Differential Response of the Rheumatoid Factor and Anticitrullinated Protein Antibodies During Adalimumab Treatment in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate the effect of anti-tumor necrosis factor (TNF) treatment on rheumatoid factor (IgM-RF) and anticitrullinated protein antibodies (ACPA) and its association with treatment response and acute-phase reactants.

Methods. In a cohort of 188 consecutive patients with rheumatoid arthritis (RA) treated with adalimumab, baseline IgM-RF and ACPA were determined by ELISA, and compared to levels after 28 weeks of treatment. ACPA were measured as antibodies to cyclic citrullinated peptide (anti-CCP). The relative change of antibody levels was correlated to the European League Against Rheumatism response criteria and to the change in acute-phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)].

Results. The median decline in IgM-RF levels was greater than the decline in ACPA levels (31% vs 8%; $p < 0.001$). The decrease in antibody levels was greater in the group of good responders than in the group of nonresponders [43% vs 7% for IgM-RF ($p < 0.0001$) and 16 vs –4% for ACPA ($p = 0.03$)]. Seventeen percent of IgM-RF-positive patients at baseline turned negative at 28 weeks; this qualitative effect was not observed for ACPA. Further, the decline in IgM-RF, but not ACPA, was associated with a decrease in CRP and ESR ($p = 0.004$ and $p = 0.006$, respectively).

Conclusion. TNF treatment directly influences IgM-RF and ACPA levels, but in those responding to treatment only. The effect on IgM-RF levels and positivity status is greater than on ACPA levels and is associated with the decline in markers of inflammation. These results further emphasize the differential role these autoantibodies may play in RA; IgM-RF as marker of inflammatory activity, and ACPA as qualitatively stable hallmark of RA. (First Release Sept 1 2008; J Rheumatol 2008; 35:1972–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — RHEUMATOID FACTOR
ANTICITRULLINATED PROTEIN ANTIBODIES — ADALIMUMAB
EUROPEAN LEAGUE AGAINST RHEUMATISM RESPONSE

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which may lead to joint destruction[1]. One of the characteristics of the disease is the presence of anticitrullinated protein antibodies (ACPA) and/or IgM rheumatoid factor (IgM-RF), although these are not present in all patients with RA. ACPA comprise a group of antibodies highly specific for RA; among those described are antibodies against cyclic citrullinated peptide (CCP)[2], citrullinated fibrinogen[3], citrullinated alpha-enolase[4], and mutated citrullinated vimentin (MCV)[5]. They share a similar high sensitivity and specificity for RA and are present in early and even preclinical disease[6,7]. Citrullinated proteins have been detected in inflamed joints of patients with RA, but also in non-RA inflamed joints[8,9]. The latter suggests that the antibody response against citrullinated proteins, but not the presence of citrullinated proteins, is specific for RA. Therefore, a pathophysiological role for ACPA in RA has been suggested[10,11] and several studies have addressed the question whether ACPA levels can be influenced by aggressive antirheumatic treatment using tumor necrosis factor-α (TNF-α)-blocking agents. Most authors report a significant decrease of ACPA after TNF treatment[12-16], but in those

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responding to treatment only[12,14,15]. On the other hand, unaltered or temporarily decreased ACPA levels in patients treated with anti-TNF agents have also been reported[17-20]. The effect of anti-TNF treatment on ACPA may be restricted to the IgG4 subclass, suggesting a beneficial effect of anti-TNF treatment on the chronic antigenic stimulation by citrullinated proteins necessary for IgG4 ACPA production[21].

IgM-RF targets the Fc fragment of IgG and is observed in about 75% of patients with RA, but it is also frequently observed in other inflammatory diseases[22,23]. This suggests properties more as a general marker of inflammation instead of a disease-specific marker[11,24]. Indeed, all studies reporting IgM-RF levels after anti-TNF treatment have shown a reduction of these levels, in some restricted to those responding to treatment[12-20].

IgM-RF and ACPA levels also decreased in response to diverse nonbiological treatments[25]. In our study, the reduction in IgM-RF was associated with effective treatment, whereas the decrease in ACPA was associated with shorter disease duration, suggesting a "window of opportunity." The apparent differential response of IgM-RF and ACPA during antirheumatic treatment suggests that IgM-RF acts as a marker for inflammation in RA and other (non)rheumatic diseases, while ACPA, being more disease-specific, is less susceptible to aggressive antirheumatic treatment[26].

We previously reported that the decrease in IgM-RF is greater than ACPA in response to anti-TNF treatment[16]. We tried to confirm these observations in a separate and larger cohort and to correlate the decline in autoantibody levels to treatment response and decline in acute-phase reactants during anti-TNF treatment.

Therefore, we investigated whether intensive antirheumatic treatment has a greater influence on the qualitative and quantitative aspects of IgM-RF than ACPA; we studied its relation to clinical response and the presence of anti-adalimumab antibodies; and we explored the possible association of the autoantibody and acute-phase response in a cohort of 188 RA patients treated with adalimumab.

MATERIALS AND METHODS

Patients. The cohort consisted of 188 consecutive patients with RA treated with adalimumab at the Department of Rheumatology of the Jan van Breemen Institute, Amsterdam. Patients were treated with either adalimumab alone or adalimumab and concomitant disease modifying antirheumatic drugs (DMARD) [74% of patients used adalimumab and methotrexate (MTX)]. Sixty-three of 188 patients used a median of 7.5 mg [interquartile range (IQR) 5–10] of prednisone (or equivalent) daily. Serum samples were collected just before the first injection with adalimumab at baseline, and at 4, 16, and 28 weeks. The primary analysis was performed using the samples obtained at baseline and after 28 weeks of treatment. Four patients had discontinued treatment after at least 4 weeks and 12 after at least 16 weeks of followup. Among these 16 patients, 8 were nonresponders, 6 moderate responders, and 2 good responders. In these patients, the last observation was carried forward.

All patients fulfilled the American College of Rheumatology 1987 revised criteria for RA and had active disease according to the Dutch consensus statement on the initiation and continuation of TNF-blocking therapy in RA[27]. Our study was approved by the local medical ethics committee. All patients gave written informed consent.

Clinical response. Disease activity was assessed at baseline and after 4, 16, and 28 weeks of treatment using the Disease Activity Score (DAS)28. Clinical response was assessed by the European League Against Rheumatism (EULAR) criteria[28].

Antibody measurements. Baseline laboratory measures (determined using the blood samples that were obtained at inclusion and after 28 wks of treatment) included IgM-RF by in-house enzyme linked immunosorbent assay (ELISA) and ACPA (measured as anti-CCP) by ELISA (second-generation anti-CCP ELISA, Axis Shield, Dundee, UK). IgM-RF was calibrated with a national reference serum containing 200 international units/ml (IU)[29]; the cutoff level for IgM-RF antibody positivity is set at 30 IU determined on the basis of receiver-operating characteristic curves, as described[7]. The cutoff level for anti-CCP antibody positivity was set at 5 arbitrary units/ml (AU) (according to the manufacturer's instructions). Anti-adalimumab antibodies were measured as described[30].

Statistical analysis. The analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL, USA). Antibody levels were analyzed in the positive patients for each test only. Kruskal-Wallace test, general linear model univariate analysis with post-hoc Bonferroni test for multiple comparisons, or chi-squared for trend was used when appropriate to compare baseline characteristics and the relative change in antibody levels among the 3 EULAR response groups. Wilcoxon's signed-rank test was used when appropriate to detect changes in levels of IgM-RF or ACPA in time. Log transformation to gain normality was applied when necessary. Linear regression analysis was used to study the association between the acute-phase response and autoantibody levels.

RESULTS

Baseline characteristics. Table 1 shows the baseline characteristics for the adalimumab cohort stratified for EULAR response.

Sex distribution, mean age, and disease duration was similar among the 3 groups, as well as the number of patients with erosive and/or nodular disease and the number of prior DMARD. The erythrocyte sedimentation rate (ESR) was lower in good responders compared to nonresponders. Further, the DAS28 was higher in moderate responders compared to good and nonresponders. Moreover, MTX use was more frequent and the median dose was higher in good and moderate responders compared to nonresponders.

Fifty-seven percent of patients were positive for IgM-RF; 75% were positive for ACPA. The percentage of patients positive for each antibody and baseline antibody levels among the patients positive for each antibody were similar among the 3 response groups (Table 2). Moreover, baseline ACPA levels were weakly correlated with the DAS28 at baseline ($r = 0.21$, $p = 0.012$).

Decrease in antibody levels is associated with response to anti-TNF treatment. IgM-RF and ACPA levels decreased significantly during the study period of 28 weeks (Table 2; both $p < 0.001$). The decrease from baseline values was 8% for ACPA, but 31% for IgM-RF ($p < 0.001$). Eighteen patients (17%) became negative for IgM-RF, predominantly those responding to treatment (10%, 16%, and 21% in nonresponders, moderate, and good responders, respectively).

Table 1. Baseline characteristics, stratified for EULAR response criteria[28].

	Nonresponse, n = 43	Moderate, n = 79	Good, n = 66	p
Female, n of patients (%)	37 (86)	65 (82)	47 (71)	0.120
Age, mean (SD) yrs	53.9 (13.1)	54.6 (12.0)	52.4 (10.8)	0.528
Disease duration, yrs†	9.5 (1.7–52.2)	8.5 (1.2–59.8)	7.9 (1.0–62.8)	0.628
ESR, mm/h†	22.0 (3.9–122.9)	28.3 (5.5–146.5)	17.3 (3.4–88.1)	0.003*
CRP, mg/l†	10.9 (1.2–99.6)	12.6 (0.9–176.0)	11.1 (1.1–112.5)	0.761
Baseline DAS, mean (SD)	4.86 (1.3)	5.42 (1.2)	4.90 (1.0)	0.009#*
Erosive disease, n of patients (%)	33 (77)	62 (79)	57 (86)	0.359
Prior DMARD, mean (SD)	3.4 (1.5)	3.1 (1.4)	3.1 (1.4)	0.499
Nodular disease, n of patients (%)	13 (30)	24 (30)	16 (24)	0.818
Methotrexate use, n of patients (%)	24 (56)	58 (73)	57 (88)	0.001
Methotrexate dose in mg, median (IQR)	8.75 (0–25)	18.75 (7.5–25)	25 (15–25)	0.000#§
IgM-RF-positive, n of patients (%)	21/43 (49)	43/79 (54)	43/66 (65)	0.205
ACPA-positive, n of patients (%)	31/43 (72)	53/79 (72)	53/66 (80)	0.466

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS: Disease Activity Score, IQR: interquartile range, IgM-RF: IgM-rheumatoid factor, ACPA: anti-citrullinated protein antibodies, DMARD: disease modifying antirheumatic drugs. †log-transformed to gain normality; geometric mean and 95% confidence interval is reported. p values: chi-square for trend, Kruskal-Wallace or univariate ANOVA with post-hoc Bonferroni when appropriate ($p < 0.05$ for #nonresponse versus moderate, *moderate versus good, §nonresponse versus good).

Table 2. Levels of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) at baseline and after 28 weeks of adalimumab treatment, stratified for EULAR response. Values are mean (interquartile range).

	Baseline	28 Weeks	p
IgM-RF			
All	81 (49–181)	63 (34–119)	0.000
Nonresponse	81 (46.5–292)	79 (55.5–192.5)	0.305
Moderate	87 (50–182)	63 (33–141)	0.000
Good	77 (49–179)	53 (31–90)	0.000
ACPA			
All	100 (28–252)	98 (28–216)	0.000
Nonresponse	98 (24–241)	112 (29–216)	0.474
Moderate	117 (25–265)	97 (20–219)	0.175
Good	100 (42–248)	100 (37–214)	0.000

p values: Mann-Whitney U-test.

Table 3. Percentage of baseline levels of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) at baseline and after 28 weeks of adalimumab treatment, stratified for EULAR response. Data are geometric mean (95% CI).

	Nonresponse, %	Moderate, %	Good, %	p
IgM-RF	93 (39–222)	73 (31–172)	57 (27–120)	0.000*§
ACPA	104 (37–292)	95 (49–182)	84 (52–137)	0.027§

p values: univariate ANOVA with post-hoc Bonferroni ($p < 0.05$ for *moderate versus good, §nonresponse versus good).

All ACPA-positive patients remained positive after 28 weeks of treatment.

As shown in Table 2, median IgM-RF and ACPA levels decreased significantly after 28 weeks in the good-responder group ($p < 0.001$ for both), but not in the nonresponder group ($p = 0.31$ and 0.47, respectively). In the group of moderate responders, IgM-RF levels decreased ($p < 0.001$), but ACPA levels did not ($p = 0.18$).

To investigate whether the changes in antibody levels were greater in moderate and good responders compared to nonresponders, ratios of antibody levels at baseline and at 28 weeks were determined and expressed as percentage. The baseline antibody levels were not different among the responders groups and were not correlated with the calculated change from baseline value (data not shown). As shown in Table 3, IgM-RF levels decreased by 7%, 27%, and 43% ($p < 0.001$), ACPA levels by –4%, 5%, and 16% ($p = 0.03$) in nonresponders, moderate, and good responders, respectively.

The decrease in acute-phase reactants is associated with the decrease in IgM-RF, but not in ACPA. As expected, acute-phase reactants, as measured by C-reactive protein (CRP) and ESR, decreased significantly during the study period ($p < 0.001$ for the whole study group, but also for the groups of IgM-RF or ACPA-positive patients separately). Therefore, we explored the association between the decrease in ESR and CRP and the decrease in autoantibody levels (Figure 1). Linear regression analysis, using the 28 weeks:baseline ratio of the acute-phase reactants as the independent variable and the 28 weeks:baseline ratio of the autoantibody levels as dependent variable, revealed a relationship between the decrease in acute-phase reactants and the decrease in ratio of IgM-RF [B=0.2; 95% confidence interval (95% CI) 0.06–0.35; $p = 0.006$ and B=0.2; 95% CI 0.07–0.34; $p = 0.004$, for CRP and ESR, respectively]. In contrast, the decrease in CRP and ESR was not associated with the decrease in ACPA ratio (B=0.1; 95% CI –0.02 to 0.29; $p = 0.09$ and B=0.1; 95% CI –0.06 to 0.24; $p = 0.25$, for CRP

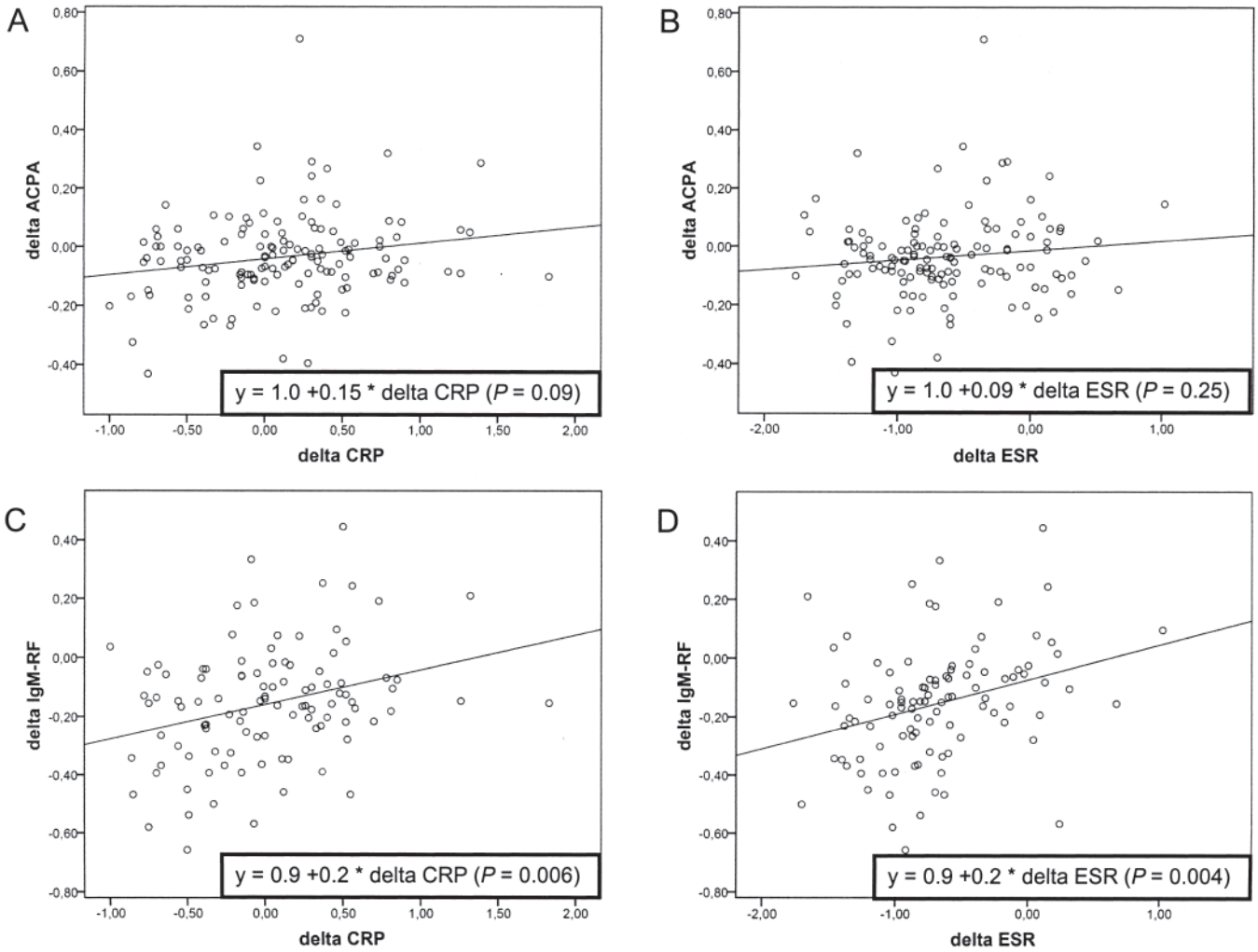

Figure 1. Decrease in IgM-RF, but not ACPA, is associated with the decrease in acute-phase reactants. A and B. No statistically significant association between the decrease in ACPA and ESR or CRP levels after 28 weeks of adalimumab treatment. C and D. A statistically significant association between the decrease in IgM-RF and ESR or CRP levels after 28 weeks of adalimumab treatment. Ratios between the levels at 28 weeks and baseline were calculated and log-transformed to gain normality. IgM-RF: IgM-rheumatoid factor; ACPA: anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

and ESR, respectively). Correcting for sex did not alter these results.

The magnitude of decrease in IgM-RF is associated with the presence of anti-adalimumab antibodies. To further extend the observed association between treatment response and decrease in autoantibody levels, we assessed whether the observed decrease in IgM-RF and ACPA was associated with the presence of anti-adalimumab antibodies, since these antibodies are one of the main determinants of treatment response[30]. For IgM-RF, the median decrease in autoantibody level was 32% in those without (n = 89) and 16% in the group of patients with anti-adalimumab antibodies (n = 18; p = 0.03). For ACPA, a similar, although not statistically significant trend was observed [11% vs 4%, in the patient group without (n = 119) and with (n = 22) anti-adalimumab antibodies, respectively; p = 0.2].

DISCUSSION

In this study of patients with RA who received the TNF-blocking agent adalimumab, IgM-RF and ACPA levels decreased, but only in patients responsive to treatment.

Our results, which show that IgM-RF and ACPA levels decrease more in patients responsive to anti-TNF treatment, substantiate previous observations that IgM-RF and ACPA levels only decline in patients responsive to treatment. The latter had been suggested by others, but was not previously shown[12,14,15]. Further, in agreement with our previous observations in infliximab-treated patients[16], the decline in median IgM-RF levels was greater than for ACPA levels, further suggesting that IgM-RF and ACPA are 2 different autoantibody systems. Indeed, none of the ACPA-positive patients at baseline became negative, whereas 17% of the

IgM-RF-positive patients at baseline became negative after 28 weeks of adalimumab treatment.

The apparent differential response of IgM-RF and ACPA during antirheumatic treatment suggests that IgM-RF acts as a marker for inflammation in RA and other (non)rheumatic diseases and fluctuates with disease activity in both in quantitative and qualitative aspects[12-20,25]. In contrast, ACPA is highly disease-specific and has a stable phenotype[12-20,25,31,32], and its concentration decreases in some[12-17,25] but not in all studies[18,19] after aggressive antirheumatic treatment.

Our results confirm this hypothesis, since the decrease in IgM-RF was associated to the decrease in acute-phase reactants as measured by ESR and CRP. In contrast, the smaller reduction in ACPA levels was not correlated to the diminished acute-phase response as a result of anti-TNF treatment. The latter is in contrast to Chen, *et al*; in their study of etanercept treatment the decrease in ACPA was associated to the reduction of CRP, but not ESR, whereas an association with IgM-RF was not reported[13].

A specific treatment effect is suggested by the observation that the decrease in antibodies is seen only in those patients without antibodies to adalimumab, since the presence of antibodies against adalimumab is associated with lower therapeutic adalimumab levels[30].

The different effects of anti-TNF treatment on IgM-RF and ACPA are probably not attributable to the difference in clearance rate between the IgG subclass of ACPA and the IgM subclass of the IgM-RF, since others have shown equal reduction of all RF isotypes after anti-TNF treatment[20], but also after treatment with the B cell-targeting monoclonal antibody rituximab[33].

The mechanism of the reduction in autoantibody levels in response to anti-TNF treatment is not completely understood, although the effect of anti-TNF treatment on the B cell compartment has recently been studied by Anolik, *et al*. They report impaired B cell function via effects on follicular dendritic cells and disruption of germinal center formation and maintenance[34]. The effect of anti-TNF treatment on autoantibody-producing B cells, however, has not been directly shown.

To gain more insight into the interaction between the decrease of IgM-RF and acute-phase response, it would have been of interest to study the temporal relationship between both markers. IgM-RF and ACPA were only measured at 2 timepoints and therefore this kind of analysis could not be performed. Concomitant MTX use may have influenced the results since MTX usage was not similar in the 3 EULAR response groups and in the groups with and without anti-adalimumab antibodies. However, Chen, *et al* did not observe a decrease in IgM-RF or ACPA in patients treated mostly with MTX (90%), whereas MTX plus etanercept resulted in a significant reduction of antibody levels after 3 weeks[13].

Patients with RA treated with the TNF-blocking agent adalimumab show a reduction in IgM-RF and ACPA levels, but in those responding to treatment only. The reduction in IgM-RF levels is greater than for ACPA, and correlates to measures of the acute-phase response. These results underscore the differential role these antibodies may play in RA.

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