Clinical Activity After 12 Weeks of Treatment with Nonbiologics in Early Rheumatoid Arthritis May Predict Articular Destruction 2 Years Later

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ABSTRACT. ***Objective.*** To investigate earlier prediction of future articular destruction in patients with early rheumatoid arthritis (RA).

Methods. We randomly allocated patients with RA with disease duration < 2 years to different nonbiologic disease modifying antirheumatic drug (DMARD) therapies in a double-blind trial. Progression of articular destruction over the 96-week treatment period was assessed using the modified Sharp method.

Results. Progression of articular destruction correlated more strongly with the American College of Rheumatology (ACR) core set measures after 12 weeks of treatment than with pretreatment values. Multiple regression analysis of data after 12 weeks yielded a correlation coefficient of 0.711. The sensitivity and specificity to predict articular destruction over the 75th percentile of the cohort were 78.6% and 84.6%, respectively. Patients who showed articular destruction over the 75th percentile of the cohort had low response to treatment at 12 weeks, and continued to have high clinical disease activity thereafter. Contrasting data were found in patients with slow progression of articular destruction.

Conclusion. In patients with early RA, ACR core set measures after 12 weeks of nonbiologic DMARD treatment may predict articular destruction 2 years later. Low response to treatment at 12 weeks and continuing high disease activity thereafter were found in patients with rapid radiological progression. These data can be used to determine the appropriateness of treatment at 12 weeks and aid the decision to introduce biologic DMARD. (J Rheumatol First Release March 1 2010; doi:10.3899/ jrheum.090776)

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The usefulness of biologic disease-modifying antirheumatic drug (DMARD) therapy is well known in the treatment of rheumatoid arthritis (RA), and in particular the effects in suppressing articular destruction are revolutionary[1-3]. These therapies are expensive, however, and sometimes cause severe adverse reactions. It is necessary to select those patients who will benefit most from the treatment.

In general, treatment commences with nonbiologic DMARD, and biologic DMARD are introduced when disease activity cannot be fully controlled, progression of articular destruction is rapid, or prognosis is otherwise poor[4,5]. Conversely, patients with a rather benign disease course would prefer treatment without biologic DMARD in order to avoid the potential adverse reactions and added expense.

It has been reported that rheumatoid factor (RF) positivity[1,6-12], anticyclic citrullinated peptide (CCP) antibody positivity[10-14], presence of HLA-DRB1 genes for shared epitope[7,9,12,14,15], and female sex[16] are poor prognostic factors for articular destructions in patients with early RA. Other prognostic factors include indicators of disease activity, such as swollen joint count[12], serum C-reactive protein (CRP)[13], and erythrocyte sedimentation rate (ESR)[7,12]. The averaged values of clinical activities over an observation period correlated significantly with the progression of articular destruction[17,18]. However, it is important to be able to anticipate bone destruction at an early stage, rather than depending on mean values over a longer period.

We conducted a randomized double-blind controlled study evaluating prognostic factors, including pretreatment of clinical disease activity and treatment at 12-week intervals thereafter, with the aim of determining the measures that better and earlier predict the progression of articular destruction over 96 weeks of treatment.

MATERIALS AND METHODS

We conducted a double-blind controlled trial of the efficacy and safety of methotrexate (MTX) monotherapy 8 mg/week, bucillamine monotherapy 200 mg/day (BUC; with molecular structure similar to that of D-penicillamine[19]), and MTX and BUC combination therapy for 96 weeks[20]. At the same time, we investigated prognostic factors for the progression of articular destruction. Because the dosage of MTX, 8 mg per week at most, is set by official regulation in Japan, the initial dosage was determined accordingly.

We enrolled 55 patients who fulfilled the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA[21], with symptoms for < 2 years. The Institutional Review Board of St. Marianna Medical College approved the study protocol, and all participants provided informed consent at the time of enrollment. All patients had a tender joint count of at least 6 out of 48 joints and a swollen joint count of at least 3 of 46 joints, and either serum CRP ≥ 1.0 mg/dl or ESR ≥ 30 mm/h. All subjects had taken no DMARD previously, and were receiving a corticosteroid dosage ≤ 7.5 mg/day prednisolone equivalent.

The study was conducted at 15 participating institutions, using a double-dummy double-blind method. The following factors were assessed at 12-week intervals: tender joint count, swollen joint count, patient's pain estimation using a visual analog scale (VAS), patient's global assessment of disease activity using a VAS, physician's overall assessment of disease activity by VAS, the modified Health Assessment Questionnaire (MHAQ)[22], ESR using the Westergren method, and serum CRP.

HLA-DRB1 typing was done using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method (SRL Inc., Tokyo, Japan). Anti-CCP antibody was assayed by MBL Co., Ltd. (Nagoya, Japan).

The initially allocated DMARD could be changed after 24 weeks if an ACR20 response was not achieved, and DMARD could be changed if adverse reactions did not permit continuation. Subsequent treatment was at the discretion of the treating physician, including the dose of MTX being increased more than 8 mg per week.

Articular destruction was evaluated using Sharp's method modified by van der Heijde[23], scoring plain radiographs of both hands taken at commencement of treatment and after 96 weeks' treatment simultaneously, with the dates concealed. The total Sharp score, the erosion score, and the joint space narrowing score were the mean of scores determined independently by 3 rheumatologists (YI, NH, and HY).

We examined the relationships between the ACR core criteria measures[24] and the increase in the total Sharp score during 96 weeks using simple and multiple linear regression analyses. We used stepwise methods to determine a multivariate model. We used the StatView statistical analysis software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Findings at the start of the study in the 55 patients are shown in Table 1. The mean duration of disease was 9.2 months. The mean serum CRP was 4.09 mg/dl and the mean DAS28 4.78. The mean increase in total Sharp score during the 96-week study period was 24.2 ± SD 26.4; median and 25th and 75th percentiles were 16.0, 6.3, and 30.1, respectively.

The mean increase in total Sharp score was more than twice as rapid in patients positive for HLA-DRB1*0405 or with shared epitope than in patients who were negative ($p = 0.034$, $p = 0.037$, respectively; Table 2). Progression of articular destruction in patients positive for RF and positive for anti-CCP antibody was also more than twice as rapid as in the corresponding negative patients, although the differences were not statistically significant.

Simple linear regression analysis of laboratory data and radiographic findings, other than ACR core set measures, at enrollment and the progression of articular destruction during 96 weeks were studied. The initial total Sharp score (correlation coefficient $R = 0.382$, $p = 0.0004$), erosion score ($R = 0.363$, $p = 0.007$), joint space narrowing score ($R = 0.327$, $p = 0.015$), and serum matrix metalloproteinase (MMP-3) levels ($R = 0.327$, $p = 0.022$) correlated significantly with the progression of articular destruction, but no significant correlation was seen with the RF titer (R =

Table 1. Characteristics of study patients at enrollment.

Characteristics	Mean ± SD or %
Age, yrs	51.2 ± 12.0
Female, %	78.2
Duration of joint symptoms before study, mo	9.2 ± 5.1
No. of tender joints (0–48)*	14.4 ± 8.8
No. of swollen joints (0–46)*	10.0 ± 6.1
MHAQ (0–3)*	0.76 ± 0.40
Pain estimation by patients (0–100)*	66.4 ± 24.2
Global assessment of disease activity by patient (0–100)*	67.0 ± 24.3
Global assessment of disease activity by physician (0–100)*	66.4 ± 18.4
ESR, mm/h	68.7 ± 32.2
CRP, mg/dl	4.09 ± 3.84
MMP-3, ng/ml	280 ± 297
DAS28-4 (CRP)	4.78 ± 0.91
Total Sharp score, mean ± SD, median, 25th, 75th percentile	18.7 ± 14.8 13.3, 6.9, 27.9
Positive rheumatoid factor, % (> 20 IU/ml)**	90.9
Positive anti-CCP antibody, % (≥ 4.5 U/ml)**	89.6
Positive antinuclear antibody, % (≥ 40)**	60.0
HLA-DRB1*0405+, %	65.5
HLA shared epitope, %†	74.5
Corticosteroid therapy, %	23.6
Dose (prednisolone equivalent), mg/day	4.7 ± 1.7
Treatment: MTX/BUC/combination	19/20/16

* Ranges of possible values, ** Values that are considered positive. † includes HLA-DRB1*0405+, 0101+, and 0401+.

Table 2. Patients' characteristics and increase in total Sharp score over 96 week study period.

Characteristic	+/–	Increase in Total Sharp Score, mean ± SD +	–	p
HLA-DRB1*0405	36/19	29.7 ± 30.3	14.0 ± 11.4	0.034
HLA-DRB1 shared-epitope*	41/14	28.6 ± 28.7	11.7 ± 10.4	0.037
Rheumatoid factor-positive	50/5	25.7 ± 27.1	10.3 ± 9.6	0.216
Anti-CCP antibody-positive	43/5	23.9 ± 27.2	10.9 ± 13.5	0.304
Female/male	43/12	27.1 ± 28.8	14.2 ± 9.1	0.136
Age > 52 yrs	28/27	26.3 ± 31.2	27.3 ± 25.6	0.570

* Includes HLA-DRB1*0405+, 0101+, 0401+.

0.060, p = 0.661) or anti-CCP antibody titer (R = 0.069, p = 0.641).

Table 3 shows the correlation coefficients between the ACR core set measures, at pretreatment and at 12 and 24-week intervals, and the increase in the total Sharp score over 96 weeks' treatment. Of the core set measures evaluated at baseline, only CRP levels and the swollen joint count showed significant correlation. However, high correlation coefficients around 0.5 were seen for many core set measures and for Disease Activity Score 28 [DAS28-4(CRP); http://www.das-score.nl][25] after 12 weeks of treatment. The mean values of many measures over the 96-week period yielded high correlation coefficients > 0.5.

As shown in the upper part of Table 4, "Articular destruction A," the initial total Sharp score (b1), swollen joint count at 12 weeks treatment (b2), CRP at 12 weeks (b3), and pain estimation by patients at 12 weeks (b4) were all significantly and independently involved in the multiple linear regression model. The predicted value, $y = -13.097 + 0.590 \times b1 + 1.365 \times b2 + 1.761 \times b3 + 0.308 \times b4$, correlated well with the actual progression of articular destruction ($R = 0.711$, $p < 0.0001$). With $R^2 = 0.505$, this regression model was able to explain more than 50% of the progression of articular destruction. Multivariate logistic regression analysis with the core set measures at 12 weeks of treatment and the dichotomous variables, such as positivity of HLA shared-epitope alleles, RF positivity, and anti-CCP antibody positivity, failed to yield higher correlation coefficients than linear regression analysis (data not shown). The results of multiple linear regression analysis with the initial total Sharp score and the mean values of measures over 96 weeks as independent variables are shown in the lower part of Table 4, "Articular destruction B." The predicted values correlated well with the progression of articular destruction ($R = 0.728$, $p < 0.0001$).

The sensitivity and specificity of the prediction of articular destruction greater than the 75th percentile of the cohort were calculated by receiver-operating characteristic (ROC) curve analysis, where the predicted values of the multiple regression model at 12 weeks were used as cutoff points. The sensitivity and specificity with a cutoff of 32.06 were 78.6% and 84.6%, respectively. The sensitivity and specificity for the prediction of articular destruction less than the 25th percentile of the cohort were 78.6% and 76.9%, respectively, where the cutoff was 17.68.

In Table 5, patients are divided into 3 groups, whose progression of articular destruction over 96 weeks was greater than 75th percentile, between 75th and 25th percentiles, and less than 25th percentile of the cohort. The mean swollen joint count, serum CRP level, and pain estimation by patients, which were selected as independent variables in the multiple regression analysis, in the 3 patient groups at baseline and after 12 weeks treatment are given in Table 5. The percentage decrease from the mean of initial values to the mean of 12-weeks values ranged from 8.8% to 21.6%, 28.2% to 50.6%, and 51.7% to 62.6%, respectively.

Differences of distribution of initial DMARD treatments among the 3 groups were not statistically significant. Patients whose DMARD regimens were changed because of insufficient effectiveness as defined above were 57.1%, 23.1%, and 6.7% of patients in the respective groups. DMARD regimens were changed between Weeks 24 and 60 (mean 34.4 ± 15.0 weeks) to MTX with dosage up to 12.5 mg per week in 6 cases, to MTX + BUC combination therapy in 5, to sulfasalazine in 2, and others. Total Sharp score at start and HLA-DRB1*0408 positivity tended to be higher in the group above the 75th percentile.

Table 3. Correlation coefficients between ACR core set measures and DAS28 determined at 12 to 24 week intervals and means of these variables over the 96 week period, and the increase in total Sharp score over 96 weeks.

	Initial	12 Weeks	24 Weeks	48 Weeks	72 Weeks	96 Weeks	Mean[#]
CRP	0.292*	0.477***	0.562***	0.521***	0.479***	0.227	0.573***
ESR	0.235	0.491***	0.402**	0.350*	0.055	0.028	0.380**
MHAQ	0.138	0.183	0.210	0.250	0.246	0.005	0.272
Patients' pain estimation[†]	0.163	0.521***	0.428**	0.405**	0.472**	0.025	0.531***
Patients' global assessment[††]	0.152	0.500***	0.470***	0.382**	0.563***	0.049	0.554***
Swollen joint count	0.279*	0.434**	0.411**	0.518***	0.266	0.214	0.523***
Tender joint count	0.085	0.257	0.149	0.202	0.240	0.031	0.275*
Physicians' global assessment[†††]	0.253	0.449***	0.478***	0.453***	0.419**	0.101	0.524***
DAS28-(CRP)	0.384**	0.592***	0.610***	0.538***	0.447**	0.293*	0.618***

[†] Patients' estimation of pain on visual analog scale (VAS). [††] Patients' global assessment of disease activity on VAS. [†††] Physicians' global assessment of disease activity on VAS. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. [#] Mean of values determined every 12 weeks over 96 week treatment period.

Table 4. Multiple linear regression analysis of prognostic factors for articular destruction.

Dependent Variable	Independent Variable	Regression Coefficient	Standardized Regression Coefficient	p
Articular destruction A*			0.711***	< 0.0001
	Constant	–13.097		0.0455
	Initial total Sharp score	0.590	0.332	0.0032
	Swollen joint count after 12 wks	1.365	0.278	0.0213
	CRP after 12 wks	1.761	0.228	0.0491
	Patients' pain after 12 wks[†]	0.308	0.283	0.0229
Articular destruction B**			0.728***	< 0.0001
	Constant	–11.902		0.0383
	Initial total Sharp score	0.477	0.272	0.0120
	Mean swollen joint count[††]	3.521	0.407	0.0002
	Mean CRP[††]	4.837	0.354	0.0021

* Determined by multiple linear regression analysis of relationship between initial total Sharp score and the ACR core set measure after 12 weeks' treatment and the progression of articular destruction. ** Determined by multiple linear regression analysis with the initial total Sharp score and the mean values of measures over the 96 week study period as independent variables. *** Multiple regression coefficient. [†] Patients' pain estimation after 12 weeks. [††] Mean of values determined every 12 weeks for 96 weeks.

As shown in Table 6, the means of both serum CRP levels and DAS28 of the group above the 75th percentile showed definitely higher values than those of patients in the other groups at 12 weeks, and continued at higher values thereafter to 72 weeks. Contrary results were observed in CRP and DAS28 of the group under the 25th percentile.

DISCUSSION

If RA is considered to be an aggregation of different disease types, then RF positivity and anti-CCP antibody positivity denote a patient group with typical disease. A patient group possessing a genetic predisposition in the HLA shared-epitope alleles can also be considered a representative group. The degree of articular destruction seen on plain radiographs at the commencement of observation has been reported to correlate well with the degree of articular destruction one or several years later[7-10,12]. This may indicate the presence of a patient group with rapid articular destruction, or another core group of RA. Other proposed factors include female sex[16] and advanced age[9,10].

In addition to these prognostic factors that do not change during the course of treatment, the connection between various inflammatory markers and articular destruction is well known. Initial levels of inflammatory markers that correlate significantly with the progression of bone destruction are ESR[7,12,16], CRP[13], MMP-3[26], swollen joint count[1,12], patient's global health assessment[8], and grip strength[12]. However, it has also been reported that initial level of CRP[27] or ESR[9] did not correlate with articular destruction.

The time-averaged DAS and CRP over 1 to 5 years were also reported to correlate significantly with changes in the Sharp score[2,17,18]. In our study, mean values over the 96 weeks' study period of all ACR core set measures, apart

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.

REFERENCES

1. Smolen JS, van der Heijde DM, St. Clair EW, Emery P, Bathon JM, Keystone E, et al. Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) Study Group. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum 2006;54:702-10.
2. Landewe R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis Rheum 2006;54:3119-25.
3. Lipsky PE, van der Heijde DM, St. Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594-602.
4. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002;46:328-46.
5. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Care Res 2008;59:762-84.
6. Brennan P, Harrison B, Barrett E, Chakravarty K, Scott D, Silman A, et al. A simple algorithm to predict the development of radiological erosions in patients with early rheumatoid arthritis: prospective cohort study. BMJ 1996;313:471-6.
7. Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. Arthritis Rheum 2001;44:1736-43.
8. Guillemin F, Gerard N, van Leeuwen M, Smedstad LM, Kvien TK, van den Heuvel W; EURIDISS Group. Prognostic factors for joint destruction in rheumatoid arthritis: a prospective longitudinal study of 318 patients. J Rheumatol 2003;30:2585-9.
9. Goronzy JJ, Matteson EL, Fulbright JW, Warrington KJ, Chang-Miller A, Hunder GG, et al. Prognostic markers of radiographic progression in early rheumatoid arthritis. Arthritis Rheum 2004;50:43-54.
10. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B; BARFOT Study Group. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63:1090-5.
11. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, Schreuder GM, Ewals JA, Terwiel JP, et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1,

rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis Rheum 2008;58:1293-8.
12. Dixey J, Solymossy C, Young A; Early RA Study. Is it possible to predict radiological damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the Early RA Study (ERAS). J Rheumatol 2004;31 Suppl 69:48-54.
13. Lindqvist E, Eberhardt K, Bendtzen K, Heinegard D, Saxne T. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005;64:196-201.
14. Quinn MA, Gough AK, Green MJ, Devlin J, Hensor EM, Greenstein A, et al. Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. Rheumatology 2006;45:478-80.
15. Listing J, Rau R, Muller B, Alten R, Gromnica-Ihle E, Hagemann D, Zink A. HLA-DRB1 genes, rheumatoid factor, and elevated C-reactive protein: independent risk factors of radiographic progression in early rheumatoid arthritis. Berlin Collaborating Rheumatological Study Group. J Rheumatol 2000;27:2100-9.
16. Fex E, Jonsson K, Johnson U, Eberhardt K. Development of radiologic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. Br J Rheumatol 1996;35:1106-15.
17. Plant MJ, Williams AL, O'Sullivan MM, Lewis PA, Coles EC, Jessop JD. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. Arthritis Rheum 2000;43:1473-7.
18. Welsing PM, Landewe RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, et al. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis: a longitudinal analysis. Arthritis Rheum 2004;50:2082-93.
19. Chatham WW, Blackburn WD Jr. Gold and D-penicillamine. In: Coopman WJ, editor. Arthritis and allied conditions. 14th ed. Philadelphia: Lippincott Williams and Wilkins; 2001:717-33.
20. Ichikawa Y, Saito T, Yamanaka H, Akizuki M, Kondo H, Kobayashi S, et al, and MTX–BUC Combination Study Group. Therapeutic effects of the combination of methotrexate and bucillamine in early rheumatoid arthritis: a multicenter, double-blind, randomized controlled study. Mod Rheumatol 2005;15:323-8.
21. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
22. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 1983;26:1346-53.
23. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999;26:743-5.
24. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum 1993;36:729-40.
25. van Riel PL, van Gestel AM, van de Putte LBA. Development and validation of response criteria in rheumatoid arthritis: steps towards an international consensus on prognostic markers. Br J Rheumatol 1996;35 Suppl 2:4-7.
26. Yamanaka H, Matsuda Y, Tanaka M, Sendo W, Nakajima H, Taniguchi A, et al. Serum matrix metalloproteinase 3 as a predictor of the degree of joint destruction during the six months after measurement, in patients with early rheumatoid arthritis. Arthritis Rheum 2000;43:852-8.
27. Aman S, Paimela L, Leirisalo-Repo M, Risteli J, Kautiainen H, Helve T, et al. Prediction of disease progression in early rheumatoid arthritis by ICTP, RF and CRP. A comparative 3-year follow-up study. J Rheumatol 2000;39:1009-13.
28. Wakitani S, Murata N, Toda Y, Ogawa R, Kaneshige T, Nishimura Y, et al. The relationship between HLA-DRB1 alleles and disease subsets of rheumatoid arthritis in Japanese. Br J Rheumatol 1997;36:630-6.
29. Kochi Y, Yamada R, Kobayashi K, Takahashi A, Suzuki A, Sekine A, et al. Analysis of single-nucleotide polymorphisms in Japanese rheumatoid arthritis patients shows additional susceptibility markers besides the classic shared epitope susceptibility sequences. Arthritis Rheum 2004;50:63-71.