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ORIGINAL ARTICLE

Evaluating various radiographic methods of shoulder joint damage in patients with rheumatoid arthritis receiving biological disease-modifying antirheumatic drugs

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ABSTRACT

Objectives: This study aims to clarify shoulder joint damage in rheumatoid arthritis patients receiving biological disease-modifying antirheumatic drugs (bDMARDs) and the relationship between joint damage and clinical factors.

Patients and methods: In this retrospective study conducted between April 2005 and December 2008, 36 shoulders in 19 patients (2 males, 17 females; mean age: 58.9 years; range 42 to 75 years) were evaluated at baseline and two years after the initiation of bDMARD therapy with infliximab (n=14) or etanercept (n=5). Standard anteroposterior radiographs of the shoulder joints were taken at baseline and two years after institution of biological therapy. Structural damage in the shoulder joints was assessed using the Larsen scoring method, the medial displacement index (MDI), and the upward migration index (UMI).

Results: There was a significant correlation between MDI, UMI, and Larsen grade before biological therapy. Univariate analysis revealed that the disease activity score 28-count erythrocyte sedimentation rate (ESR) at baseline (odds ratio [OR]: 4.298) was associated with progression of MDI. But multivariate logistic regression revealed that there was no association with the progression of MDI. Univariate analysis revealed that ESR at baseline (OR: 0.967) and matrix metalloproteinase-3 (MMP-3) at baseline (OR: 0.996) were associated with the progression of UMI. Multivariate logistic regression revealed that MMP-3 at baseline (OR: 0.994) was independently associated with the progression of UMI.

Conclusion: Medial displacement index and UMI correlated with the Larsen grade of the shoulder joint strongly and moderately, respectively. This study suggests that MDI and UMI may help to evaluate radiographic progression of damage in shoulder joints in patients on bDMARDs, which is difficult to detect using the Larsen grade.

Keywords: Rheumatoid arthritis, shoulder joint, tumor necrosis factor-alpha.

Shoulder joint involvement is often observed in patients with rheumatoid arthritis (RA), and the majority of patients suffer from varying degrees of shoulder symptoms.[1] In the shoulder joint, the synovial inflammation primarily targets the glenohumeral joint and leads to bony erosions and pain. Such structural damage is common in the shoulder and only a small portion of patients with RA has normal shoulder radiographs throughout the course of their disease.[2] In affected shoulders with bone and cartilage damage, the subacromial bursa is also involved and the rotator cuff may become trapped between the subacromial bursa and glenohumeral joint is gradually impaired.

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Range of motion decreases due to pain and structural damage to cartilage, bone and the rotator cuff, causing further functional disability of the shoulder. In the upper extremities, the shoulder joints play a central role in the physical function of RA,[3] and, thus, detailed evaluation of the shoulder during medical treatment is indispensable.

Recently, biological agents have shown a major impact on the treatment of RA in controlling disease activity, inhibiting joint destruction, and improving functional status.[4] Specifically, tumor necrosis factor (TNF)-blocking therapies with biological disease-modifying antirheumatic drugs (bDMARDs) have been shown to inhibit the progression of damage to the small joints in the hands and feet.[5] Destruction in large joints of the lower extremity, such as hip and knee, is also suppressed by bDMARDs.[6,7] However, their effects in the glenohumeral joint remain to be clarified. Hirooka et al.[8] reported that they devised two radiographic parameters: a medial displacement index (MDI) and an upward migration index (UMI) of the humeral head. They studied the natural course and the possibility of making prognoses about shoulder joint destructions in RA patients using these parameters.

The purpose of our study was two-fold. First, it was to evaluate glenohumeral joint damage using several radiographic parameters. We hypothesized that MDI and UMI were useful parameters to detect minor radiographic changes. In addition, it was to analyze factors related to radiographic progression during bDMARD therapy. We hypothesized that there were several factors such as disease activity in association with radiographic progression. Therefore, in this study, we aimed to clarify shoulder joint damage in RA patients receiving bDMARDs and the relationship between joint damage and clinical factors.

PATIENTS AND METHODS

This study is a retrospective review of consecutive shoulders that received bDMARD therapy between April 2005 and December 2008 in the Faculty of Medicine, University of Toyama. A total of 19 patients (2 males, 17 females; mean age: 58.9 years; 42 to 75 years) were enrolled in this study. All patients fulfilled the American College of Rheumatology 1987 revised criteria for a diagnosis of RA.[9] bDMARD therapy was in accordance with the Japan College of Rheumatology Guidelines.[10,11] Inclusion criteria were active RA with ≥6 swollen joints, ≥6 tender joints, C-reactive protein (CRP) of ≥2.0 mg/dL, and an erythrocyte sedimentation rate (ESR) of ≥28 mm/h. All patients had had an inadequate response to one or more recommended levels of conventional DMARDs. Patients were also required to have white blood cell counts of ≥4,000/mm^3 and peripheral blood lymphocyte counts of ≥1,000/mm^3. In addition, patients were required to be serum negative for interferon-gamma release assay and β-D-glucan to avoid possible opportunistic infections, including tuberculosis and Pneumocystis jirovecii pneumonia. Patients were treated with methotrexate (MTX) and a standard dose of infliximab of 3 mg/kg intravenously at zero, two, and six weeks, and every eight weeks thereafter, or with etanercept at a dose of 25 mg once or twice weekly by subcutaneous injection. The study protocol was approved by the Faculty of Medicine, University of Toyama Ethics Committee (Approval No: 19-11). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Routine laboratory tests, including ESR, CRP, and matrix metalloproteinase-3 (MMP-3), were performed for each patient at baseline and at regular intervals thereafter. As a parameter of disease activity, the Disease Activity Score in 28 joints (DAS28-CRP)[12,13] was used. Clinical response at one year was defined according to the European League Against Rheumatism (EULAR) response criteria based on the DAS28.[14] Body mass index that may influence joint damage[15,16] was also measured at baseline.

Standard anteroposterior radiographs of the shoulder were taken at baseline and two years after initiation of bDMARD therapy. Joints that had already undergone total joint arthroplasty before the initiation of TNF-blocking therapies were excluded from the radiographic analysis. Structural damage to the joints was assessed by two observers according to Larsen et al.[17] using standard reference films. In cases of disagreement, a consensus was reached by the observers. The method of Larsen et al.[17] has reasonable sensitivity and satisfactory intra- and

inter-observer reliability.[18,19] The six grades of the Larsen classification are as follows: Grade 0 (no change), the normal status of the joint; Grade I (slight changes), periarticular soft tissue swelling, osteoporosis, and slight joint space narrowing; Grade II (definite early changes), erosion and joint space narrowing correspond to the standards, erosion is obligatory except in the weight-bearing joints; Grade III (medium destructive changes), erosion and joint space narrowing correspond to the standards; Grade IV (severe destructive changes), erosion and joint space narrowing correspond to the standards; and Grade V (mutilating changes), the original articular surfaces have disappeared, gross bone deformation is present.

In addition to the Larsen grade for large joint evaluation, detailed evaluation of joint spaces including the glenohumeral joint and subacromial space were compared for each set of radiographs from each patient as previously described[8] and as shown in Figure 1. The MDI was obtained by dividing the distance between the center of the humeral head and the glenoid surface (M) by the radius of the humeral head (R). The center of the humeral head was determined using a circle-fitting technique, and then R was measured. The UMI was obtained by dividing the distance between the center of the humeral head and the central point of the subacromial surface (U) by R. Changes in MDI or UMI were defined as the value resulting from subtracting the post-treatment value from the pre-treatment value.

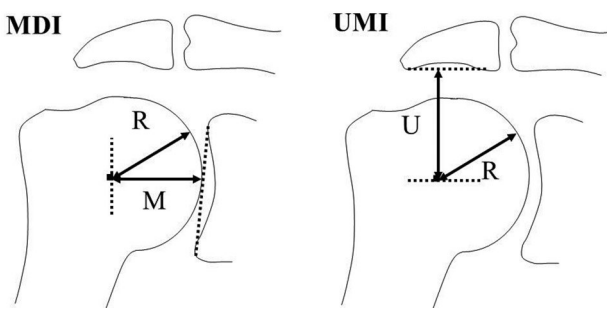

Figure 1. Illustration of measurement methods used in this study.

Left panel: Medial displacement index (MDI); M: Distance between center of humeral head and glenoid surface; R: Radius of humeral head. MDI=M/R. Right panel: Upward migration index (UMI); U: Distance between center of humeral head and central point of subacromial surface. UMI=U/R.

Statistical analysis

Wilcoxon's rank sum test was used for continuous variables and the chi-squared test for categorical variables. The frequency of progression of damage in shoulders was compared between Larsen grades and deterioration of MDI and UMI, using Fisher's exact test. Statistical comparison between shoulders with different grades of destruction was performed using analysis of variance. Multivariate logistic analysis was performed to identify the factors associated with the deterioration of MDI or UMI. Variables were considered for the multivariate models if

Table 1. Baseline characteristics of the patients

	n	%	Mean±SD
Demographics variables			
Age (year)			58.9±9.1
Sex			
Male	2		
Female	17		
Disease characteristics			
Disease duration (year)			15.9±15.3
Stage			
I	1		
II	5		
III	2		
IV	11		
Class			
I	0		
II	11		
III	8		
IV	0		
Larsen grade of each shoulder joint			
0	13		
I	12		
II	3		
III	5		
IV	1		
V	2		
Body mass index (kg/m^2)			22.5±2.5
CRP (mg/dL)			3.98±2.4
ESR (mm/1st h)			78.7±24.4
MMP-3 (ng/mL)			319.2±206.6
DAS28-ESR			5.83±0.76
Concomitant treatment			
Concomitant methotrexate	17	89.5	
Methotrexate dose (mg/week)			6.16±2.6
Concomitant corticosteroids	15	78.9	
Corticosteroid dose (mg/day)			3.33±2.4

Except where indicated otherwise, values are the median (interquartile range). SD: Standard deviation; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MMP-3: Matrix metalloproteinase-3; DAS28: Disease Activity Score 28-joint assessment; MTX: Methotrexate.

Table 2. Radiographic assessment according to Larsen grade, MDI and UMI at baseline

	Number of shoulders before TNF-blocking therapies		MDI (pre)	UMI (pre)
	n	%	Mean±SD	Mean±SD
Larsen grade				
0	13	36.1	1.007±0.069	1.375±0.108
I	12	33.3	1.001±0.019	1.421±0.067
II	3	8.3	0.871±0.027	1.309±0.069
III	5	13.9	0.865±0.038	1.314±0.046
IV	1	2.8	0.682	1.045
V	2	5.6	0.646±0.105	1.111±0.072
Total	36	100	0.945±0.121	1.353±0.131
ANOVA* (p value)			<0.0001	0.0012

*ANOVA: Analysis of variance. p values were analyzed between different Larsen groups. MDI: The medial displacement index; UMI; The upward migration index; SD: Standard deviation.

their univariate p value was <0.05 and two or three variables of fewer p values, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Values of p<0.05 were considered statistically significant. Post hoc power analysis for comparing deterioration of MDI and UMI and no deterioration of MDI and UMI were performed. A minimum sample size recruited into each arm was calculated to detect deterioration of MDI and UMI, with type-I (alpha) error set at 0.05 and type-II (beta) error set at 0.2 (80% power). Standard deviation of MDI and UMI were 0.067 and 0.0977, respectively. The mean difference of deterioration and no deterioration of MDI and UMI were 0.1403 and 0.163, respectively. The calculated effect size of MDI and UMI were 10 and 14, respectively. All analyses were performed using JMP for Windows, version 14.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the baseline characteristics of patients. Most patients (89.5%) received MTX before bDMARD therapy either as

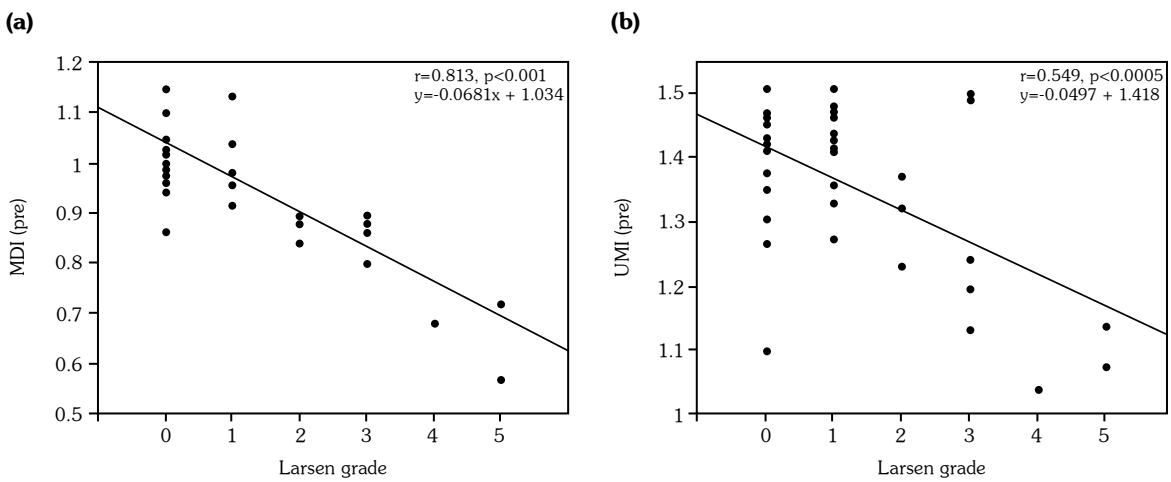

Figure 2. **(a)** Correlation between medial displacement index and Larsen grade pre-biological disease-modifying antirheumatic drug therapy. There was a significant correlation between medial displacement index and Larsen grade (r=0.813, p<0.001). **(b)** Correlation between upward migration index and Larsen grade pre-biological disease-modifying antirheumatic drug therapy. There was a significant correlation between upward migration index and Larsen grade (r=0.549, p=0.0005).

MDI: Medial displacement index; UMI: Upward migration index.

monotherapy or in combination with different conventional DMARDs. A total of 15 patients (78.9%) received corticosteroids, with a mean dose of 3.33 (interquartile range, 2-7) mg/day. Patients had moderate (n=16) or high (n=3) disease activity. Infliximab (n=14) and etanercept (n=5) were administered to patients (including cases that switched from infliximab). A total of 36 glenohumeral joints, excluding joints with preceding surgery, were analyzed for their baseline Larsen grades as follows: Grade 0, 13 joints (36.1%); Grade I, 12 joints (33.3%); Grade II, three joints (8.3%); Grade III, five joints (13.9%); Grade IV, one joint (2.8%); and Grade V, two joints (5.6%).

We compared the values of MDI and UMI among the Larsen grades. Mean values of MDI and UMI were both significantly related to increased Larsen grades pre-bDMARD therapy (Table 2). There was a strong correlation between MDI and Larsen grade at baseline (correlation coefficient: r=0.813, p<0.001) (Figure 2a). Similarly, there was a moderate correlation between UMI and Larsen grade (correlation coefficient: r=0.549, p=0.0005) (Figure 2b). Therefore, both MDI and UMI might be useful markers of radiographic damage similar to the Larsen grading system.

Figure 2a and 2b show the tilt of generalized linear model. For each increase in Larsen grade, MDI decreased by 0.0681 and UMI decreased by 0.0497. In this study, we defined that deterioration of MDI and UMI would result in a negative number after the subtraction of the post-treatment MDI and UMI values from the pre-treatment MDI and UMI values, respectively.

Assessment of radiographs of the 36 glenohumeral joints indicated Larsen grade progression in nine joints (25%) (two joints from Grades 0 to I, one joint of Grade 0 to II, one joint of Grade II to III, three joints of Grade III to IV, one joint of Grade III to V, and one joint of Grade IV to V) (Figure 3a).

Next, we compared MDI and UMI changes pre- and post-bDMARD therapy (Figure 3b and 3c). There was no significant difference between pre- and post-treatment MDI values (p=0.451). Similarly, there was no significant difference between pre- and post-treatment UMI values (p=0.835).

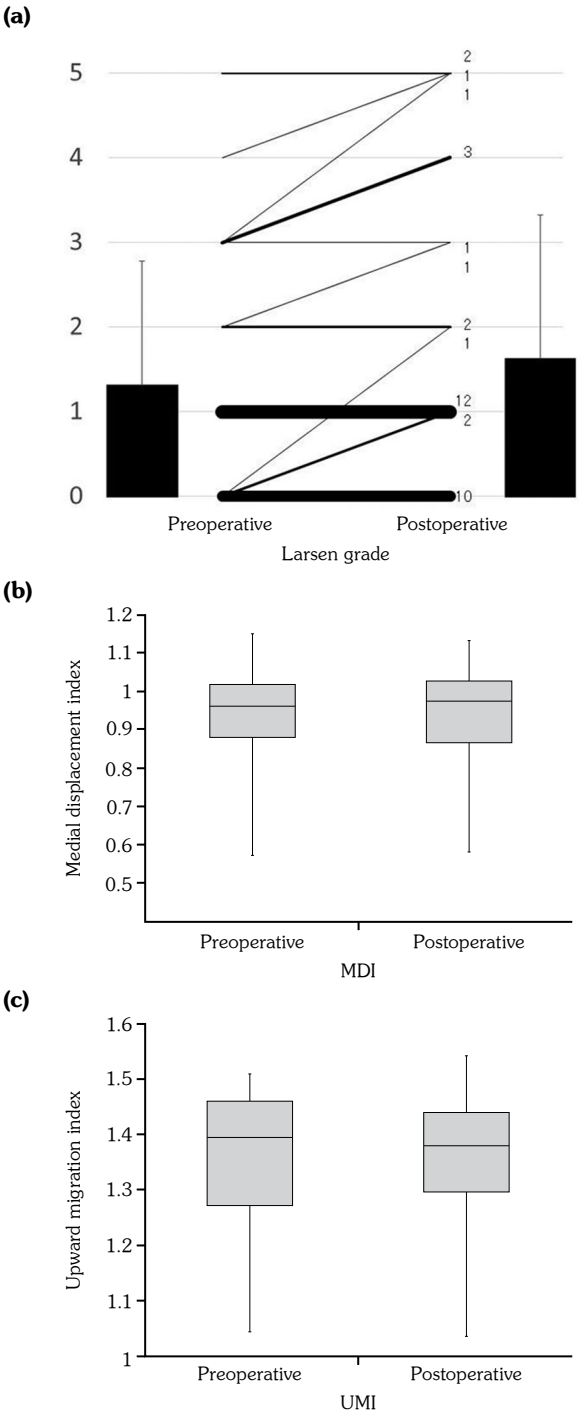

Figure 3. **(a)** Comparison of Larsen grade of pre- and post-biological disease-modifying antirheumatic drug therapy. Line graph presenting Larsen grade of each shoulder. Numbers on right side are shoulders at each grade. Bar graph presents mean and standard deviation of Larsen grade. **(b)** Box plot for medial displacement index changes between pre- and post-treatment. **(c)** Box plot for upward migration index changes between pre- and post-treatment.

MDI: Medial displacement index; UMI: Upward migration index.

Table 3. Logistic analysis of factors associated with deterioration of MDI

	Deterioration of MDI								Univariate			Multivariate		
Variables	n	%	Mean	Range	n	%	Mean	Range	*p*	OR	95% CI	*p*	OR	95% CI
Age (year)			59.0	51.0-66.0			58.0	53.0-66.0	0.797	0.995	0.922-1.072			
Sex									0.407	2.647	0.248-28.24			
Male	1				3									
Female	15				17									
Disease duration (year)			18.0	2.3-20			9.0	2.5-22	0.774	1.008	0.963-1.054			
Stage									0.0303*	1.276	0.667-2.537			
I	2				0									
II	3				8									
III	0				4									
IV	11				8									
Class									0.111	0.333	0.084-1.318			
I	0				0									
II	7				14									
III	9				6									
IV	0				0									
Larsen grade of each shoulder joint									0.045*	1.062	0.663-1.706	0.99	0.997	0.598-1.629
0	3				10									
I	8				4									
II	1				2									
III	4				1									
IV	0				1									
V	0				2									
Body mass index			23.1	21.0-24.4			22.8	21.3-24.7	0.861	0.978	0.743-1.287			
CRP (mg/dL) at baseline			3.65	2.2-5.8			3.15	2.3-4.9	0.434	1.098	0.832-1.482			
CRP (mg/dL) at 1 year of treatment			0.25	0.1-1.0			0.5	0.1-1.0	0.661	1.215	0.714-2.227			
ESR (mm/1st h) at baseline			94	78-102			73	45-99	0.049*	1.031	1.000-1.068	0.049*	1.031	1.000-1.069
ESR (mm/1st h) at 1 year of treatment			39	26-95			36	16-67	0.498	1.01	0.989-1.032			
MMP-3 (ng/mL) at baseline			406.2	151.1-575			266.0	151.1-330.5	0.435	1.001	0.997-1.004			
MMP-3 (ng/mL) at 1 year of treatment			105.1	36.3-220.2			85.3	69.1-153.8	0.591	1.002	0.994-1.011			
DAS28-ESR at baseline			5.75	5.33-7.11			5.42	5.06-5.90	0.17	2.057	0.814-5.832			
DAS28-ESR at 1 year of treatment			4.43	3.03-4.84			4.42	3.36-4.90	0.972	1.073	0.631-1.849			
Concomitant methotrexate	14	87.5			18	90.0			0.772	0.778	0.084-7.145			
Concomitant corticosteroids	11	68.8			16	80.0			0.81	0.55	0.200-2.521			

Except where indicated otherwise, values are the median (interquartile range); MDI: The medial displacement index; OR: Odds ratio; CI: Confidence interval; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MMP-3: Matrix metalloproteinase-3; DAS28: Disease Activity Score 28-joint assessment; MTX: Methotrexate.

Table 4. Logistic analysis of factors associated with deterioration of UMI

Variables	Deterioration of UMI								Univariate			Multivariate		
	Yes (n)	No (%)	Mean	Range	Yes (n)	No (%)	Mean	Range	*p*	OR	95% CI	*p*	OR	95% CI
Age (year)			58.0	52.0-70.0			58.0	51.5-62.0	0.873	1.023	0.950-1.106			
Sex									0.238	3.857	0.439-82.72			
Male	1				3									
Female	18				14									
Disease duration (year)			18.0	2.8-20			8.0	2.2-25.5	0.611	1.002	0.959-1.049			
Stage									0.792	0.887	0.457-1.691			
I	1				1									
II	6				5									
III	3				1									
IV	9				10									
Class									0.955	1.039	0.273-3.989			
I	0				0									
II	11				10									
III	8				7									
IV	0				0									
Larsen grade of each shoulder joint									0.259	0.763	0.453-1.216			
0	6				7									
I	9				3									
II	1				2									
III	3				2									
IV	0				1									
V	0				2									
Body mass index			22.2	21.3-23.4			23.6	21.0-25.1	0.188	0.871	0.647-1.143			
CRP (mg/dL) at baseline			3.5	2.4-6.0			3.2	2.25-4.0	0.332	1.143	0.864-1.591			
CRP (mg/dL) at 1 year of treatment			0.5	0.1-1.1			0.2	0.1-0.6	0.092	1.643	0.900-4.094	0.0416*	2.121	1.023-6.334
ESR (mm/1st h) at baseline			90	68.5-99.8			77	45.8-94.0	0.201	1.017	0.989-1.049			
ESR (mm/1st h) at 1 year of treatment			36	26-95			37	16-46	0.378	1.017	0.995-1.044			
MMP-3 (ng/mL) at baseline			281.9	262-563.2			200.9	125.8-305.9	0.016*	1.005	1.001-1.011	0.0112*	1.005	1.001-1.011
MMP-3 (ng/mL) at 1 year of treatment			103.3	77.0-221.6			89.7	38.7-105.1	0.124	1.008	0.999-1.020			
DAS28-ESR at baseline			5.83	5.4-6.24			5.42	5.02-6.40	0.067	1.674	0.667-4.694	0.37	1.729	0.514-6.202
DAS28-ESR at 1 year of treatment			4.52	3.72-4.9			3.45	2.68-4.89	0.072	1.826	1.025-3.760			
Concomitant methotrexate	17	89.5			15	88.2			0.901	1.113	0.123-10.41			
Concomitant corticosteroids	15	80.0			12	70.6			0.563	1.562	0.341-7.581			

Except where indicated otherwise, values are the median (interquartile range); UMI: The upward migration index; OR: Odds ratio; CI: Confidence interval; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MMP-3: Matrix metalloproteinase-3; DAS28: Disease Activity Score 28-joint assessment; MTX: Methotrexate.

We performed logistic regression analysis to reveal the factors associated with the progression of joint space narrowing, which was given signs of MDI and UMI.

Univariate analysis revealed that Steinbrocker stage (OR: 1.276, 95% CI: 0.667-2.537), Larsen grade at baseline (OR: 1.062, 95% CI: 0.663-1.706), and ESR at baseline (OR: 1.031, 95% CI: 1.000-1.068) were associated with the deterioration of MDI (Table 3). Before multivariate analysis, we checked multicollinearity among these factors using Spearman's rank correlation coefficient. This analysis showed significant correlations between Steinbrocker stage and Larsen grade (p=0.003, r=0.488). We excluded Steinbrocker stage and performed multivariate analysis with Larsen grade and ESR at baseline. Multivariate logistic regression revealed that ESR at baseline was independently associated with the deterioration of MDI (OR: 1.031, 95% CI: 1.000-1.069).

Univariate analysis revealed that MMP-3 at baseline (OR: 1.005, 95% CI: 1.001–1.011) was associated with the deterioration of UMI (Table 4). Next, we included CRP at one year of treatment, MMP-3 at one year of treatment, DAS28-ESR at baseline, and DAS28-ESR at one year of treatment in multivariate analysis. Before multivariate analysis, we checked multicollinearity among these factors using Spearman's rank correlation coefficient. This analysis showed the significant correlations between MMP-3 at one year of treatment and DAS28-ESR at one year of treatment (p=0.015, r=0.425), MMP-3 at one year of treatment and DAS28-ESR at baseline (p=0.027, r=0.392), MMP-3 at one year of treatment and DAS28-ESR at one year of treatment (p=0.015, r=0.425), CRP at one year of treatment and DAS28-ESR at one year of treatment (p<0.001, r=0.670). We excluded MMP-3 at one year of treatment and DAS28-ESR at one year of treatment and performed multivariate analysis with CRP at one year of treatment, MMP-3 at baseline, and DAS28-ESR at baseline. Multivariate logistic regression revealed that CRP at one year of treatment (OR: 2.121, 95% CI: 1.023–6.334) and MMP-3 at baseline (OR: 1.005, 95% CI: 1.001-1.011) were independently associated with the deterioration of UMI.

Receiver operating characteristic (ROC) curves for ESR at baseline and the deterioration of MDI were constructed. The area under the ROC curve (AUC) was 0.698 and cut-off ESR at baseline was 78.0. The sensitivity and specificity of the ESR at baseline were 86.7% and 63.2%, respectively. OR for the deterioration of MDI was 1.031.

The ROC curves for CRP at one year of treatment and MMP-3 at baseline and the deterioration of UMI were constructed. The AUC was 0.661 and cut-off CRP at one year of treatment was 0.400. The sensitivity and specificity of the CRP at one year of treatment were 68.4% and 70.6%, respectively. OR for the deterioration of UMI was 1.643. The AUC was 0.743 and cut-off MM-3 at baseline was 266.0. The sensitivity and specificity of the MMP-3 data were 72.2% and 68.7%, respectively. OR for the deterioration of UMI was 1.005.

DISCUSSION

A report from the Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT) study showed that increases of modified total Sharp scores were inhibited by infliximab administration in comparison with MTX alone. Approximately 50% of patients receiving infliximab showed radiological improvement.[5] Previously, Seki et al.[6] reported that bDMARD therapy could inhibit the progression of weight-bearing joint damage as well as in small joints. However, hip and knee joints with Larsen Grade III or IV damage at baseline showed progression even in patients with a good response to the bDMARD treatment. In the previous work of Matsushita et al.,[7] it was also demonstrated that independent factors associated with progression of damage in the hip and knee were baseline Larsen grade and disease activity at one year after bDMARD therapy. There have been few reports regarding the effects of bDMARD therapy on shoulder joints. In the present study, we observed a similar therapeutic effect on the shoulder joints of RA patients receiving bDMARDs. There were few damaged joints of baseline Larsen Grades 0-II and there was a low rate of progression of Larsen grade after bDMARD therapy was initiated. Therefore, shoulder

joints responded similarly to weight-bearing joints after bDMARD therapy. Thus, it is expected that the progression of shoulder joint destruction can be controlled when damage of the joint is scored as Larsen Graderade 0-II.

Although the most widely used evaluation of the large joints of RA is the Larsen grade, it is not specifically designed for rheumatoid shoulder lesions, and it is often difficult to differentiate among Larsen Grades III-V. Several reports have described the use of the acromiohumeral interval and glenohumeral joint space as an index of deviations of the humeral head.[20-22] However, shoulders are difficult to assess, particularly when severe destruction is present and they can be easily affected by the photographic method such as radiographic amplification and gaps in the photographic direction. Therefore, we also used two indices, MDI and UMI, reported by Hirooka et al.,[8] to evaluate the shoulder joints of RA patients. Similar to Hirooka et al.'s[8] report, our results suggested that MDI and UMI were useful parameters for quantitatively assessing the radiographic progression of shoulder joints in RA patients receiving bDMARD therapy.

Univariate analysis demonstrated that stage, Larsen grade, and ESR at baseline were higher in patients with MDI deterioration pre-treatment. Moreover, ESR at baseline was correlated with the deterioration of MDI at multivariate analysis. CRP at one year of treatment and MMP-3 at baseline were higher in the patients with pre-treatment UMI deterioration. On the other hand, MMP-3 might have statistical significance in UMI at pre- and post-bDMARD therapy. MMP-3 is known to be a major cartilage-degrading enzyme, which is produced by synovial lining cells and chondrocytes themselves.[23,24] It is reported that levels of MMP-1 and MMP-3 in knee synovial fluid were significantly higher in RA than in osteroarthrits.[25] Yoshihara et al.[26] reported that levels of MMP-1, MMP-3, tissue inhibitor of metalloproteinase-1, and glycosaminoglycan in synovial fluid from patients with full-thickness tears of the rotator cuff appeared to be higher than those with partial-thickness tears. Therefore, MMP-3 might be a significant factor influencing UMI deterioration that might be affected by a rotator cuff tear. In the previous work of Matsushita et al.,[7] it was reported that the progression of damage in hip and knee joints was influenced by baseline Larsen grade. On the other hand, baseline Larsen grade was not affected by the deterioration of MDI and UMI in multivariate analysis of non-weight-bearing joints. We speculate that the shoulder joint is less susceptible to mechanical stress.

In our results, radiographic progression of shoulder joints was 9 of 36 (25%) by Larsen grade. But in detail, there was no significant difference between pre- and post-treatment MDI values. Moreover, there was no significant difference between pre- and post-treatment UMI values. Matsushita et al.[7] reported that radiographic evidence of damage progression by Larsen grade was present in 11.5%-15.9% of hip, knee, ankle, and subtalar joints at one-three years after bDMARDs therapy. There might be some difference of effectiveness of joint damage between shoulder joints and weight-bearing joints after bDMARDs therapy.

Lehtinen et al.[27] reported that upper migration of the humeral head slightly precedes medial migration. In addition, the upward migration of the humeral head might rapidly progress when it is accompanied by a rotator cuff tear due to inflammation, even in the presence of minimal joint destruction.[28] Weiner and Macnab[20] examined 59 shoulders with surgically detected rotator cuff tears and found that half of these patients had a subacromial space <6 mm, compared with no values <7 mm in 60 normal shoulders. In this study, we observed subacromial space narrowing (<7 mm) in seven shoulders. Moreover, there were only two shoulders with 6 mm of subacromial space in joints of Larsen Grade 0-II. We should consider the presence of a rotator cuff tear if progression of UMI is observed without good clinical response as assessed by the EULAR criteria. According to our univariate analysis, DAS28-ESR at baseline and one year of treatment was not significantly different between deterioration and no deterioration of MDI and UMI.

The present study has several limitations. First, the current results were obtained from a small number of patients treated with two types of bDMARDs at a single center. Moreover, a small number of joints with deterioration may decrease the reliability of the results of the multivariate analysis. Second, we did not analyze radiographic changes of shoulder joints in patients without

bDMARD therapy. Nevertheless, the data from this study should be useful for understanding the effects and limits of bDMARD therapy on shoulder joints with different degrees of baseline radiographic damage. In the future, the relationship of the change of MDI and UMI and the deterioration of shoulder destruction should be revealed and the difference of MDI and UMI according to shoulder destruction pattern.

In conclusion, both MDI and UMI were strongly and moderately correlated with Larsen grade of the shoulder joint, respectively. Our results showed that the parameters of MDI and UMI can be easily used to detect minor radiographic changes, which are hard to detect using the Larsen grade. Multivariate logistic regression revealed that ESR at baseline was independently associated with the progression of MDI. Multivariate logistic regression revealed that MMP-3 at baseline and CRP at one year of treatment were independently associated with the progression of UMI.

Declaration of conflicting interests

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