Acta Med. Okayama, 2021
Vol. 75, No. 6, pp. 699–704

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Guideline-based Treatment of Glucocorticoid-induced Osteoporosis in Patients with Rheumatoid Arthritis: A Retrospective Study with the AORA Registry

Tetsuya Kawano[a]*, Naohisa Miyakoshi[a], Hiroyuki Tsuchie[a], Takeshi Kashiwagura[b], Moto Kobayashi[c], Hiroshi Aonuma[d], Yusuke Sugimura[e], and Yoichi Shimada[a]

[a]*Department of Orthopedic Surgery, Akita University Graduate School of Medicine, Akita 010-8543, Japan,*
[b]*Department of Orthopedic Surgery, Akita City Hospital, Akita 010-0933, Japan,*
[c]*Department of Orthopedic Surgery, Hiraka General Hospital Yokote City, Akita 013-8610, Japan,*
[d]*Department of Orthopedic Surgery, Ogachi Central Hospital Yuzawa City, Akita 012-0055, Japan,*
[e]*Department of Orthopedic Surgery, Nakadori General Hospital Akita City, Akita 010-8577, Japan*

Glucocorticoid-induced osteoporosis (GIOP) is one of the side effects associated with glucocorticoid (GC) therapy. In 2014, the Japanese Society for Bone and Mineral Research (JSBMR) provided new guidelines for the management and treatment of GIOP. The aim of the present study was to clarify the prevalence of patients with rheumatoid arthritis (RA) requiring treatment according to the new guidelines and to identify risk factors associated with lack of treatment in these patients. Patients in the 2018 Akita Orthopedic group on Rheumatoid Arthritis (AORA) database were enrolled. Of 2,234 patients with RA in the database, 683 (30.6%) met the 2014 JSBMR guideline treatment criteria, and 480 (70.3%) had been treated. The untreated group included a larger number of males, younger patients, and patients treated in clinics rather than hospital ($p<0.001$, $p=0.015$, and $p<0.001$, respectively). Multivariate analyses found that male sex, younger age, and clinic-based RA care were significant risk factors associated with lack of treatment ($p<0.001$, $p=0.013$, and $p<0.001$, respectively). Thus, male sex, younger age, and clinic-based care were identified as risk factors associated with lack of treatment for RA patients requiring treatment according to the new guidelines.

Key words: glucocorticoid, glucocorticoid-induced osteoporosis, rheumatoid arthritis, osteoporosis, osteopenia

Rheumatoid arthritis (RA) is associated with reduced bone density due to many factors, including age, menopause, immobility, chronic inflammation, and especially, glucocorticoid (GC) use. Despite the advent of biological disease-modifying antirheumatic drugs for RA, GCs are still one of the common treatment options. However, GCs are associated with several adverse effects. Glucocorticoid-induced osteoporosis (GIOP), a bone metabolism disorder, is frequently associated with GC therapy, and >3 months use of these agents has been shown to lead to fragility fractures in 30% to 50% of patients [1]. Moreover, the risk of fractures increases before bone mineral loss is detectable [2]. Therefore, adequate prevention and treatment of GIOP is critically important for RA patients.

In Japan, guidelines for the management and treatment of GIOP were first published by the Japanese Society for Bone and Mineral Research (JSBMR) in

Received December 17, 2020; accepted June 10, 2021.
*Corresponding author. Phone: +81-18-884-6148; Fax: +81-18-836-2617
E-mail: iwtbagdtk@gmail.com (T. Kawano)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

2004 [3]. These guidelines applied to patients aged 18 years or older who were using or planning to use oral GCs for more than 3 months. In this earlier version, measurement of lumbar bone mineral density (BMD) was essential for identifying patients needing treatment for GIOP, particularly if the patient had no history of fragility fracture or developed a new fracture during treatment. However, because of the difficulty of obtaining BMD at some institutions, adherence to these guidelines was reported to be low [4]. Therefore, JSBMR provided new guidelines for the management and treatment of GIOP in 2014 [5]. Again, the guidelines applied to patients aged 18 years or older who were using or planning to use GCs for more than 3 months. The presence or absence of fragility fractures, age, GC dose, and lumbar BMD were scored as fracture risk factors, and treatment intervention was required when the score was 3 or more. These guidelines can identify a subset of patients requiring therapeutic interventions to prevent and treat GIOP without the use of BMD scoring.

To the best of our knowledge, no study has reported the prevalence of GC-treated RA patients requiring GIOP treatment according to the new guidelines. The aims of this study were to clarify this statistic and to identify risk factors associated with lack of treatment using the database of the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) registry.

Materials and Methods

AORA registry. The AORA registry was established in 2010 as a multi-institutional cohort of Japanese patients with RA in Akita Prefecture [6, 7]. The registry is maintained by the Department of Orthopedic Surgery at Akita University Graduate School of Medicine and at 29 affiliated institutions. Data are collected once per year. AORA is one of the larger-scale RA cohorts in Japan, together with those of the National Database of Rheumatic Diseases of iR-net in Japan (NinJa) and the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) database [8, 9].

Study participants. This was a retrospective, multicenter study. In 2018 the AORA registry contained 2,234 patients with RA. All patients were diagnosed with RA according to the 1987 American College of Rheumatology (ACR) classification criteria and/or the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria [10, 11]. Patients whose scores for fracture risk were 3 or more based on the JSBMR 2014 guidelines for the management and treatment of GIOP were identified. Other patient information collected included sex, age, prednisolone (PSL)-equivalent GC dose, disease duration of RA, treatment facility (clinic or hospital), and fracture risk score based on the JSBMR 2014 guidelines, excluding the history of prior fragility fractures and lumbar BMD as these data are not collected in AORA. Treatments for GIOP included medications such as bisphosphonates (BPs), denosumab, activated vitamin D_3, selective estrogen receptor modulators (SERMs), and teriparatide. Patients with scores ≥ 3 were divided into 2 groups according to the presence (treated group) or absence (untreated group) of treatment for GIOP, and patient characteristics were compared between the 2 groups. Risk factors associated with a lack of a therapeutic intervention for patients with scores ≥ 3 were examined.

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2013. The Institutional Review Board for Clinical Research at Nakadori General Hospital approved this study (approval number: 254), and informed consent was obtained from all individual participants included in the study.

Statistical analyses. Comparisons between groups were performed using the Mann-Whitney *U* test. Data regarding proportions were analyzed using the chi-squared test. Multiple logistic regression analysis was performed to assess associations between clinical variables and GIOP treatment. All statistical analyses were performed using the Statistical Package for the Biosciences software (SPBS version 9.68; Akita University Graduate School of Medicine, Akita, Japan) [12]. Values of $p < 0.05$ were considered significant.

Results

There were 683 patients (30.6%) who met the treatment criteria of the guidelines (138 males and 545 females). The mean age was 75.4 ± 8.6 years (range: 27-100 years), and 99.4% of patients were older than 50 years. The median PSL-equivalent GC dose was 3 mg/day (range: 2-5 mg/day), and 94.8% of patients received a dose less than 7.5 mg/day. The median disease duration of RA was 139 months (range: 65-247 months). A total of 185 patients were treated in clinics, and 498 were

treated in hospitals. The mean fracture risk score based on the 2014 guidelines was 4.4 ± 1.1 (range: 3-8) (Table 1). The fracture risk score was 3 in 39 patients (5.7%), 4 in 413 patients (63.3%), 5 in 200 patients (29.2%), 6 in 5 patients (0.7%), and 8 in 26 patients (3.8%). A total of 480 patients (70.3%) had been treated with some type of osteoporosis medication. The most frequently used drugs were BPs (181 patients), followed by denosumab (101 patients), activated vitamin D_3 (54 patients), SERMs (29 patients), and teriparatide (17 patients).

The untreated group had a significantly higher percentage of males ($p < 0.001$). Furthermore, the mean age was significantly younger in the untreated group ($p = 0.001$). Disease duration of RA was significantly shorter in the untreated group than in the treated group ($p < 0.001$). In the untreated group, a significantly larger number of patients received treatment in clinics than in hospitals ($p < 0.001$) (Table 2). Univariate analysis showed that clinic-based care, male sex, younger age, and shorter disease duration of RA were significant risk factors associated with lack of treatment intervention ($p < 0.001$, $p < 0.001$, $p = 0.015$, and $p = 0.012$, respectively). Multivariate analysis also showed that clinic-based care, male sex, and younger age were significant risk factors for lack of treatment intervention ($p < 0.001$, $p < 0.001$, and $p = 0.013$, respectively) (Table 3).

Table 1 Characteristics of RA patients with GIOP

		All
Number		683
Sex Male/Female		138/545
Age (years), mean ± SD		75.4 ± 8.6
Age distribution, %	< 50	4 (0.6)
	50 ≦ < 65	44 (6.6)
	≧ 65	635 (92.8)
GC dose (PSL equivalent mg/day), median (IQR)		3 (2–5)
GC dose distribution, %	< 5	409 (59.9)
	5 ≦ < 7.5	239 (34.9)
	≧ 7.5	35 (5.2)
Disease duration of RA (months), median (IQR)		139 (65–247)
Facility clinic/hospital		185/498
Scores in new guidelines, mean ± SD		4.4 ± 1.1
Treatment for GIOP Present/None		480/203

RA, rheumatoid arthritis; GIOP, glucocorticoid-induced osteoporosis; GC, glucocorticoid; PSL, prednisolone; SD, standard deviation; IQR, interquartile range.
Data represent mean ± SD or median (25–75 th centiles) or number of patients.

Discussion

This study investigated the prevalence of RA patients requiring GIOP treatment per the 2014 guidelines and identified risk factors associated with lack of treatment in those patients. The results showed that the prevalence of RA patients requiring treatment according to the new JSBMR guidelines was 30.6%; of those, only 70.3% had indeed been treated with some type of osteoporosis medication. Clinic-based care, male sex, and younger age were significant risk factors for lack of treatment.

The prevalence of osteoporosis (OP) was reported to be 2.7 times higher in patients with RA than in a normal control group [13]. Moreover, it was reported that the prevalence of OP was 1.4 times higher in RA patients treated with GCs than in those not treated with GCs [13]. A previous study from France reported that only 22.6% and 27.3% of patients with RA who needed osteoporosis treatment were actually treated, depend-

Table 2 Characteristics of RA patients with treated or untreated GIOP

	Treated	Untreated	*P*-value
Number	480	203	
Male, %	56 (11.7)	82 (40.4)	0.001
Age (years), mean ± SD	76.1 ± 8.4	73.8 ± 8.8	0.001
GC dose (PSL equivalent mg/day), median (IQR)	3 (2.5–5)	3 (2–5)	0.171
Disease duration (months), median (IQR)	151 (76.5–247)	111 (31–223)	0.001
Clinic, %	109 (22.7)	76 (37.4)	0.001

RA, rheumatoid arthritis; GIOP, glucocorticoid-induced osteoporosis; GC, glucocorticoid; PSL, prednisolone; SD, standard deviation; IQR, interquartile range.
Data represent mean ± SD or median (25–75 th centiles) or number of patients.

Table 3 Univariate and multivariate analysis of factors associated with lack of therapeutic intervention for GIOP in RA patients

Variables	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Clinic	2.037	1.427–2.906	0.001	2.481	1.685–3.655	0.001
Male	5.131	3.456–7.619	0.001	5.437	3.601–8.210	0.001
Age	0.969	0.951–0.988	0.015	0.967	0.947–0.987	0.013
Disease duration (months)	0.998	0.997–1.000	0.012	0.999	0.997–1.000	0.078
GC dose (PSL equivalent mg/day)	0.935	0.857–1.021	0.133			

OR, odds ratio; 95% CI, 95% confidence interval.
GIOP, glucocorticoid-induced osteoporosis; GC, glucocorticoid; PSL, prednisolone.

ing on whether they applied the 2014 or 2003 GIOP guidelines [14]. Moreover, compliance with the 2010 Canadian osteoporosis treatment guidelines was low in patients with RA [15]. In Japan, a previous study showed that the compliance rate with the JSBMR 2004 guidelines for GIOP was 23.3%, and that awareness of the management of GIOP was lacking in both physicians and patients [4]. That study also reported that male sex, younger age, and low-dose GC therapy were shown to reduce the compliance rate with the guidelines [4]. In the present study, 70.3% of patients had been treated with some type of anti-osteoporotic medication, and male sex and younger age were identified as risk factors associated with lack of treatment of GIOP. The mean age of the patients with RA in the AORA registry is greater than that of the patients with RA in other registries, such as NinJa and IORRA [8,9]. Some studies have shown that the factors associated with osteoporosis treatment in patients with RA were older age and postmenopausal status [16]. Therefore, one of the reasons for the higher treatment rate in the present study compared to previous reports may have been the inclusion of a larger number of older patients being treated for primary osteoporosis. While postmenopausal women have a higher likelihood of being treated for primary osteoporosis, male patients are less likely to receive treatment, likely due to the low recognition of male osteoporosis [17]. Meanwhile, GCs are used in many diseases for both men and women, including autoimmune disorders, pulmonary diseases, and gastrointestinal diseases. GIOP is characterized by an increased risk of fractures regardless of sex and age. Therefore, recognizing the need for therapeutic intervention for male and younger patients will be essential to increasing the treatment rate for patients with GIOP.

The present study also showed that patients who visited clinics instead of hospitals were less likely to be treated for GIOP. Kirigaya *et al.* reported that factors such as the inability of clinics to perform clinical tests, especially BMD measurements, may explain the lower rate of GIOP treatment in these facilities [4]. However, the new guidelines do not require lumbar vertebral BMD measurements to identify patients who need osteoporosis treatment. Therefore, physicians need to be aware that BMD measurement is not an absolute requirement under the new guidelines.

In GIOP, OP progresses rapidly from the start of GC administration and is dose-related, and the risk of fracture increases before BMD shows a decline [18]. In the present study, the median PSL-equivalent dose of GC was 3 mg/day (range: 2-5 mg/day), which was associated with a score of 0 points for fracture risk based on the new guidelines. However, the period of GC administration is also an important factor associated with fracture risk. EULAR recommendations state that short-term GCs should be considered when physicians initiate or change conventional synthetic disease-modifying antirheumatic drugs, and GCs should be tapered as soon as clinically feasible because of the many risks associated with these agents [19]. Balasubramanian *et al.* reported that patients who discontinued GCs for about 2 to 6 months had about a 30% reduction in fracture risk compared to patients on continuous GCs [20]. Therefore, attempts to decrease the GC dose and shorten the period of GC administration are also considered important to prevent the occurrence of various side effects caused by GCs.

To the best of our knowledge, this is the first report after publication of the new guidelines in 2014 to clarify the prevalence of GC-treated RA patients requiring treatment and to identify the risk factors associated with lack of treatment in those patients. Despite the advent

of new guidelines, the factors related to lack of treatment remained the same.

Several limitations of this study should be acknowledged. First, the presence or absence of fragility fractures and lumbar BMD could not be investigated in all patients. Therefore, some patients with GIOP may not have been included in this study. Second, the 2014 guidelines apply to patients aged 18 years or older who were using or planning to use GCs for more than 3 months; unfortunately, the duration of GC use among patients could not be investigated. Therefore, it is possible that the number of patients who met the treatment criteria for GIOP was overestimated. Third, this was a cross-sectional study; longitudinal studies are needed to determine whether treatment for GIOP should be initiated and whether fractures can be prevented. Fourth, disease activity indices, such as the 28-joint count Disease Activity Score and Steinbrocker's Stage, which may be related to the risk of osteoporosis, could not be investigated. Fifth, data on comorbidities related to GIOP such as diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, hyperuricemia, hyperlipidemia, smoking, and drinking were not collected.

In conclusion, the present study demonstrated that the prevalence of RA patients in the AORA registry requiring osteoporosis treatment per the 2014 guidelines was 30.6%; of these, 70.3% were treated. Male sex, younger age, and clinic- as opposed to hospital-based care were identified as risk factors associated with lack of treatment in patients with RA. Physicians should take care to ensure such patients are treated appropriately.

Acknowledgments. We would like to thank Drs. Toshiaki Aizawa, Nobuhiro Ishizawa, Hiroki Ito, Masakazu Urayama, Masashi Oba, Masaaki Ogino, Yoichi Kataoka, Keiji Kamo, Hiroyuki Kodama, Natsuo Konishi, Norikazu Konno, Tsutomu Sakuraba, Takeshi Sato, Kazuhiro Shoji, Norio Suzuki, Hiroshi Tazawa, Takanori Tomite, Takayuki Tani, Yasuki Tamura, Yoshihiro Tsutsumi, Hidekazu Abe, Hiromi Morita, Kunitaka Yan, Hidetoshi Watanabe, Wataru Watanabe, and Takayuki Yoshikawa of the AORA registry for data collection.

References

1. Weinstein RS: Clinical practice. Glucocorticoid-induced bone disease. New Engl J Med (2011) 365: 62–70.
2. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM and Cooper C: Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum (2003) 48: 3224–3229.
3. Nawata H, Soen S, Takayanagi R, Tanaka I, Takaoka K, Fukunaga M, Matsumoto T, Suzuki Y, Tanaka H, Fujiwara S, Miki T, Segawa A, Nishizawa Y, Seino Y and Subcommittee to Study Diagnostic Criteria for Glucocorticoid-Induced Osteoporosis: Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research. J Bone Miner Metab (2004) 23: 105–109.
4. Kirigaya D, Nakayama T, Ishizaki T, Ikeda S and Satoh T: Management and treatment of osteoporosis in patients receiving long-term glucocorticoid treatment: current status of adherence to clinical guidelines and related factors. Intern Med (2011) 50: 2793–2800.
5. Suzuki Y, Nawata H, Soen S, Fujiwara S, Nakayama H, Tanaka I, Ozono K, Segawa A, Takayanagi R, Tanaka H, Miki T, Masunari N and Tanaka Y: Guidelines on the management and treatment of glucocorticoid-induced osteoporosis of the Japanese Society for Bone and Mineral Research: 2014 update. J Bone Miner Metab (2014) 32: 337–350.
6. Sugimura Y, Miyakoshi N, Miyamoto S, Kasukawa Y, Hongo M and Shimada Y: Prevalence of and factors associated with lumbar spondylolisthesis in patients with rheumatoid arthritis. Mod Rheumatol (2016) 26: 342–346.
7. Kinoshita H, Miyakoshi N, Kashiwagura T, Kasukawa Y, Sugimura Y and Shimada Y: Comparison of the efficacy of denosumab and bisphosphonates for treating secondary osteoporosis in patients with rheumatoid arthritis. Mod Rheumatol (2017) 27: 582–586.
8. Matsumoto T, Nishino J, Izawa N, Naito M, Hirose J, Tanaka S, Yasui T, Saisho K and Tohma S: Trends in Treatment, Outcomes, and Incidence of Orthopedic Surgery in Patients with Rheumatoid Arthritis: An Observational Cohort Study Using the Japanese Nation Databese of Rheumatic Diseases. J Rheumatol (2017) 44: 1575–1582.
9. Yamanaka H, Tanaka E, Nakajima A, Furuya T, Ikari K, Taniguchi A, Inoue E and Harigai M: A large observational cohort study of rheumatoid arthritis, IORRA: Providing context for today's treatment options. Mod Rheumatol (2020) 30: 1–6.
10. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger Jr TA, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL and Hunder GG: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum (1988) 31: 315–324.
11. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Menard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovsky J, Wolfe F and Hawker G: 2010 Rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis (2010) 69: 1580–1588.
12. Murata K and Yano E: Medical statistics for evidence-based medicine with SPBS user's guide. Nankodo Publisher, Tokyo (2002) (in Japanese)
13. Ma CC, Xu SQ, Gong X, Wu Y, Qi S, Liu W and Xu JH: Prevalence and risk factors associated with glucocorticoid-induced osteoporosis in Chinese patients with rheumatoid arthritis. Arch Osteoporosis (2017) 12: 33.

14. Ozen G, Kamen DL, Mikuls TR, England BR, Wolfe F and Michaud K: Trends and determinants of osteoporosis treatment and screening in patients with rheumatoid arthritis compared to osteoarthritis. Arthritis Care Res (2018) 70: 713–723.
15. Malochet-Guinamand S, Lambert C, Gossec L, Soubrier M and Dougados M: Evaluation of the Implementation of Guidelines on the Treatment of Osteoporosis in Patients with Rheumatoid Arthritis. J Rheumatol (2020) 47: 6–14.
16. Sim IeW and Ebeling PR: Treatment of osteoporosis in men with bisphosphonates: rationale and latest evidence. Ther Adv Musculoskelet Dis (2013) 5: 259–267.
17. Compston J (2018) Glucocorticoid-induced osteoporosis: an update 61: 7–16.
18. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K et al.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis (2017) 76: 960–977.
19. Balasubramanian A, Wade SW, Adler RA, Lin CJF, Marcic M, O'Malley CD, Saag K and Curtis JR: Glucocorticoid exposure and fracture risk in patients with new-onset rheumatoid arthritis. Osteoporos Int (2016) 27: 3239–3249.