Table 5. Improvement of inflammatory indices after 12 weeks of treatment and the observed characteristics in 3 groups of different radiological progression.

	Radiological Progression		
	≥ 75th Percentile†	75–25th Percentile	≤ 25th Percentile
Improvement of core set at 12 weeks			
No. cases	14	26	15
Swollen joint count			
Basal	12.2 ± 6.9	9.4 ± 6.6	8.9 ± 3.9
At 12 weeks	9.6 ± 6.5**	4.7 ± 4.3	4.3 ± 3.3
% decrease††	21.6	50.6	51.7
CRP			
Basal	6.0 ± 2.9*	4.4 ± 4.5	1.8 ± 2.1**
At 12 weeks	5.5 ± 3.4**	3.1 ± 3.5	0.7 ± 0.9**
% decrease††	8.8	28.2	62.6
Patient's estimation of pain			
Basal	70.4 ± 22.4	69.5 ± 25.1	57.2 ± 23.1#
At 12 weeks	59.0 ± 26.2**	42.3 ± 21.5	26.0 ± 16.5**
% decrease††	16.1	39.2	54.5
Characteristics of 3 groups			
Initial treatment (MTX, BUC, MTX+BUC, respectively)	5, 7, 2	11, 6, 9	3, 7, 5
No. cases, initial DMARD regimens changed (%)†††	8 (57.1)**	6 (23.1)	1 (6.7)*
Total Sharp score at start	24.9 ± 15.0#	19.8 ± 16.0	10.9 ± 8.49*
Increase of total Sharp score during 96 weeks	60.0 ± 28.1***	17.3 ± 7.4	3.12 ± 3.12***
HLA-DRB1*0405-positive, %	85.7#	61.5	53.3
RF-positive, %	100.0	92.3	80.0
Anti-CCP antibody-positive, %	90.0	95.7	80.0

† Progression of articular destruction during 96 weeks is greater than the 75th percentile of the cohort. †† Percentage decrease from mean of initial values to mean of 12 week values. ††† Regimen was changed when ACR20 was not achieved after 24 weeks. # $p < 0.1$ vs cases other than this group; * $p < 0.05$ vs cases other than this group; ** $p < 0.01$ vs cases other than this group; *** $p < 0.0001$ vs cases other than this group.

Table 6. Time courses of CRP levels and DAS28 in 3 groups of different radiological progression.

	No. Cases	0 Week	12 Weeks	24 Weeks	48 Weeks	72 Weeks	96 Weeks
Serum CRP							
≥ 75 percentile group †	14	5.99 ± 2.93*	5.46 ± 3.37**	5.24 ± 3.65***	3.75 ± 2.74***	2.03 ± 2.21*	1.00 ± 0.85
75–25 percentile group	26	4.36 ± 4.45	3.13 ± 3.53	1.28 ± 1.21	1.40 ± 1.58	1.21 ± 1.34	0.72 ± 0.83
≤ 25 percentile group††	15	1.84 ± 2.09**	0.69 ± 0.92**	0.55 ± 1.16**	0.81 ± 1.53*	0.43 ± 0.61*	0.50 ± 0.84*
DAS28-4 (CRP)							
≥ 75 percentile group†	14	5.30 ± 0.95*	4.72 ± 0.91#	4.00 ± 1.06***	3.75 ± 0.97***	3.10 ± 1.45*	2.31 ± 0.61
75–25 percentile group	26	4.72 ± 0.86	3.66 ± 0.92	2.92 ± 0.86	2.73 ± 1.08	2.47 ± 1.18	2.26 ± 1.08
≤ 25 percentile group††	15	4.41 ± 0.80	2.96 ± 0.85**	2.35 ± 0.94**	2.30 ± 0.90*	1.62 ± 0.84**	1.43 ± 0.56**

† Cases showed radiological progression greater than 75 percentile of the cohort. †† Cases showed radiological progression less than 25 percentile of the cohort. * $p < 0.05$ vs cases of the other 2 groups; ** $p < 0.01$ vs cases of the other 2 groups; *** $p < 0.001$ vs cases of the other 2 groups; # $p < 0.0001$ vs cases of the other 2 groups.

from the MHAQ, correlated strongly with the progression of articular destruction.

It is important, however, to be able to anticipate bone destruction at an early stage. Patients with higher DAS28 scores at Week 14 showed greater progression of joint damage from baseline to Week 54 than those with lower DAS28 scores[1]. In this study, the initial values of a few measures correlated significantly with the progression of articular destruction, whereas most measures correlated strongly after 12 weeks of treatment. The levels of inflammatory markers measured after 12 weeks of treatment would be influenced by the therapeutic effect of DMARD administered and patients' responsiveness to DMARD.

The correlation coefficients between the ACR core set measures and the DAS28 at 12 weeks' treatment and the progress of articular destruction were similar to those of the corresponding mean values over 96 weeks. Multiple linear regression analysis of initial values yielded a correlation coefficient of 0.548 for the progression of articular destruction (data not shown), whereas values after 12 weeks of

treatment yielded a higher correlation coefficient of 0.711, about the same as that obtained from the mean values over the 96 weeks' study period. These results indicate that measures assessed after 12 weeks of DMARD therapy can predict the progression of articular destruction 2 years later as well as mean values over the entire 2-year period.

The predicted value of 32.06 for articular destruction obtained by multiple regression analysis of the ACR core set measures at 12 weeks' treatment was used as the cutoff point of ROC analysis that could select patients whose articular destruction would be greater than the 75th percentile of the cohort with a sensitivity and specificity around 80%. This patient group may be considered candidates for a change of nonbiologic DMARD therapy, or for treatment with biologic DMARD. On the other hand, ROC analysis with a cutoff point of 17.68 could select patients with minimal articular destruction, less than the 25th percentile of the cohort, with sensitivity and specificity of nearly 80%. These patients would not require any changes in their DMARD therapy.

The decision to change initial RA treatment is usually 3 months after start of treatment[4,9]. Our findings support the clinical status quo that one considers changes in DMARD therapy 3 months after initiation of therapy from the viewpoint of articular destruction 2 years later.

In this study, 3 kinds of treatment were randomly allocated for patients studied, who were divided into 3 groups according to radiological progression during 96 weeks (Tables 5 and 6). In patients with radiological progression greater than the 75th percentile of the cohort, clinical activity was not definitely high at commencement, but responses to treatment were small at 12 weeks. Moreover, a relatively high level of clinical activity continued thereafter in these patients, although most of the patients changed their initial DMARD because of not achieving ACR20. In contrast, patients whose radiological progression was less than the 25th percentile of the cohort showed good response at 12 weeks, and continued with low clinical activity thereafter, while DMARD regimens were rarely changed because of insufficient effectiveness.

Although 3 DMARD regimens were allocated randomly and the distribution of initial DMARD regimens was not significantly different between the 3 groups, clinical activity at 12 weeks and responses to treatment at 12 weeks showed definite differences between the groups. The different clinical activities observed at 12 weeks in the 3 groups continued thereafter.

The question is, what caused differences in responsiveness to DMARD treatment at 12 weeks and in different continuing activity thereafter in the 3 groups of patients. HLA shared-epitope, RF, and anti-CCP antibody positivity may be involved. High total Sharp score at commencement may also be important, although it is not clear what factors influence this phenomenon. There may still be other unknown prognostic factors that result in the difference in treatment responses and clinical activities thereafter.

HLA-DRB1*0405 positivity was found to be common in Japanese patients with RA[28,29]. Wakitani, *et al* reported that the HLA-DRB1*0405 genotype was more common in patients in the more erosive subset and the most erosive subset with mutilating disease than in the least erosive subset[28]. In our study, the progression of articular destruction, determined by Sharp's method modified by van der Heijde, was more rapid in HLA-DRB1*0405-positive or HLA shared-epitope-positive than in the respectively negative patients.

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