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Oral steroid decreases the progression of joint destruction of large joints in the lower extremities in rheumatoid arthritis

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Abstract

To identify the risk factors for destruction of large joints in the lower extremities in patients with rheumatoid arthritis (RA) during a 4-year follow-up period in a prospective study.

We enrolled consecutive patients who participated in both 2012 and 2016. Clinical data, disease activity, and types of medication were collected in 2012. Standard anteroposterior radiographs of weight-bearing joints (hips, knees, and ankles) were taken in 2012 and 2016. Radiographic progression was defined as progression in the Larsen grade or the need for joint arthroplasty or arthrodesis. The association between baseline characteristics and the incidence of radiographic progression was statistically assessed.

A total of 213 patient were enrolled, and, after exclusion, 186 patients were analyzed. Sixty 9 patients (37.1%) showed radiographic progression in 1 of the large joints in the lower extremities. Multivariate regression analysis showed that radiographic progression was associated with older age, higher disease activity, and the presence of radiographic destruction at the baseline. The lower dosage of oral prednisolone was a significant risk factor compared with higher dosage when used.

Patients with the risk factors should be followed closely to limit the progression of large joint destruction in the lower extremities.

Abbreviations: ACPA = anti-CCP antibody, ACR = American College of Rheumatology, bDMARD = biological disease-modifying antirheumatic drug, EULAR = the European League Against Rheumatism, HAQ = the Health Assessment Questionnaire, mTSS = modified total Sharp score, MTX = methotrexate, PSL = prednisolone, RA = rheumatoid arthritis, RF = rheumatoid factor, SDAI = the Simple Disease Activity Index.

Keywords: cohort study, corticosteroid, joint destruction, rheumatoid arthritis

1. Introduction

Several major organisations, such as the European League Against Rheumatism (EULAR), recommend the use of methotrexate (MTX), biological disease-modifying antirheumatic drugs (bDMARDs) and the short-term glucocorticoid for the management of RA, including the prevention of joint destruction.[1]

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Written informed consent for this study was obtained from all participating patients.

This study was designed in accordance with the Helsinki declaration and was approved by the Medical Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (E1308).

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However, in most of the major studies, only the destruction of small joints were assessed. The destruction of large joints in the lower extremities is strongly associated with walking disability.[2,3] Better prevention of the destruction of large joints is needed, but the risk factors are unknown. Therefore, we conducted a prospective, longitudinal study with a 4-year follow-up period in the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) cohort from 2012 to 2016.[4]

2. Patients and methods

The inclusion criteria were provision of written informed consent, age ≥ 18 years, and meeting the 1987 American College of Rheumatology (ACR) revised criteria or the 2010 ACR/EULAR criteria for RA. The exclusion criteria were missing data and lack of participation in the second survey in 2016. This study was designed in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Kyoto University Graduate School and Faculty of Medicine before the start of the study.

Clinical and laboratory data included are shown in Table 1 such as age, answers provided in the Health Assessment Questionnaire (HAQ), rheumatoid factor (RF), and anti-CCP antibody (ACPA) levels. We evaluated disease activities using the Simple Disease Activity Index (SDAI). Patients treated with prednisolone (PSL) were classified into 3 groups according to the dosage, <5, 5, and 5 mg/day, according to the tertiles of the entire study group.

Standard anteroposterior, weight-bearing radiographs of large joints in the lower extremities (hips, knees, and ankles) were taken in 2012 and 2016. Structural damage to the joints was assessed according to the Larsen grade. Radiographic progression was defined if the Larsen grade increased by 1 or more grade (progression from grade 0 to 1 was excluded) or a joint had received total joint arthroplasty or arthrodesis. We adopted van der Heijde modified total Sharp score (mTSS) for small joints.

Statistical analysis was performed using JMP Pro, version 13.0.0 (SAS, Institute Inc., Cary, NC, USA). The associations between baseline characteristics and the incidence of radiographic progression were assessed. For univariate analysis, simple logistic regression was used. Multivariate regression models were then created using multiple logistic regression analysis. In the full model, explanatory parameters were selected from variables whose *P*-values were <0.10 in the univariate analysis. In the reduced model, explanatory parameters were selected from parameters that previous reports had shown to be important to the progression of joint destruction in RA.[5–7] A p-value <0.05 was considered to be significant.

3. Results

A total of 213 patients were enrolled in this study. Four patients who did not participate in the 2016 survey, and 23 patients who did not have X-rays in 1 of the investigated joints were excluded; thus, 186 patients were included in the final analyses. The clinical parameters in 2012 are summarized in Table 1. Radiographic progression in any joints in the lower extremities was observed in 69 patients (37.1%). We assessed the association between the initial Larsen grade of each joints and the incidence of radiographic progression. Both in hip and knee joints, higher initial Larsen grade was the risk factor for the radiographic progression ($P < .0001$).

The results of the univariate analysis are shown in Table 2. The presence of radiographic progression in any joint in the lower extremities was significantly associated with older age, higher HAQ and SDAI score, the presence of joint destruction, and others. The difference between patients with PSL <5 and >5 mg/day approached significance ($P = .0587$), but the use of PSL was not significantly associated with the progression of joint destruction ($P = .5504$). The progression of joint destruction was also not significantly associated with the presence of ACPA or RF, or the use or dose of MTX or bDMARDs. In the full model based on the multivariate regression analysis, radiographic progression was significantly associated with older age and higher SDAI score. The difference between patients with PSL <5 mg/day and >5 mg/day was also significant in the full model. In the reduced model, a similar set of factors, including lower dosage of PSL, were significantly associated with the progression of joint destruction. Furthermore, when we divide all 186 patients into 3 groups, 0 mg, <5 mg, and 5 or more mg, the multivariate regression analysis shows that the difference between the latter 2 groups approached nearly significance ($P = .0506$).

Disease duration was significantly longer in patients with PSL than patients without PSL ($P < .05$). Each mean duration was 16.8 years and 14.1 years. However, disease duration was not associated with the dosage of PSL nor the incidence of radiographic progression. In 2012, 81 patients took PSL, and mean dosage was 4.51 mg. In 2016, 56 patients took PSL, and

Table 1

The clinical parameters in 2012.

No. of patients	186	CRP, mean ± SD (min–max) mg/L	7.6 ± 13.9 (0–117)
Age, mean ± SD (min–max) years	62.6 ± 11.1 (32–83)	ESR, mean ± SD (min–max) mm/h	27.1 ± 21.7 (1–95)
Disease duration, mean ± SD (min–max) years	15.3 ± 11.0 (0–48)	SDAI, mean ± SD (min–max)	8.97 ± 6.91 (0.3–40.5)
Female, No. (%)	166 (89.2)	CDAI, mean ± SD (min–max)	8.20 ± 6.30 (0.2–34.8)
BMI, mean ± SD (min–max)	21.5 ± 3.1 (13.9–29.9)	mTSS, mean ± SD (min–max)	128.6 ± 112.1 (0–443)
ACR class, mean ± SD (min–max)	1.99 ± 0.66 (1–4)	bDMARDs use, No. (%)	50 (26.9)
Steinbrocker's stage, mean ± SD (min–max)	3.09 ± 1.04 (1–4)	MTX Use, No. (%)	135 (76.2)
Full HAQ, mean ± SD (min–max)	0.92 ± 0.80 (0–3)	MTX Dosage, mean ± SD (min–max) mg/week	7.29 ± 3.10 (2–20)
TJC 28, mean ± SD (min–max)	1.39 ± 1.86 (0–11)	PSL Use, No. (%)	81 (43.5)
SJC 28, mean ± SD (min–max)	1.48 ± 2.11 (0–12)	PSL Dosage, mean ± SD (min–max) mg/day	4.51 ± 2.81 (0.5–18)
ACPA Positive, No. (%)	158 (84.9)	PSL Dosage No. (%) <5 mg/Day, 5 mg/Day, 5 < mg/Day	36 (19.4), 31 (16.7), 14 (7.5)
RF Positive, No. (%)	156 (83.9)		

ACPA = anti-cyclic citrullinated peptide antibody, *ACR Class* = American College of Rheumatology Class, *bDMARDs* = biological disease-modifying anti-rheumatic drugs, *BMI* = body mass index, *CDAI* = Clinical Disease Activity Index, *CRP* = C-reactive protein, *ESR* = erythrocyte sedimentation rate, *Full HAQ* = Full Health Assessment Questionnaire, *mTSS* = modified Total Sharp Score, *MTX* = methotrexate, *PSL* = prednisolone, *RF* = rheumatoid factor, *SDAI* = Simplified Disease Activity Index, *SJC 28* = 28-swollen joint count, *TJC 28* = 28-tender joint count.

Table 2

Univariate and multivariate regression analyses of factors influencing radiographic progression in any joint in the lower extremities.

	Univariate logistic regression analysis		Multivariate logistic regression analysis (full model)		Multivariate logistic regression analysis (reduced model)	
	Unit OR or OR (95% CI)	*P* value	Unit OR or OR (95% CI)	*P* value	Unit OR or OR (95% CI)	*P* value
Age (years)	1.06 (1.03–1.10)	<.001	1.05 (1.01–1.09)	.005	1.05 (1.01–1.08)	.005
ACR Class	1.75 (1.10–2.80)	.019	0.65 (0.34–1.26)	.198		
Full HAQ	1.77 (1.21–2.59)	.003				
ACPA Positive (yes/no)	1.65 (0.66–4.11)	.285				
RF Positive (yes/no)	0.62 (0.28–1.37)	.235				
No. of destroyed joints in the lower extremities	1.36 (1.14–1.63)	<.001	1.18 (0.93–1.50)	.172	1.22 (1.01–1.49)	.042
mTSS	1.01 (0.99–1.01)	.064	1.01 (0.99–1.01)	.669		
No. of swollen joints in the lower extremities	1.52 (1.00–2.36)	.049				
Swollen of any joint in the lower extremities (yes/no)	2.23 (1.05–4.73)	.037	1.81 (0.74–4.43)	.195		
Ph VAS	1.02 (1.01–1.04)	.011				
ESR	1.02 (1.00–1.03)	.014				
MMP-3	1.01 (1.00–1.01)	.018	1.00 (0.99–1.01)	.138		
SDAI	1.07 (1.02–1.12)	.004	1.07 (1.00–1.13)	.032	1.07 (1.02–1.12)	.008
CDAI	1.07 (1.02–1.12)	.009				
bDMARDs use (yes/no)	0.79 (0.39–1.58)	.499				
MTX use (yes/no)	0.65 (0.33–1.26)	.197				
MTX Dosage	1.00 (0.89–1.12)	.994				
PSL use (yes/no)	1.20 (0.66–2.18)	.550				
PSL Dosage						
<5 mg/Day	Reference		Reference		Reference	
5 mg/Day	0.55 (0.20–1.46)	.230	0.42 (0.14–1.27)	.125	0.47 (0.16–1.33)	.157
5< mg/Day	0.27 (0.05–1.05)	.059	0.18 (0.04–0.89)	.036	0.22 (0.04–0.94)	.040

ACPA=anti-cyclic citrullinated peptide antibody, *ACR*=*Class* American College of Rheumatology Class, *bDMARDs*=biological disease-modifying anti-rheumatic drugs, *CDAI*=Clinical Disease Activity Index, *CI*=Confidence interval, *ESR*=erythrocyte sedimentation rate, *Full HAQ*=Full Health Assessment Questionnaire, *MMP-3*=Matrix Metalloproteinase-3, *mTSS*=modified Total Sharp Score, *MTX*=methotrexate, *OR*=odds ratio, *Ph VAS*=physician's visual analog scale, *PSL*=prednisolone, *RF*=rheumatoid factor, *SDAI*=Simplified Disease Activity Index.

mean dosage was 3.65 mg, so the number of patients and dosage was decreased in 4 years. Eighty 1 patients were divided to 3 groups, patients with PSL dosage increased from 2012 to 2016, equal, and decreased. Each number was 6, 16, and 59 patients. The associations between these groups and the incidence of radiographic progression was not significant.

4. Discussion

This study suggests that a higher SDAI score is a risk factor for radiographic progression as reported in previous studies.[8,9] However, in contrast to previous studies of small joint destruction,[10,11] serological factors such as ACPA were not associated with progression of joint destruction in the large joints. This suggests that the risk factors for joint destruction may differ between large and small joints. Another expected finding was that destruction of joints at baseline was a strong risk factor for further destruction, even in the large joints as reported previously in small studies,[6,12] but that of small joints (mTSS) was not for large joints. The presence of joint destruction in large joints may be partially independent of that in small joints.

A notable finding of this study was that, although the use of PSL was not itself a risk factor, a lower dosage of PSL (<5 mg/day) was a risk factor for radiographic progression. It is previously reported that the combination of PSL with MTX reduces radiographic erosion compared with MTX only in small joints;[13,14] our findings are consistent with their data, but in the large joints, reported for the first time. However, this result would not indicate to recommend the use of PSL in every situation but might indicate that PSL should be used at a sufficient dosage when needed to reduce inflammation quickly. This notion has not been investigated so far and should therefore be carefully tested in studies of the large joints in large cohorts.

Despite several limitations of this study such as the sample size and changes in treatments during the follow-up period, this study showed that older age, higher disease activity score, the presence of destroyed large joints, and lower dosages of oral PSL, when taken, appear to be risk factors for radiographic progression of RA in large joints in the lower extremities. Patients with these risk factors should be followed closely to prevent or limit joint destruction.

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