated for antiosteoporotic treatment. When we applied the NOF guidelines to patients in the low-risk group and those not eligible for GIOP recommendations, the number of candidates for antiosteoporotic treatment increased to 56 (56%). If we added screening radiography for detecting prevalent VFs in both guidelines, 67 of the 100 RA patients (67%) were indicated for antiosteoporotic treatment (Table 3).

DISCUSSION

The approach to osteoporosis in RA patients must differ from that in the general population. Although it shares some similarities with postmenopausal osteoporosis, GIOP has distinct characteristics, including the rapidity of bone loss early after initiation of therapy, the accompanying increase in fracture risk

Table 1. Baseline characteristics of participants according to glucocorticoid use

Characteristic	Total (n = 100)	No glucocorticoid use (n = 43)	Glucocorticoid use (n = 57)	*p* value
Age, yr	61.2 ± 8.2	60.8 ± 7.2	61.5 ± 8.8	0.68
Weight, kg	53.9 ± 7.9	55.0 ± 6.5	53.1 ± 8.9	0.24
Height, cm	153.5 ± 5.5	154.1 ± 4.7	153.2 ± 6.1	0.46
Body mass index, kg/m^2	22.8 ± 3.2	23.2 ± 2.9	22.6 ± 3.5	0.35
Disease duration, yr	6.5 ± 6.0	6.8 ± 5.7	6.3 ± 6.3	0.65
DAS28-ESR	3.3 ± 1.0	2.9 ± 1.0	3.5 ± 0.1	< 0.01
Lumbar spine BMD, g/cm^2	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	0.57
Lumbar spine total T-score				0.51
> –1	21 (21.0)	13 (30.2)	8 (14.0)	
–2.5 to –1	43 (43.0)	21 (48.8)	22 (38.6)	
≤ –2.5	26 (26.0)	9 (20.9)	17 (29.8)	
Left femur neck BMD, g/cm^2	0.6 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.20
Right femur neck BMD, g/cm^2	0.7 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.14
Femur total T-score (n = 98)				0.51
> –1	54 (55.1)	24 (55.8)	30 (52.6)	
–2.5 to –1	38 (38.8)	19 (44.2)	19 (33.3)	
≤ –2.5	6 (6.1)	0 (0.0)	6 (10.5)	
Prevalence of osteoporosis	37 (37.0)	14 (32.6)	23 (40.4)	0.42
Prior history of fracture	32 (32.0)	9 (20.9)	23 (40.4)	0.03
Prior history of hip or vertebral fracture	15 (15.0)	5 (11.6)	10 (17.5)	0.41
10-Year probability of a major fracture with FRAX, %	13.7 ± 9.3	8.8 ± 3.9	17.4 ± 10.3	< 0.01
10-Year probability of a hip fracture with FRAX, %	5.2 ± 6.1	2.5 ± 2.1	7.3 ± 7.3	< 0.01

Values are presented as mean ± SD or number (%).
DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; BMD, bone mineral density; FRAX, fracture risk assessment.

during this time, and the combination of suppressed bone formation and increased bone resorption during the early phase of therapy [10]. Thus, the risk of osteoporosis and osteoporotic fractures, regardless of other factors, is serious for patients using glucocorticoids. Our study showed that the high-risk group identified by the GIOP recommendations corresponded to groups indicated for treatment by NOF guidelines. Also, four patients classified as medium-risk by the GIOP recommendations would not receive treatment indicated by the NOF guidelines. That an indication group not meeting NOF guidelines is relevant to GIOP recommendations may be considered in terms of a preventative approach. In this case, the GIOP recommendations can be applied effectively. As the GIOP recommendations have assumed a role in secondary prevention, as well as primary prevention, by its nature, the drawbacks may be partially evident. As not all patients with RA take glucocorticoids, it is difficult to evaluate every indication based on the GIOP recommendations alone. In our study, two of 18 patients who were classified as low-risk and 19 among 43 not eligible for the GIOP recommendations were indicated for treatment according to the NOF guidelines. This indicates that a more comprehensive set of guidelines for the treatment and prevention of osteoporosis in RA patients is needed, that the GIOP recommendations should not be applied to patients using glucocorticoids unconditionally, and that low-risk groups who are not indicated for antiosteoporotic therapy according to the

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Table 2. Agreement between GIOP recommendations and NOF guidelines for identifying candidates of antiosteoporotic treatment in rheumatoid arthritis patients taking glucocorticoids (n = 57, κ = 0.76)

NOF guidelines	GIOP recommendations		
	Indication	No indication	Total
Indication	35 (61.4)	2 (3.5)	37 (64.9)
No indication	4 (7.0)	16 (28.1)	20 (35.1)
Total	39 (68.4)	18 (31.6)	57 (100)

Values are presented as number (%).
GIOP recommendations, 2010 American College of Rheumatology recommendations for glucocorticoid-induced osteoporosis; NOF, National Osteoporosis Foundation.

Table 3. The number of candidates for antiosteoporotic treatment according to the tools of risk assessment of fracture in patients with rheumatoid arthritis (n = 100)

Risk assessment tools	GIOP recommendations				Total
	High-risk	Medium-risk	Low-risk	Not applicable	
GIOP recommendations					
Indication	23	16	0	0	39
No indication	0	0	18	43	61
GIOP recommendations or NOF guidelines					
Indication	23	16	2	19	56
No indication	0	0	16	24	44
GIOP recommendations or NOF guidelines or vertebral fracture screening					
Indication	23	16	4	24	67
No indication	0	0	14	19	33
Total	23	16	18	43	100

GIOP recommendations, 2010 ACR recommendations for glucocorticoid-induced osteoporosis; NOF, National Osteoporosis Foundation.

GIOP recommendations should be assessed using the NOF guidelines.

A limitation of the GIOP recommendations is that the categorization of high-, medium-, and low-risk for fracture assessment is based largely on the FRAX tool. Several of the clinical risk factors contributing to FRAX do not take into account dose-response, but use average dose or exposure [3]. However, the precision of screening among those who need treatment has required further revision and comparison. Although screening for the presence of previous VF is recommended by the GIOP guidelines, it is usually underestimated. In RA patients, the use of analgesics for painful disease may decrease back pain and decrease the opportunity to screen patients with VF by spine radiography [11]. More importantly, among cases of RA patients, we are apt to neglect investigations for VF, instead concentrating on only BMD and steroid use. There is at least a 2-fold increase in VFs in patients with RA with up to a 6-fold increase reported in RA patients with long-standing disease [12,13]. In a large meta-analysis, it was shown that fracture was associated with an increased relative risk of subsequent fractures [14]. Based on our results, regular examination for VFs would be helpful in finding unknown VFs and preventing future fractures. As patients with RA are at high risk for VFs, more frequent recurrent fractures, and multiple fractures, particular attention is required

for these patients. In our study, among the 57 patients taking glucocorticoids, four with VFs were classified as low-risk by the GIOP recommendations. We also found five patients with VFs among 24 RA patients who were not recommended for antiosteoporotic treatment according to the NOF guidelines. These patients would have been excluded from antiosteoporotic treatment despite a high risk of subsequent VFs. Thus, periodic radiographic examinations are required to detect VFs regardless of risk classification by current guidelines.

The main limitation of our study is the small study population. However, we were able to assess each guideline and the diversified risk factors for each of our subjects with osteoporosis-concomitant fractures by close follow-up. Applying the developed guidelines effectively and regular assessment of VFs are essential in all RA patients regardless of history of VFs or use of glucocorticoids to identify candidates for antiosteoporotic treatment. In the future, further studies in larger populations are needed to develop truly appropriate guidelines for RA patients with osteoporosis. Also, outcome assessments of osteoporotic treatments according to the two guidelines need further evaluation.

In conclusion, the GIOP recommendations using FRAX are insufficient to determine antiosteoporotic treatment for RA patients. The application of the NOF guidelines in patients not eligible for or classified as low-risk by the GIOP recommendations and screening for VFs may be helpful in deciding on antiosteoporotic treatment in RA patients.

KEY MESSAGE

1. Use of the glucocorticoid-induced osteoporosis (GIOP) recommendations could be insufficient with regard to antiosteoporotic treatment for rheumatoid arthritis (RA) patients.
2. The application of National Osteoporosis Foundation (NOF) guidelines in patients not eligible for or classified as low-risk, by the GIOP recommendations, and screening for vertebral fractures may be helpful in deciding on antiosteoporotic treatment in RA patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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