Decrease of Disease Activity Under Ineffective Therapy in DMARD-Naive Patients with Early Rheumatoid Arthritis: Role of Antibody Profiles and Carriage of the HLA Shared Epitope in Predicting Decrease of Disease Activity

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ABSTRACT. ***Objective.*** To evaluate whether the baseline presence of rheumatoid arthritis (RA)-associated biomarkers could define subgroups of patients that are more prone to show a spontaneous decrease of RA disease activity. In a previous placebo-controlled phase II trial that failed to show any superiority of the experimental compound versus placebo, a remarkable decrease of such disease activity was observed despite the lack of effective treatment.

Methods. A subgroup of 83 disease modifying antirheumatic drug-naive RA patients with disease duration < 3 years was analyzed. Rheumatoid factor (RF), anti-citrullinated protein/peptide antibodies (ACPA), and HLA shared epitope (SE) were determined at baseline.

Results. RF-positive patients tended to have higher levels of disease activity at baseline compared to RF-negative patients [Disease Activity Score (DAS) 6.12 vs 5.65, p = 0.02 at screening], but the decrease in disease activity was similar in both subgroups (DAS –1.23 vs –1.07). In contrast, ACPA-positive patients showed similar baseline disease activity scores compared to ACPA-negative patients, but tended to show a smaller decrease of disease activity than patients without ACPA (∅DAS –1.53 vs –0.79, p = 0.013). Presence of the HLA-SE seemed not to have any effect on the baseline DAS or on the spontaneous decrease of DAS.

Conclusion. The predictive value of baseline RA-associated biomarkers for spontaneous decrease of disease activity under placebo or ineffective treatment is limited. Yet the data analyzed here might be useful for the design of future placebo-controlled trials in RA. (J Rheumatol 2007;34:1992–6)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE ACTIVITY ANTIBODIES HLA SHARED EPITOPE

In order to avoid joint destruction, new therapeutic strategies are under development to treat patients with rheumatoid arthritis (RA) as early as possible[1]. Patients at high risk for progression should be identified to enable treatment with an early intensive regimen. In order to select those patients at high risk to develop erosive disease or radiological progression, prediction models have been developed. In such models, a baseline high disease activity, the presence of rheumatoid factor (RF), anti-citrullinated protein/peptide antibodies (ACPA), or carriage of the HLA shared epitope (HLA-SE) are predictors of erosive disease or (radiological) progression[2,3].

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Also, as spontaneous remission does occur in patients with early undifferentiated arthritis[4], patients at lower risk for progression should be identified to avoid unnecessary treatment. As most recent placebo-controlled trials take place on a background of disease modifying antirheumatic drug (DMARD) therapy, little is known about placebo effects or spontaneous decrease of disease activity in patients with early RA fulfilling the RA classification criteria[5-7]. Moreover, the predictive value of biomarkers for placebo responses or spontaneous remission in the absence of active treatment in patients with early RA is not known.

MATERIALS AND METHODS

Patients. This analysis is based on a multicenter (16 centers) double-blind, placebo-controlled phase II trial that failed to demonstrate any superiority of the experimental compound compared to placebo[8,9]. Between March 2000 and April 2001, patients were included in the trial if fulfilling American College of Rheumatology (ACR) criteria for RA[6] and having a Disease Activity Score (DAS28) of more than 4.5. Two hundred ninety-two patients were included and DMARD were washed out in case of DMARD failures. Evaluations of patients were performed at screening, baseline, and every

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month until the end of the study at Week 12. Clinical evaluations included the core set variables to calculate the DAS28 and the ACR response score[10,11]. Our analysis is based on a subgroup of 83 DMARD-naive patients with disease duration < 3 years further defined as early DMARD-naive patients. Disease duration < 3 years was used as this was also the definition of "early RA" in several clinical trials[12-14]. Eighteen of them received placebo; 17, 16, 13, and 19 patients received respectively 30, 150, 300, and 600 µg of the compound (Org 39141, Organon) that failed to demonstrate any treatment effect and will be further considered as ineffective treatment.

Fifty-eight percent of patients were female. The median symptom duration was 9 months and the median time of diagnosis was 1 month. All patients signed an ethically approved informed consent. Serum samples were taken at baseline and stored at –20˚C. Other baseline characteristics are shown in Table 1.

Determination of RA-associated biomarkers. RF was determined by the latex fixation test (Difco Laboratories, Detroit, MI, USA). A 95% specific cutoff was defined at a dilution of 1/160 in an independent cohort of patients[15].

ACPA, measured by anti-cyclic citrullinated peptide (CCP) antibodies, were detected by a commercial ELISA containing synthetic CCP (Immunoscan RA, mark 2, Eurodiagnostica, Arnhem, The Netherlands) according to the manufacturer's instructions. A 98.5% specificity cutoff was previously set at 42 U/ml (sensitivity = 75.4%)[16]. HLA-DR oligotyping was performed using the routine procedures of the local centers.

Statistics. Differences between groups in normally distributed continuous variables were evaluated by the calculation of means, standard error (SE) of means, and t-tests. Differences in categorical variables were evaluated by percentages and chi-square statistics. Statistics were computed by the SPSS software package (SPSS, Chicago, IL, USA). Power analysis was performed for the evaluation of the ACR20 response.

RESULTS

Overall, a 35% ACR20 response was observed and DAS28 decreased with 1.15 units (SEM 0.15) between Week 0 and Week 12 (Table 2).

Forty-four (53%) patients were RF-positive and 44 (53%) patients were ACPA-positive. The HLA-SE was present in 54 (68%) patients and undetermined in 3 patients.

RF-positive patients tended to have more disease activity at screening/baseline compared to RF-negative patients (DAS 6.12 vs 5.65, p = 0.02 at screening), but the decrease in disease activity was similar in both subgroups (DAS –1.23 vs –1.07). In contrast, ACPA-positive patients showed similar screening/baseline disease activity scores (Table 2) compared to ACPA-negative patients, but the latter group tended to show a more pronounced spontaneous decrease of disease activity under placebo or ineffective treatment compared to ACPA-positive patients (∅DAS –1.53 vs –0.79, p = 0.013). Presence of

Table 1. Baseline characteristics of patients in relation to biomarker status.

	Overall		RF–		RF+		ACPA–		ACPA+		SE–		SE+	
Female Sex, %	58		59		57		61		55		46		64	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, yrs	59.2	13.5	60.8	12.8	57.8	14.1	62.1	14.0	56.7	12.7	57.1	14.9	59.4	12.8
Disease duration, mo	0.8	0.6	0.6	0.4	0.9	0.6	0.6	0.4	0.9	0.6	0.8	0.4	0.8	0.6
Erosion score	4.1	8.5	2.3	5.1	5.6	10.4	1.5	2.9	6.3	10.8	3.6	10.8	4.5	7.3
DAS28 score	6.0	1.1	5.8	1.2	6.2	0.9	6.0	1.2	6.0	1.0	5.9	1.1	6.1	1.1
CRP	29.2	33.7	23.2	36.0	34.7	30.9	26.6	36.3	31.6	31.4	26.5	37.9	28.6	31.0
ESR	33.3	22.3	25.9	22.5	40.1	20.0	31.3	23.1	35.2	21.6	29.1	22.9	34.2	22.0
28TJC	12.5	6.2	13.2	6.5	11.9	5.9	13.6	6.8	11.5	5.5	11.5	4.8	12.8	6.9
28SJC	12.1	4.7	12.6	5.2	11.7	4.2	13.2	5.3	11.1	4.0	11.7	4.5	12.3	4.9

RF: rheumatoid factor, ACPA: anti-citrullinated protein/peptide antibodies, SE: HLA shared epitope, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, 28TJC: 28 tender joint count, 28SJC: 28 swollen joint count.

Table 2. Evolution of disease activity in relation to the presence of the different RA-associated biomarkers.

	Overall (n = 83)		RF				ACPA					HLA-SE				
			Neg (n = 39)		Pos (n = 44)		p	Neg (n = 39)		Pos (n = 44)		p	(Neg (n = 26)		Pos (n = 54)		p
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
DAS28 at screening	5.9	0.1	5.65	0.15	6.12	0.12	0.02	5.91	0.16	5.9	0.13	0.94	5.83	0.19	5.9	0.12	0.63
DAS28 at baseline	6.03	0.12	5.84	0.19	6.2	0.14	0.13	6.03	0.19	6.03	0.15	0.99	5.87	0.21	6.08	0.15	0.37
DAS28 at Week 12	4.75	0.16	4.46	0.22	5.03	0.22	0.07	4.35	0.21	5.13	0.22	0.014	4.33	0.3	4.92	0.19	0.15
Decrease of DAS28 between baseline and Week 12	–1.15	0.15	–1.23	0.23	–1.07	0.19	0.61	–1.53	0.2	–0.79	0.21	0.013	–1.29	0.26	–1.07	0.19	0.4
	Proportion, %		Proportion, %		Proportion, %			Proportion, %		Proportion, %			Proportion, %		Proportion, %		
ACR20 response	35		34		35		0.60	44		26		0.11	38		32		0.66
ACR50 response	15		17		13		0.67	21		11		0.33	19		12		0.48
ACR70 response	4		0		8		0.24	0		8		0.24	0		6		0.55

RF: rheumatoid factor, ACPA: anti-citrullinated protein/peptide antibodies, HLA-SE: HLA shared epitope. ACR responses are defined as having at least an ACR20, ACR50, or ACR70 response.

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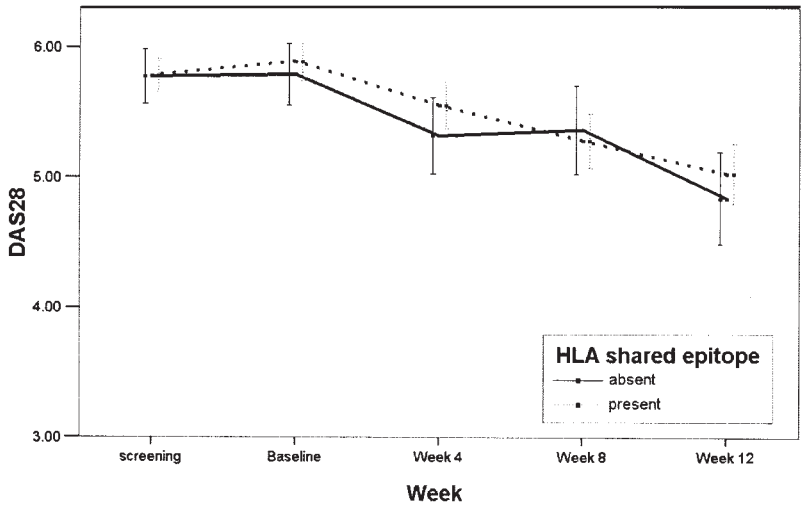

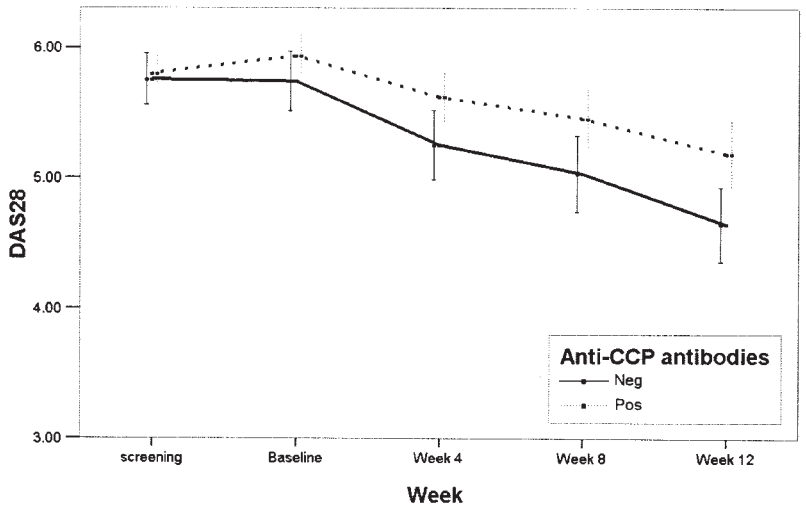

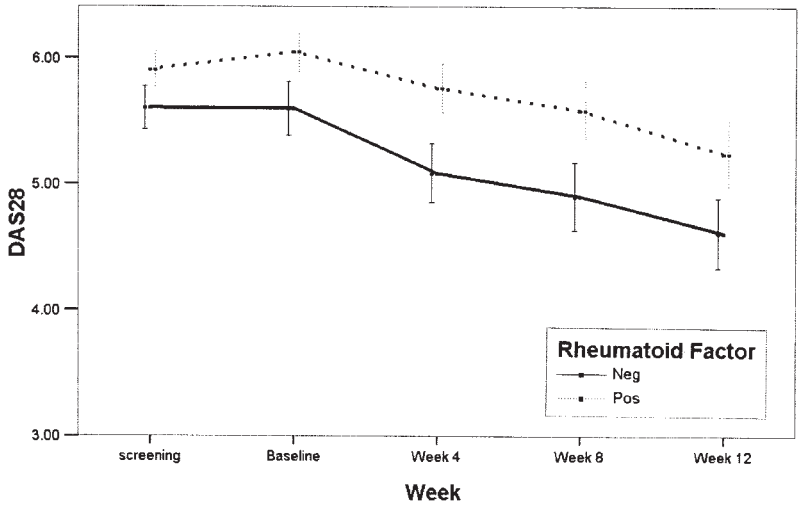

Figure 1. Evolution of DAS28 in function of time and status of the RA-associated biomarkers RF, ACPA, and HLA-SE. RF: rheumatoid factor; ACPA: anti-citrullinated protein/peptide antibodies; HLA-SE: HLA shared epitope; Neg: negative; Pos: positive.

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the HLA-SE seemed not to have any effect on the baseline DAS or on the spontaneous decrease of DAS (Table 2, Figure 1).

Similarly, ACPA-negative patients tended to have a higher ACR20 response under placebo or ineffective treatment compared to ACPA-positive patients (44% vs 26%, p = 0.113) (Table 2). Although there was an observed 18% difference in ACR20 response between ACPA-positive versus ACPA-negative patients this was not statistically significant due to the low power of only 40% to reject the null hypothesis.

DISCUSSION

Our analysis describes a unique cohort of DMARD-naive patients with early RA who were treated with placebo or an ineffective treatment and were followed over 12 weeks, thus providing information on the natural course of early RA. This is in contrast to other, current placebo-controlled trials in (early) RA patients where patients are treated on a background of methotrexate[12-14].

As the inclusion criteria for the trial were based on the DAS28, a spontaneous decrease of the disease activity/placebo effect under ineffective treatment can be expected as explained by a regression to the mean effect[17]. As little is known about the natural course of RA — which tends to become milder — in today's rheumatologist practice, it is difficult to obtain a correct estimate of the proportion of patients that showed a spontaneous decrease of disease activity attributable to this regression to the mean-like effect or the occurrence of real spontaneous remissions[17,18]. Also, subjective factors could contribute to the overall observed decrease of disease activity.

In this analysis, we showed that patients with positive RF tend to have higher DAS at baseline, but no significant differences in the further disease course were observed compared to RF-negative patients; the slopes of the curves are parallel for RF-positive and RF-negative patients (Figure 1). In contrast, the presence of ACPA was seen to have no effect on the baseline disease activity score, but patients with ACPA tended to show a smaller decrease of disease activity under placebo or ineffective treatment than patients without ACPA. The presence of the HLA-SE seemed to have no effect on the baseline DAS. Also, the presence of the HLA-SE did not affect the response to placebo or ineffective treatment.

Thus, patients with ACPA tend to be less prone to show a decrease of disease activity under placebo or ineffective treatment.

Whether this information can be used in a prediction model for spontaneous remission remains unclear. Although some statistically significant differences were observed, our study was not sufficiently powered to detect relevant differences between subgroups. The relatively low number of patients is also a major drawback to evaluate the predictive value of combinations of biomarkers in patients with untreated early RA[16]. Due to ethical considerations, it can be expected that larger studies to address this issue in more detail will not be possible.

The predictive value of baseline serological status on the spontaneous decrease of disease activity can be different from its predictive value on the clinical response to therapy, such as tumor necrosis factor blockers, where ACPA status does not seem to be a predictor of response to therapy[19]. However, our data further support the hypotheses that differences exist between ACPA-positive and ACPA-negative disease and that RF and ACPA may be different antibody systems[16,20].

Although ACPA and the HLA-SE are associated with each other[21], the HLA-SE seemed not to be associated with differences in baseline disease activity or with differences in improvement of disease activity. This could be explained by the imperfect association between both markers, which could be improved by other classification systems of the HLA-DRB1 alleles[22].

To compare the results of this analysis with results from other studies in the context of early arthritis, it is important to note that definitions of early disease differ between 2 or 3 years[4,12-14]. Also, patients included in our study fulfilled the ACR criteria for RA and received no active treatment. This is in contrast to some of the well known early arthritis registries from which prediction models are derived[4,23].

Placebo response and spontaneous decrease of disease activity under placebo or ineffective treatment does occur, and, although the predictive value of those biomarkers for spontaneous decrease of disease activity is limited, we showed that a spontaneous decrease of disease activity can be observed, especially in ACPA-negative patients. This information might be useful for the design of future placebo-controlled trials.

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