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Antibodies Against Citrullinated Vimentin in Rheumatoid Arthritis

Higher Sensitivity and Extended Prognostic Value Concerning Future Radiographic Progression as Compared With Antibodies Against Cyclic Citrullinated Peptides

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Objective. **The Sa autoantigen can be found in inflamed synovium of patients with rheumatoid arthritis (RA), and at least part of the humoral RA-specific anti-Sa response is directed against citrullinated vimentin. This study was undertaken to evaluate the sensitivity, specificity, and prognostic value of determination of levels of antibodies against modified citrullinated vimentin (anti-MCV) as compared with antibodies against cyclic citrullinated peptides (anti-CCP) in an inception cohort of patients with early RA.**

Methods. **Clinical data, radiographs, and measurements of levels of anti-MCV and anti-CCP antibodies were obtained in 273 patients with early RA at baseline, after 3 months, and after 1, 2, 3, and 5 years. Autoantibodies were also analyzed in 100 healthy controls.**

Results. **Of the 273 patients, 193 (70.7%) were anti-MCV positive and 158 (57.9%) were anti-CCP positive at the time of diagnosis, with nearly equal specificities (95% and 96%, respectively). Forty (14.7%) were anti-MCV positive only, and 5 (1.8%) were anti-CCP positive only. Anti-MCV–positive and anti-MCV–negative patients had similar disease activity at baseline, but presence of anti-MCV was predictive of subsequent high disease activity and continued radiographic progression. Changes in anti-MCV level showed stronger correlation with changes in clinical parameters than did changes in anti-CCP level. The subgroup of patients who were anti-MCV positive and anti-CCP negative showed a higher rate of radiographic destruction than did patients who were negative for both anti-MCV and anti-CCP.**

Conclusion. **These findings show that when patients with early RA are compared with healthy controls, analysis of anti-MCV yields greater sensitivity and unchanged specificity as compared with analysis of anti-CCP. Anti-MCV also appears to perform better than anti-CCP in identifying poor radiographic prognosis in patients with early RA.**

Several different autoantibodies with varying specificity have been found in serum from patients with RA (1,2), but rheumatoid factor (RF) is at present the only autoantibody included in the American College of Rheumatology (ACR) classification criteria (3). However, antibodies recognizing citrullinated proteins/peptides (4), especially the peptide mixture designated cyclic citrullinated peptides (CCP) (5), have reasonable sensitivity and high specificity for RA and are increas-

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ingly used in the evaluation of patients who may have RA.

Another RA-related antibody, anti-Sa, has >95% specificity for RA (6–8). The sensitivity of anti-Sa, however, is <50% (2,7). Anti-Sa antibodies have been associated with more erosive disease compared with other RA-related autoantibodies (7,9), including anti-CCP and RF (10). The Sa antigen is found in placenta, spleen, and rheumatoid synovial tissue (11). A recent study demonstrated that antibodies in anti-Sa–positive RA sera bind to citrullinated vimentin (12), indicating that anti-Sa belongs to the group of antibodies against citrullinated proteins or peptides. Anti-Sa reactivity has been shown to consist at least partially of antibodies against citrullinated vimentin (12,13), but the pattern of reactivity for anti-Sa/vimentin is not identical to that for anti-CCP and might involve additional antibody reactivities (8). Thus, it should be of interest to investigate whether analysis of immunoreactivity with citrullinated vimentin adds to the information concerning diagnosis and prognosis of RA gained from the anti-CCP assay.

A recently developed enzyme-linked immunosorbent assay (ELISA) for the quantification of antibodies against both Sa/vimentin and citrulline, a modified citrullinated vimentin (anti-MCV) (14,15), was used to compare analysis of antibodies anti-MCV with analysis of anti-CCP in a cohort of patients with early RA. Clinical course, radiographic destruction, and presence of anti-CCP antibodies in this cohort have previously been characterized (16).

PATIENTS AND METHODS

Patients and healthy controls. The study included 273 patients who fulfilled the ACR classification criteria for RA (3) and had previously been enrolled consecutively in a prospective cohort of patients with early RA (<12 months disease duration) followed up at Karolinska University Hospital (Solna, Sweden) between January 1995 and October 2000 (16). Patients were diagnosed and treated in the absence of any information on their serologic status regarding antibody reactivities against citrullinated proteins/peptides. Clinical evaluation has been described previously (16). Clinical data and serum samples were collected at baseline, after 3 months, and after 1, 2, 3, and 5 years. Serum levels of anti-MCV and anti-CCP were measured in all patient sera at baseline, after 3 months, and after 1 year. Serum studies were conducted in a defined subgroup of 72 patients at 2, 3, and 5 years. Clinical data were available in all patients at baseline and in 265 (97.1%) at 3 months, 238 (87.2%) at 1 year, 235 (86.1%) at 2 years, 225 (82.4%) at 3 years, and 145 (53.1%) at 5 years.

At baseline, 123 (45.1%) of the 273 patients were receiving sulfasalazine, and 64 (23.4%) were receiving methotrexate. Twenty-one patients were taking auranofin, 6 were

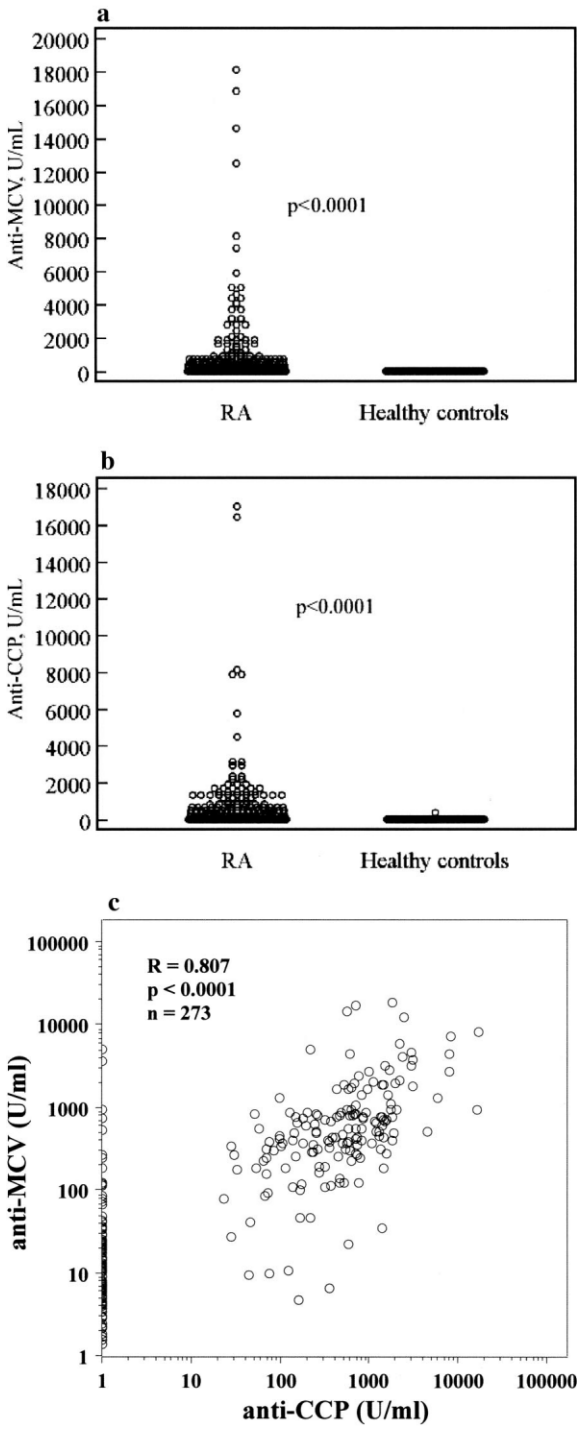

Figure 1. a and **b,** Levels of antibodies against modified citrullinated vimentin (anti-MCV) (**a**) and antibodies against cyclic citrullinated peptides (anti-CCP) (**b**) in 273 patients with early rheumatoid arthritis (RA) and 100 healthy controls, analyzed according to the instructions of the manufacturers. Each circle represents 1 individual. Both analyses were performed on the same patients and controls. **c**, Correlation between levels of anti-CCP and levels of anti-MCV in all 273 RA patients. Levels of anti-CCP <25 units/ml are depicted as 1 unit/ml.

Table 1. Baseline characteristics of the 273 RA patients*

	All patients (n = 273)	Anti-MCV–positive patients (n = 193)	Anti-MCV–negative patients (n = 80)
Age at baseline, median years	57.0	55.0	60.5†
Sex, no. (%) female	193 (70.7)	138 (71.5)	55 (68.8)
Disease duration at baseline, median months	5	6	4‡
No. RF positive§	172	156	16¶
No. anti-CCP positive	158	153	5¶
CRP level, median mg/liter	15	16	13
ESR, median mm/hour	21	24	18.5#
Physician's assessment of disease activity, median	2	2	2
No. of swollen joints, median	9	9	8
No. of tender joints, median	7	7	7
DAS28, median	5.02	5.02	5.01
Global VAS score, median	45	45	47.5
Pain VAS score, median	45	45	45.5
HAQ score, median	0.88	0.88	0.88
No. initially receiving DMARDs	231	159	72

* Differences between median values were analyzed using the Mann-Whitney U test, and differences between proportions were analyzed using the chi-square test. RA = rheumatoid arthritis; anti-MCV = antibodies against modified citrullinated vimentin; anti- CCP = antibodies against cyclic citrullinated peptides; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DAS28 = Disease Activity Score in 28 joints; VAS = visual analog scale; HAQ = Health Assessment Questionnaire; DMARDs = disease-modifying antirheumatic drugs.
† $P = 0.012$ versus anti-MCV–positive patients.
‡ $P = 0.0002$ versus anti-MCV–positive patients.
§ Information on rheumatoid factor (RF) status was available for 192 anti-MCV–positive patients and 79 anti-MCV–negative patients.
¶ $P < 0.0001$ versus anti-MCV–positive patients.
# $P = 0.016$ versus anti-MCV–positive patients.

receiving antimalarials, 3 were taking sodium aurothiomalate, and 12 were receiving other drugs. Forty-two patients (15.4%) were not taking any disease-modifying antirheumatic drugs (DMARDs) at baseline. Two patients were initially treated with a combination of 2 DMARDs. Data on anti-CCP and antibodies against type II collagen in 279 patients, including the 273 patients in the present study, have been described elsewhere (16,17). Six of the patients included in the previous study on anti-CCP (16) were excluded from the present study due to current lack of baseline serum samples, and statistical data concerning anti-CCP were recalculated for the present comparison. Sera from the same 100 healthy individuals were used as controls for both anti-MCV and anti-CCP. The study was approved by the appropriate ethics review boards, and informed consent was obtained from all patients and controls.

Anti-MCV, anti-CCP, RF, and radiographic changes. Anti-MCV levels were measured in duplicate using a commercial ELISA kit (Anti-MCV) according to the recommendations of the manufacturer (Orgentec Diagnostika, Mainz, Germany). Values >20 units/ml were considered positive, consistent with the recommendation of the manufacturer. Values above the standard curve were further diluted to obtain quantitatively definite values. The nature of the modified citrullinated vimentin antigen used in the ELISA kit has recently been described (18). Anti-CCP was measured using the Immunoscan RA Mark 2 assay (Euro-Diagnostica, Malmö, Sweden), and the cutoff point was set to 25 units/ml. We used the anti-CCP values previously determined (16) for the 273 patients in the present study. RF was measured by nephelometry and recorded at the first visit as a qualitative (positive/negative) value.

Radiographs were scored by an experienced investigator (MCW) according to the Larsen method (19), as previously described (16), and documented using "X-Ray Rheuma-Coach" software (20). Information on change in Larsen score was obtained by subtracting the baseline Larsen score from the score at 1 year or the score at 2 years or by subtracting the Larsen score at 1 year from the score at 2 years.

Statistical analysis. The Mann-Whitney U test was used for comparison of levels in different groups, whereas the chi-square test was used for comparisons of different proportions. Wilcoxon's signed rank test was used to evaluate changes in antibody levels over time. Spearman's rank correlation with correction for ties was used to analyze correlations between levels of anti-MCV and anti-CCP and between percent changes in anti-MCV or anti-CCP during the first study year and changes in clinical parameters expressed as differences between values at various time points and baseline value. Analysis of variance was used to investigate the association between the ratio of anti-MCV level at 1 year to baseline anti-MCV level and DMARD treatment at the time of diagnosis, and Fisher's protected least significant difference was used for post hoc analysis. P values less than 0.05 were considered significant. No corrections for multiple comparisons were made.

RESULTS

Higher sensitivity and equal specificity of anti-MCV compared with anti-CCP. At baseline, 193 (70.7%) of the 273 patients with RA had anti-MCV levels >20 units/ml. The median anti-MCV level in anti-MCV–positive patients was 412.0 units/ml (range

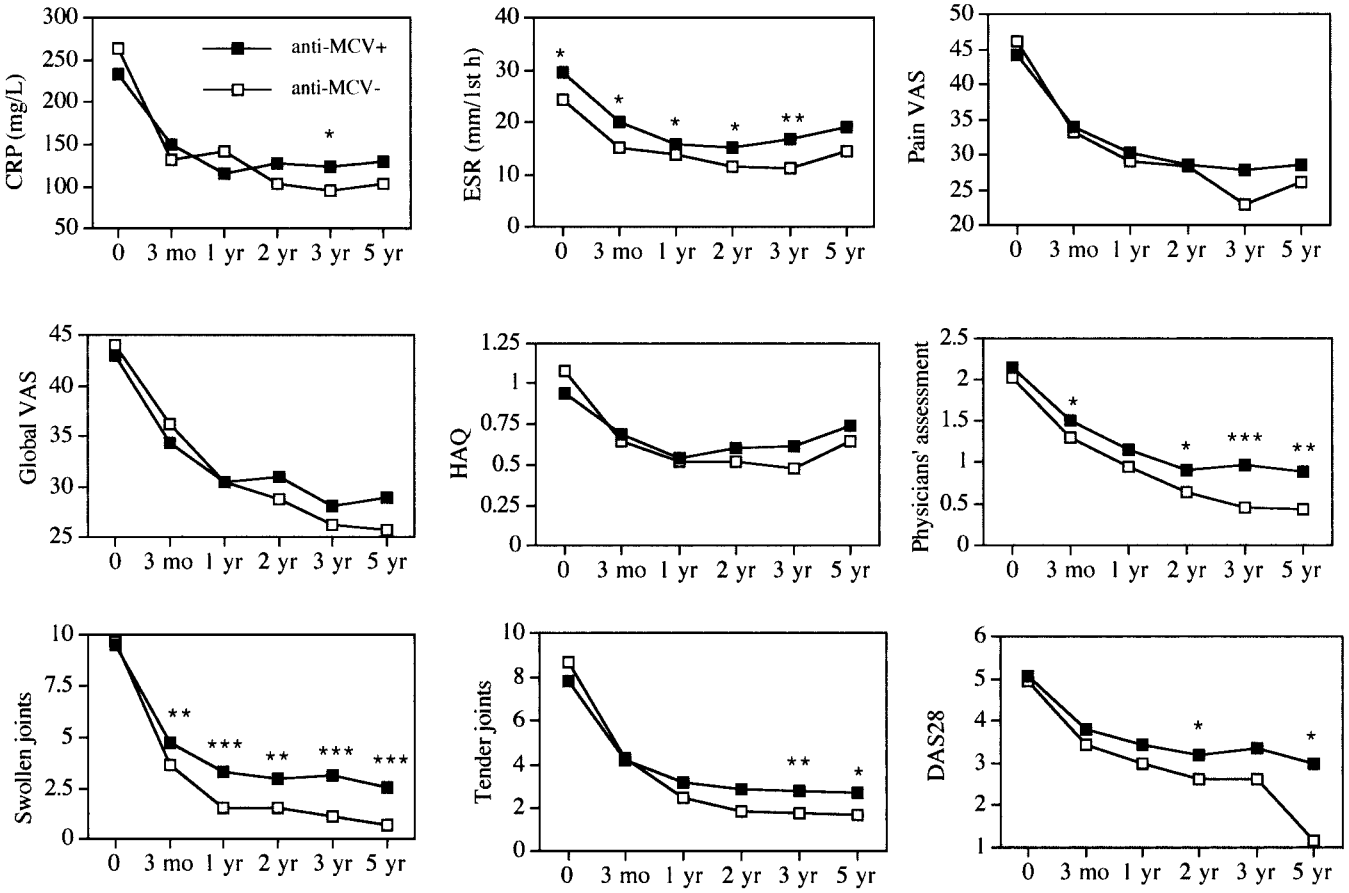

Figure 2. Changes in clinical indices in patients who were positive for antibodies against modified citrullinated vimentin (anti-MCV) (n = 193) and patients who were negative for anti-MCV (n = 80). Values are the mean. * = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$, versus anti-MCV–negative patients. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale; HAQ = Health Assessment Questionnaire; DAS28 = Disease Activity Score in 28 joints.

20.2–18,100), and the mean ± SD anti-MCV level was 1,147 ± 2,465 units/ml. Of the 100 healthy controls, 2 were found to have positive anti-MCV values (49.7 and 86.2 units/ml), and 3 were found to have borderline positive values (20.3, 23.8, and 29.1 units/ml) (Figure 1a). The difference in anti-MCV levels between RA patients and healthy controls was highly significant ($P <$ 0.0001).

At baseline, 158 (57.9%) of the 273 RA patients had anti-CCP levels >25 units/ml, and 4 of the 100 healthy controls were positive for anti-CCP (with levels of 35.5, 43.2, 44.2, and 352.5 units/ml; $P < 0.0001$ versus RA patients) (Figure 1b). Five of the 158 anti-CCP–positive patients with RA (1.8% of all patients) were anti-MCV negative, while 40 of the 115 anti-CCP–negative patients (14.7% of all patients) were anti-MCV positive. Altered anti-MCV status during the followup period was found in 12.5% of the patients (14 of the 80 initially anti-MCV–negative patients were found to be anti-MCV positive, and 20 of the 193 initially anti-MCV–positive patients were found to be anti-MCV negative at some time point during the followup period). Overall, 207 (75.8%) of the 273 patients were found to be anti-MCV positive at some point during the followup period, and 161 (59.0%) were found to be anti-CCP positive at some point during the followup period. There was a strong correlation between anti-MCV levels and anti-CCP levels at baseline for all patients (R = 0.807, $P < 0.0001$) (Figure 1c).

Prognostic value of anti-MCV status at baseline. Baseline characteristics of the patients with RA are presented in Table 1. Anti-MCV positivity was strongly associated with both anti-CCP positivity and RF positivity at baseline. Patients with detectable anti-MCV antibodies at baseline were significantly younger than anti-MCV–negative patients (median age 55 years and 60.5

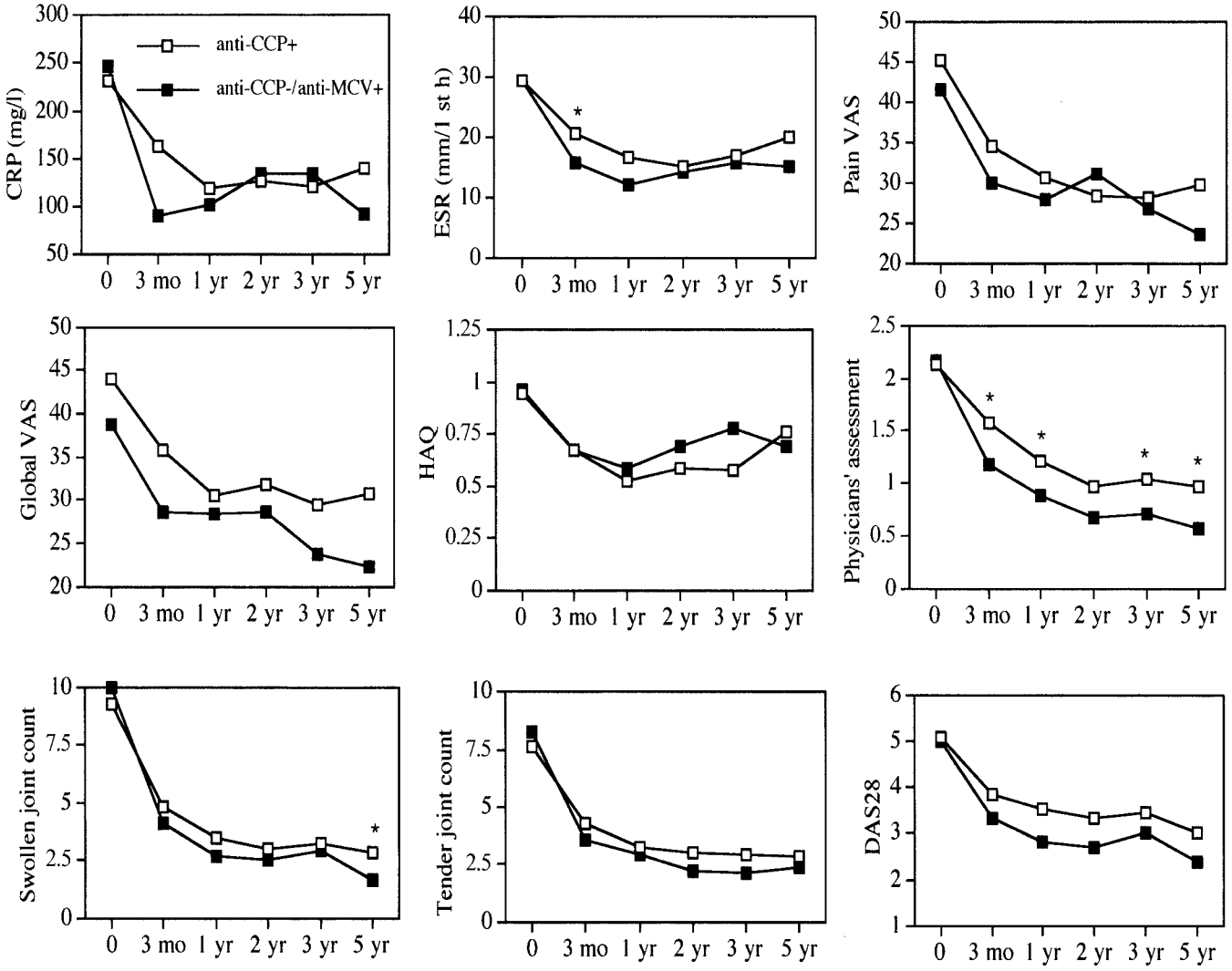

Figure 3. Changes in clinical indices in patients who were positive for antibodies against cyclic citrullinated peptide (anti-CCP) (n = 158) and patients who were negative for anti-CCP and positive for anti-MCV (n = 40). Values are the mean. * = $P < 0.05$ versus anti-CCP–negative/anti-MCV–positive patients. See Figure 2 for other definitions.

years, respectively) ($P = 0.012$). The only clinical difference between anti-MCV–positive patients and anti-MCV–negative patients at baseline was a significantly higher erythrocyte sedimentation rate (ESR) among anti-MCV–positive patients ($P = 0.016$). During the followup period, anti-MCV–positive patients showed higher disease activity according to physician's assessment and Disease Activity Score in 28 joints (DAS28) (21), and had more swollen and tender joints than anti-MCV–negative patients. These differences increased during the followup period (Figure 2).

The differences between anti-MCV–positive and –negative patients over time with regard to physician's assessment of disease activity (Figure 2) were somewhat less striking than the differences between anti-CCP–positive and –negative patients (16). We also compared the group of patients who were anti-CCP negative but anti-MCV positive (n = 40) with both the group of patients who were anti-CCP positive (n = 158) and the group of patients who were negative for both anti-MCV and anti-CCP (n = 75). We found that the anti-CCP–negative/anti-MCV–positive patients had a slightly better prognosis compared with the anti-CCP–positive patients, as measured by physician's assessment of disease activity (Figure 3).

Since this difference could be due to the use of different treatment strategies in anti-CCP–positive patients than in anti-CCP–negative/anti-MCV–positive

Table 2. Correlation between percent change in anti-MCV and anti-CCP levels during the first study year (ratio between antibody levels at 12 months and at baseline) and changes in clinical variables during the 5-year followup period*

Clinical variable, time point	Correlation with % change in anti-MCV level during the first study year		Correlation with % change in anti-CCP level during the first study year	
	R	*P*	R	*P*
Change in CRP level				
1 year	0.249	0.0014	0.251	0.0036
Change in ESR				
3 months	–	NS	0.174	0.0345
1 year	0.301	0.0001	0.288	0.0008
2 years	0.302	0.0001	0.184	0.0334
3 years	0.306	0.0002	–	NS
5 years	0.227	0.0216	–	NS
Change in pain VAS score				
1 year	0.198	0.0106	0.257	0.0027
Change in HAQ score				
1 year	0.264	0.0007	–	NS
2 years	0.226	0.0045	–	NS
5 years	0.257	0.0101	–	NS
Change in physician's global assessment				
1 year	0.295	0.0001	–	NS
2 years	0.312	<0.0001	–	NS
3 years	0.225	0.0059	–	NS
5 years	0.330	0.0009	–	NS
Change in swollen joint count				
1 year	0.190	0.0143	–	NS
2 years	0.177	0.0231	–	NS
3 years	0.193	0.0172	–	NS
5 years	0.212	0.0323	–	NS
Change in tender joint count				
3 months	–	NS	0.161	0.0499
Change in DAS28				
1 year	0.328	0.0038	–	NS
2 years	0.291	0.0165	–	NS
3 years	0.314	0.0077	–	NS

* Values were calculated using Spearman's rank correlation with correction for ties. Only patients who were anti-MCV positive at baseline (n = 193) and patients who were anti-CCP positive at baseline (n = 158) were included. All clinical variables shown in Figures 2 and 3 were assessed at the 3-month, 1-year, 2-year, 3-year, and 5-year time points; only time points with at least 1 significant correlation are shown. NS = not significant (see Table 1 for other definitions).

patients, we examined the treatments prescribed. Anti-CCP–positive and anti-CCP–negative/anti-MCV–positive patients showed the same general treatment pattern at baseline (16), except that fewer of the anti-CCP–negative/anti-MCV–positive patients were not receiving DMARDs (10% versus 20%; *P* not significant). This difference disappeared after 1 year, at which point 9.5% of the anti-CCP–positive and 12.5% of the anti-CCP–negative/anti-MCP–positive patients were not receiving DMARDs.

Except for significantly more functional disability at 3 years, as measured by the Swedish version of the Stanford Health Assessment Questionnaire (HAQ) (22), anti-CCP–negative/anti-MCV–positive patients never differed from anti-CCP–negative/anti-MCV–negative patients with regard to the variables presented in Table 1 (data not shown).

Correlation of changes in anti-MCV levels with treatment and with changes in clinical variables during followup. Anti-MCV levels among patients who were anti-MCV positive at baseline declined significantly during the first study year ($P = 0.0004$), and a parallel decline was observed during the first 2 years ($P = 0.0006$) and 3 years ($P = 0.0029$) (data not shown). Thereafter, anti-MCV levels increased, and were significantly higher at 5 years versus 1 year ($P = 0.0020$), versus 2 years ($P = 0.0183$), and versus 3 years ($P = 0.0001$). Early decrease and late increase in anti-CCP levels were previously reported in this cohort of RA patients (16).

Table 3. Comparison of median Larsen score and median Larsen score progression during the first 2 years after diagnosis, in subgroups of the 273 patients with early RA*

	Larsen score at baseline	Larsen score at 1 year	Larsen score at 2 years	Change in Larsen score from baseline to 1 year	Change in Larsen score from baseline to 2 years	Change in Larsen score from 1 year to 2 years
RF+ (n = 172)	4.000	11.000	14.250	4.500	7.250	2.500
RF− (n = 99)	5.000	10.500	13.125	4.250	6.250†	1.125‡
Anti-CCP+ (n = 158)	4.000	10.500	14.000	4.500	7.375	2.750
Anti-CCP− (n = 115)	5.125	11.625	13.250	4.250	6.250§	1.000¶
Anti-MCV+ (n = 193)	4.250	11.000	14.250	4.500	7.500	2.750
Anti-MCV− (n = 80)	5.250	10.375	10.500	4.125	5.250#	1.000**
Anti-MCV+/anti-CCP− (n = 40)	5.250	13.250	18.000	5.000	8.750	3.000
Anti-MCV−/anti-CCP− (n = 75)	5.000	10.250	10.250	4.000	5.250††	1.000‡‡
Anti-CCP+ (n = 158)	4.000	10.500	14.000	4.500	7.375	2.750
Anti-MCV+/anti-CCP− (n = 40)	5.250	13.250	18.000	5.000	8.750	3.000

* Differences between groups were analyzed using the Mann-Whitney U test. Information on RF status was available for 271 patients. See Table 1 for definitions.
† $P = 0.0258$ versus RF+ patients.
‡ $P = 0.0004$ versus RF+ patients.
§ $P = 0.0126$ versus anti-CCP+ patients.
¶ $P < 0.0001$ versus anti-CCP+ patients.
# $P = 0.0034$ versus anti-MCV+ patients.
** $P < 0.0001$ versus anti-MCV+ patients.
†† $P = 0.0160$ versus anti-MCV+/anti-CCP− patients.
‡‡ $P = 0.0075$ versus anti-MCV+/anti-CCP− patients.

The drop in anti-MCV level during the first study year was dependent on the medication used. Detailed post hoc analysis showed a greater decline in anti-MCV titers in patients initially treated with sulfasalazine or auranofin versus patients initially treated with methotrexate ($P = 0.0025$ for sulfasalazine and $P = 0.0213$ for auranofin). In these comparisons patients treated with sulfasalazine or with auranofin showed the most pronounced reductions in anti-MCV levels during the first year.

Initial levels of anti-MCV showed only weak correlations with the clinical variables detailed in Table 1 (data not shown). However, strongly significant positive correlations were found between changes in anti-MCV level among anti-MCV–positive patients during the first study year and changes in ESR, HAQ, physician's assessment of disease activity, number of swollen joints, and DAS28. The same strong relationships were not found between changes in anti-CCP levels and disease activity (Table 2).

Greater radiographic progression in anti-MCV–positive patients than in anti-MCV–negative patients. Radiographic scores did not differ between anti-MCV–positive and –negative patients at the investigated time points. However, analysis of the change in Larsen score showed faster rates of radiographic destruction in anti-MCV–positive than in anti-MCV–negative patients between baseline and 2 years ($P = 0.0034$) and especially between 1 year and 2 years ($P < 0.0001$) (Table 3). Corresponding differences were seen when anti-CCP–positive patients were compared with anti-CCP–negative patients. Similar but somewhat weaker differences were found for RF (Table 3).

We then analyzed only the subgroup of patients with RA who did not have elevated anti-CCP levels at baseline (n = 115). When these patients were split into 2 groups, anti-MCV–positive patients (n = 40) and anti-MCV–negative patients (n = 75), we noted similar findings as for anti-MCV and anti-CCP in the entire RA cohort. Although anti-CCP–negative/anti-MCV–positive and anti-CCP–negative/anti-MCV–negative patients did not differ with regard to Larsen score at any time point, we found similar differences in the change in Larsen score between the groups during the first 2 years ($P = 0.0160$), and particularly for changes during the second year ($P = 0.0075$). There was, however, no difference between anti-CCP–positive patients (n = 158) and patients positive for only anti-MCV at baseline (n = 40) (Table 3).

DISCUSSION

We compared a new diagnostic ELISA for RA, anti-MCV, with the commonly used anti-CCP ELISA (CCP2). In our cohort of patients with RA, anti-MCV had higher sensitivity at baseline than did anti-CCP. Both tests showed comparable specificity when RA patients were compared with healthy controls, consistent with preliminary results reported by Egerer et al (14).

Both anti-CCP positivity and anti-MCV positivity at the time of diagnosis predicted severe disease outcome. Autoantibody-positive patents had worse disease outcome, as measured by physician's assessment of disease activity, number of swollen and tender joints, and DAS28, compared with autoantibody-negative patients, and the differences in clinical parameters between positive and negative groups increased over time.

The subgroup of initially anti-MCV–positive patients who were anti-CCP negative was situated in between the group of anti-CCP–positive patients and the group of patients negative for both anti-MCV and anti-CCP, with regard to prognosis. Patients who were positive for anti-MCV but not anti-CCP had significantly lower disease activity, as evaluated by experienced rheumatologists, than did anti-CCP–positive patients at all followup occasions except at 2 years. However, patients who were positive for anti-MCV only and those who were anti-CCP positive both had significantly faster rates of radiographic destruction compared with anti-CCP–negative/anti-MCV–negative patients. Anti-MCV positivity therefore seems to indicate poor radiographic prognosis in a larger group of RA patients than does anti-CCP positivity.

A possible reason for the intermediate prognosis in the group of anti-CCP–negative/anti-MCV–positive patients might be that anti-MCV reactivity represents 3 different immune reactivities, against (modified) vimentin, against citrullinated epitopes, or (in the largest group) against a combination of these. According to this hypothesis, patients who were positive for anti-MCV only would have isolated vimentin reactivity without concomitant reactivity to citrullinated epitopes, and might have a different prognosis than patients in the anti-CCP–positive group.

The predictive values of baseline anti-MCV and anti-CCP levels during the 5-year followup period in the entire cohort were very similar with regard to number of swollen joints, but somewhat stronger for anti-CCP with regard to ESR, physician's assessment of disease activity, and DAS28. This discrepancy is probably due to the large number of patients expressing only anti-MCV, who had an intermediate disease course between that observed in anti-CCP–positive patients and that in patients not expressing either anti-MCV or anti-CCP.

The magnitude of the change in anti-MCV level during the first year showed a high degree of correlation with changes in clinical parameters, especially ESR, swollen joint count, physician's assessment of disease activity, and DAS28. Data regarding correlation with changes in anti-CCP levels were not that impressive. This association between marked decrease in anti-MCV levels and clinical improvement implies that anti-MCV might be a more sensitive indicator of disease activity than anti-CCP. The association between sulfasalazine treatment and decrease in anti-CCP level during the first study year, described previously (16), was also seen for anti-MCV. Patients were enrolled in this cohort before the general introduction of tumor necrosis factor α (TNFα) blocking agents, and further studies are needed to investigate the effects of TNFα blockade on anti-MCV levels.

There is a risk that RF might interfere and create false-positive results in ELISAs for evaluation of other antibodies. The data presented in Table 1 show that 36 (18.8%) of the 192 anti-MCV–positive patients for whom information on RF status was available were RF negative. We have also rerun the baseline samples in this study with quantitative RF nephelometry. Although we expected an association between RF and anti-MCV (since there is an association between RF and anti-CCP), the correlation between RF and anti-MCV was very weak ($R = 0.165$). We therefore conclude that RF probably does not interfere with the measurement of anti-MCV.

A weakness of the current study is the control population. Even though we found comparable specificity for anti-MCV and anti-CCP using healthy blood donors as a control group, the specificity analysis should be repeated using clinically relevant control groups, including patients with other rheumatic diseases and infectious diseases, as has been done for anti-CCP (5) and in a recent study of anti-MCV (15). That study was, however, limited by the small number of patients with early RA ($n = 23$) and lack of clinical and laboratory followup data, which prevented investigation of the prognostic significance of anti-MCV in RA as we have done in the present study.

Early reports that claimed antibodies against citrullinated epitopes have an exclusive specificity for RA (5) have been challenged by recent findings. Both in patients with juvenile idiopathic arthritis (23,24) and in patients with psoriatic arthritis (25–27), limited increases in frequency compared with healthy controls have been described, and subgroup analyses have demonstrated

that antibody-positive patients have RA-like disease features, such as polyarthritic disease, RF positivity, and radiographic erosions. The value of analysis of anti-MCV in patients with juvenile idiopathic arthritis and psoriatic arthritis remains an open question.

The presence of anti-Sa antibodies, which at least partly react with citrullinated vimentin (8,12), has previously been shown to correlate with clinical prognosis of RA (8–10). In our study we also found that both anti-CCP–positive and anti-MCV–positive patients have worse disease outcome and faster rates of bone destruction compared with patients who are not initially positive for these serologic markers. Thus, anti-MCV not only has higher sensitivity than anti-CCP but is also a better prognostic marker of future radiographic changes. This is consistent with the findings of Boire et al (10), who have shown that anti-Sa antibodies are better prognostic markers of radiographic destruction than are anti-CCP and RF.

Results of the present study showed the utility of measurement of humoral reactivity against citrullinated vimentin, which is one of several potentially important citrullinated autoantigens in RA. Similar evaluations of autoantibodies against other joint-targeted citrullinated autoantigens, such as fibrin (28), α-enolase (29), and type II collagen (17,30), in clinically well-characterized RA cohorts are needed.

In conclusion, anti-MCV has a higher sensitivity than anti-CCP and defines a group of patients with early RA with poor prognosis. The anti-MCV test therefore seems to be a promising diagnostic and prognostic marker in early RA.

AUTHOR CONTRIBUTIONS

Dr. Rönnelid had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Mathsson, Sjöberg, Rönnelid.

Acquisition of data. Mathsson, Mullazehi, Wick, Klareskog, Rönnelid.

Analysis and interpretation of data. Mathsson, Wick, van Vollenhoven, Rönnelid.

Manuscript preparation. Mathsson, Mullazehi, Wick, Sjöberg, van Vollenhoven, Klareskog, Rönnelid.

Statistical analysis. Mathsson, Rönnelid.

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