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EXTENDED REPORT

Predictive value of autoantibodies from anti-CCP2, anti-MCV and anti-human citrullinated fibrinogen tests, in early rheumatoid arthritis patients with rapid radiographic progression at 1 year: results from the ESPOIR cohort

Yannick Degboé,[1,2] Arnaud Constantin,[1,2] Delphine Nigon,[1] Gabriel Tobon,[3] Martin Cornillet,[4,5] Thierry Schaeverbeke,[6] Gilles Chiocchia,[7] Pascale Nicaise-Roland,[8] Leonor Nogueira,[4,5] Guy Serre,[4,5] Alain Cantagrel,[1,2] Adeline Ruyssen-Witrand[1,9]

For numbered affiliations see end of article.

Correspondence to
Dr Yannick Degboé;
degboe@gmail.com

ABSTRACT

Objectives: We compared the ability of antibodies against cyclic citrullinated peptides (anti-CCP2), against mutated citrullinated vimentin (anti-MCV) and against citrullinated fibrinogen (AhFibA) to predict 1 year rapid radiographic progression (RRP; total Sharp score variation ≥5 points), in early rheumatoid arthritis (RA).

Methods: We analysed 566 patients from the ESPOIR cohort with early RA fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria at year 1. We assayed the 3 anticitrullinated peptide antibodies (ACPA) tests on baseline sera. We compared the performance of these 3 ACPA tests to predict first-year RRP, by comparing areas under the receiver operating characteristic curves (ROCs). We assessed the 1 year RRP risk by ACPA titres. We used a logistic multivariate regression to analyse RRP risk in terms either of ACPA positivity or titre: high (>3 times the N cut-off) and low (1 to 3N).

Results: 145 patients displayed RRP. Areas under the ROCs were similar (0.60) for the 3 tests. High ACPA titres were associated with 1 year RRP, whatever the test was, and with similar ORs. Low+ anti-MCV titres were not associated with 1-year RRP, whereas low+ anti-CCP2 titres (p=0.0226) and low+ AhFibA titres (p=0.0332) were significantly associated. In multivariate analysis, 1 year RRP was associated with anti-CCP2 positivity (p<0.0001), AhFibA positivity (p<0.0001) and high anti-MCV titres (p<0.0001).

Conclusions: Anti-CCP2 antibodies and AhFibA were predictive of 1 year RRP in early RA whatever their titre was, whereas only high anti-MCV antibody titres were predictive, potentially making them more discriminant to predict 1 year RRP risk.

Key messages

What is already known about this subject?
Anticitrullinated peptide antibodies (ACPA) are among the best predictors of erosive rheumatoid arthritis (RA), but data concerning ACPA specificity and radiographic progression showed discrepancies.

What does this study add?
We showed that anticitrullinated fibrinogen antibodies (AhFibA) predict 1 year rapid radiographic progression as well as antibodies detected by anticyclic citrullinated peptide (anti-CCP2) test. We showed that antimutated citrullinated vimentin antibody (anti-MCV) titres were predictive of 1 year rapid radiographic progression.

How might this impact on clinical practice?
AhFibA test should be considered not only as a valuable test for RA diagnosis, but also for RA radiographic prognosis. Considering anti-MCV titres rather than their positivity is potentially discriminant to predict 1 year rapid radiographic progression.

INTRODUCTION

Anticitrullinated peptide antibodies (ACPA) are the most specific autoantibodies known as markers of rheumatoid arthritis (RA). In cohorts of early RA, ACPA are associated with increased clinical disease activity and progression of structural damage.[1] ACPA have high weight in the final scoring system of the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA classification criteria for RA.[2] This weight is modulated by the ACPA

titre (negative, low and high), with increased risk of RA being associated with high titres.

Data concerning the link between the structural expression of RA and ACPA detected with various tests show discrepancies. In four works performed in early RA with various ACPA tests using different antigens, the link between ACPA and structural progression was variable.[3–6] In the work of Fisher et al,[3] radiographic progression (RRP) over 2 years was greater for ACPA-positive than for ACPA-negative patients; however, anti-CEP-1 antibodies (directed to citrullinated α-enolase) did not confer additional severity. In a study by Scherer et al,[5] the structural damage progression over 5 years in ACPA-positive patients was not associated with any antibody to the six citrullinated peptides used as antigens (2 from vimentin, 2 from fibrinogen, 1 from α-enolase, 1 from myelin basic protein). The extent of the ACPA epitope directory analysed on these peptides did not modify the structural prognosis.

However, three studies considered antimutated citrullinated vimentin (anti-MCV) antibodies as an additional marker of structural severity.[7–9] Montes et al[9] found that patients with antibodies to the citrullinated vimentin peptide 60–75 show a higher prevalence of erosions than patients without, independently of their positivity for anticyclic citrullinated peptide (anti-CCP2) antibodies. Harre et al[7] found that the presence of anti-MCV antibodies could increase osteoclastogenesis and bone resorption.

Our work compared ACPA assayed with three different tests. The anti-CCP2 antibodies were considered as the reference because of their wider usage. We evaluated the anti-MCV antibodies because of the supposed direct pro-erosive role of anticitrullinated vimentin antibodies.[7] Lastly, we evaluated the anti-human citrullinated fibrinogen antibodies (AhFibA) since citrullinated fibrin is the main ACPA autoantigen in the synovial tissue of patients with RA.[10] The 3 tests have shown similar value for the diagnosis of RA in early arthritis,[11] but, to date, only a few studies have assessed their performance in terms of structural outcome and, moreover, they show some discrepancies.[12–17]

This work aimed to compare anti-CCP2 antibodies, anti-MCV antibodies and AhFibA, all assayed at baseline in the patients of the ESPOIR cohort, and to analyse their association with rapid RRP at 1 year.

METHODS
Patients
Eight hundred and thirteen patients with suspected or confirmed diagnosis of early RA, referred to 1 of 14 regional centres, were included in the French ESPOIR cohort. The inclusion criteria of ESPOIR cohort were: age 18–70 years, more than two swollen joints for >6 weeks and <6 months, suspected or confirmed diagnosis of RA and not taking any disease-modifying antirheumatic drugs (DMARDs) or steroids except for

<2 weeks before enrolment. We analysed data from 3 ACPA tests at baseline (anti-CCP2, anti-MCV, AhFibA) and from radiographic assessment at baseline and at 1 year, for 566 patients fulfilling the 2010 ACR/EULAR criteria at year 1. Patients were excluded from analysis because of 232 missing radiographs at baseline or year 1, 109 did not fulfil ACR/EULAR criteria and 115 had missing data for ACPA (crude counts; some patients had several missing data). All patients gave their written informed consent to the prospective follow-up study before inclusion. Further details concerning patients are provided in a previous publication.[18]

Clinical evaluation
For each patient, we collected data on age, sex, smoking, symptom duration, Disease Activity Score in 28 joints, patient and physician visual analogue scale score for global assessment, functional ability by Health Assessment Questionnaire-Disability Index and disease activity by the Simple Disease Activity Index.

Biological evaluation
ACPA tests were assessed at baseline. Anti-CCP2 (DiaSorin) and anti-MCV antibodies (Orgentec) were assayed in Montpellier or Paris centres. AhFibA were assayed in the Toulouse centre with an in-house ELISA.[11] For these ACPA tests, we used the positivity threshold (N) corresponding to the 95% diagnostic specificity: anti-CCP2 >25 U/mL, anti-MCV >20 UA/mL, AhFibA >0.056 AU. ACPA tests were also assessed at the 98% diagnostic specificity threshold: 40 U/mL for anti-CCP2, 35 UA/mL for anti-MCV and 0.119 AU for AhFibA. Moreover, the anti-CCP2 test was assessed at a previously validated cut-off: 50 U/mL.[11] Over the cut-off sera were considered positive. Considering the weight of ACPA titres in the 2010 ACR/EULAR criteria, we assessed the antibody titres, classified as high positive if >3 times the cut-off (3N), and low positive if 1 to 3 times the cut-off.[2] IgM rheumatoid factor (RF) (Menarini Diagnostics) was considered positive if >9 UI/mL. *HLA-DRB1* 4-digit typing and subtyping was performed in a single laboratory (Immunology laboratory, CHU Montpellier, France) using a PCR-based method. Erythrocyte sedimentation rate and C reactive protein (CRP) level were measured at baseline, then at each visit in each centre.

Radiographic evaluation
Radiographs of hands (anteroposterior view) and feet (anteroposterior and oblique views) were performed at inclusion and at 1 year. All radiographs were evaluated blinded by a single reader (GT, CHU Brest) by the van der Heijde-modified Sharp score. Results were expressed as total van der Heijde-modified Sharp score (mTSS). Intra-reader correlation coefficient was 0.97. The smallest detectable change was estimated at 1 point. RRP was defined as an increase in the mTSS ≥5 points per year.[19] In this study, 145 patients displayed RRP.

Statistical analysis

The primary end point was to compare the performance of the 3 ACPA tests to predict first-year RRP by comparing areas under the receiver operating characteristic curves (AUC). Secondary end points were (1) to assess the 1 year RRP risk linked to the baseline ACPA titres, and (2) to further analyse the 1 year RRP risk by multivariate analysis including ACPA positivity and high ACPA titres if associated on univariate analysis. For descriptive analysis, continuous quantitative data with normal distribution are expressed as mean+SD and with non-normal distribution as median+IQR. One-year RRP was compared by autoantibody titres in terms of class (negative, low and high) by χ^2 test. We modelled 1 year RRP risk by backward logistic multivariate regression, with 1 model for each test. The covariates tested included age, gender, duration of disease course before inclusion, smoking consumption, clinical centre, presence of erosions at inclusion, presence of the HLA-DRB1 shared epitope (SE) and ACPA, RF and CRP positivity. The use of steroids, or synthetic or biological DMARDs (within the first year) was included in the model. Covariates were selected if associated on univariate analysis ($\alpha=20\%$). Performance of the models was compared by area of the receiver operating characteristic curve analysis for each model. p Value <0.05 was considered statistically significant, with a 95% CI.

Further details concerning Methods section are provided in a previous publication.[18]

RESULTS

Characteristics of patients with RA

We analysed data from 566 patients with early RA, having a complete biological and radiographic set of data. The main characteristics of patients are shown in table 1. Three hundred and thirty-three patients were positive for at least one of the three ACPA tests, 2 were anti-CCP2

Table 1 Demographic, biological and radiographic data for the patients with early rheumatoid arthritis

	Patients (n=566)	Patients without RRP at 1 year (n=421)	Patients with RRP at 1 year (n=145)	p Value
Demographic data				
Age, median (IQR)	50.5 (40.2–57.0)	49.9 (40.0–56.7)	52.4 (41.7–58.6)	NS
Women, n (%)	445 (78.6)	336 (79.8)	109 (75.2)	NS
Smokers, n (%)	272 (48.1)	204 (48.5)	68 (46.9)	NS
Disease duration in months, median (IQR)	5.0 (3.1–7.4)	4.8 (3.0–7.1)	5.2 (3.5–7.8)	NS
Biological data				
ESR, mm/1 h, median (IQR)	22 (12–37)	20 (12–34)	27 (14–49)	0.0063
CRP level, mg/L, median (IQR)	9 (0–21)	8 (0–18)	14 (5–36)	<0.0001
≥1 allele encoding HLADRB1 SE, n (%)	292 (54.0%)	205 (50.9)	87 (63.0)	0.0133
RF+, n (%)	307 (54.2)	208 (49.4)	99 (68.3)	<0.0001
Anti-CCP2 titres, n (%)				<0.0001
Negative	295 (52.1)	242 (57.5)	53 (36.5)	
Low	11 (1.9)	6 (1.4)	5 (3.4)	
High	260 (45.9)	173 (41.1)	87 (60.0)	
Anti-MCV titres, n (%)				<0.0001
Negative	268 (47.3)	217 (51.5)	51 (35.2)	
Low	51 (9.0)	44 (10.4)	7 (4.8)	
High	247 (43.6)	160 (38.0)	87 (60.0)	
AhFibA titres, n (%)				<0.0001
Negative	272 (48.1)	225 (53.4)	47 (32.4)	
Low	30 (5.3)	20 (4.8)	10 (6.9)	
High	264 (46.6)	176 (41.8)	88 (60.7)	
Radiographic data				
Baseline mTSS, median (IQR)	3 (0–7)	2 (0–7)	3 (0–8)	NS
mTSS at 1 year, median (IQR)	6 (2–12)	4 (2–8)	13 (8–19)	<0.0001
mTSS progression, median (IQR)	2 (0–5)	0 (0–2)	8 (6–11)	<0.0001
Baseline therapeutic data				
Steroids	71 (12.5)	51 (12.1)	20 (13.8)	NS
Year 1 therapeutic data				
Steroids	259 (45.8)	190 (45.4)	69 (47.6)	NS
Any DMARDs	436 (82.4)	315 (80.2)	121 (89.0)	0.020
Biologics	40 (7.1)	30 (7.1)	10 (6.9)	NS

AhFibA, antihuman citrullinated fibrinogen antibodies; anti-CCP2, anticyclic citrullinated peptides generation 2 antibodies; anti-MCV, antimutated citrullinated vimentine antibodies; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; mTSS, van der Heijde modified total sharp score; DMARDs, disease modifying antirheumatic drugs; RF, rheumatoid factor; RRP, rapid radiographic progression; SE, presence of at least one allele of the shared epitope of HLA-DRB1.

+/anti-MCV−/AhFibA−, 32 were anti-CCP2−/anti-MCV +/AhFibA− and 25 were anti-CCP2−/anti-MCV −/AhFibA+ (see online supplementary table S1). Three hundred and seven patients were positive for RF and 145 showed 1 year RRP as defined above. Serological data concerning the 98% diagnostic specificity thresholds and previously validated anti-CCP2 threshold are available in online supplementary table S2.

RRP risk at 1 year by positivity of ACPA

The AUCs for anti-CCP2, anti-MCV and AhFibA antibodies were similar, and matched with modest performance: respectively, 0.601 (95% CI 0.550 to 0.651), 0.607 (95% CI 0.555 to 0.659) and 0.599 (95% CI 0.547 to 0.651). No differences were found among the tests (p=0.87; figure 1).

Predictive values of these tests were also similar (see online supplementary table S3).

RRP risk at 1 year by baseline ACPA titres

Patients with high baseline ACPA titres (>3N) showed increased risk of RRP regardless of the test (table 2). Low anti-CCP2 and AhFibA titres were associated with a significant increase in 1 year RRP, unlike low anti-MCV. Low and high anti-CCP2 and AhFibA titres showed similar performance to predict 1 year RRP. When these two tests were positive, about one-third of patients showed 1 year RRP.

High anti-MCV antibodies titres were associated with an increase in 1 year RRP with a risk similar to that given by high anti-CCP2 or AhFibA titres. Unlike patients with hi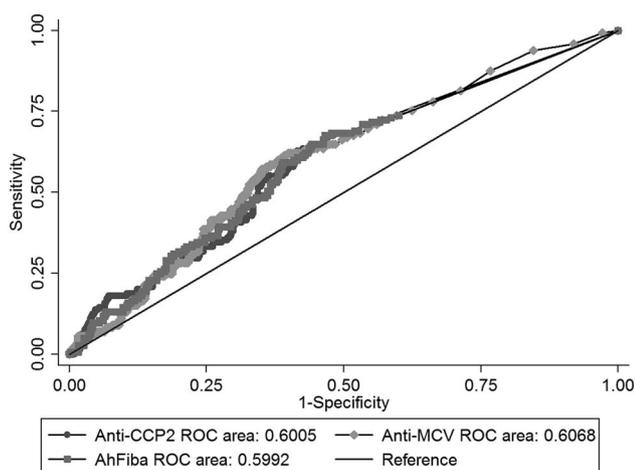gh anti-MCV titres or those positive for the other two tests, only 13.7% of the patients with low anti-MCV titres showed RRP. These results remained similar with other positivity thresholds (see online supplementary table S4).

Correlation between anti-MCV titres and mTSS evaluated by the Spearman correlation test was: 0.214; $p<10^{-6}$ (see figure 2).

RRP risk by shared epitope carriage and ACPA status

We analysed the RRP outcome in regard to the SE status and ACPA positivity (table 3). In the SE negative subgroup (249 patients), ACPA-positive patients displayed a significant higher RRP risk when compared to ACPA-negative patients. However, this increased RRP risk was observed with anti-CCP2 and AhFibA tests but not with the anti-MCV test (OR=1.86; 95% CI 0.94 to 3.64). In the SE-positive subgroup (292 patients), ORs were not different from 1, whichever the ACPA test was.

Multivariate analysis of 1 year RRP risk

To test the independence of the association of ACPA with 1 year RRP, we evaluated four multivariate models by backward logistic regression. Results are shown in table 4.

With assessment of ACPA positivity as a binary variable (presence/absence; models 1, 2 and 3), both anti-CCP2 and AhFibA tests were significantly associated with 1-year RRP (anti-CCP2: OR 2.15, 95% CI 1.43 to 3.21; AhFibA: OR 2.39, 95% CI 1.57 to 3.63). In model 2, anti-MCV positivity was not significantly associated with 1 year RRP.

In model 4, only high anti-MCV positivity was conserved among the three ACPA.

For the four models, a positive CRP level was associated with 1 year RRP, as were presence of erosions or RF positivity.

Results concerning anti-CCP2 and anti-MCV at other positivity thresholds were similar (see online supplementary table S5).

DISCUSSION

ACPA are among the best predictors of erosive RA. A direct role of the RA-specific autoantibodies in production of structural damage is highly suspected.[7] [20] In modelling the RRP risk at 1 year after inclusion in the ESPOIR cohort, we identified initial erosions, CRP positivity, RF positivity and ACPA positivity as the best prognostic markers. Even if it was expected, since AhFibA constitute a subfamily of ACPA, this work is the first to demonstrate that AhFibA positivity is comparable to anti-CCP2 positivity regarding association with the risk of 1 year RRP. For AhFibA-positive and anti-CCP2-positive patients, association with the 1 year RRP risk was significant whatever the titre. By contrast, in anti-MCV-positive patients, only those with a high titre showed increased 1 year RRP risk.

The impact of ACPA fine specificities on radiographic outcome remains difficult to specify. The discrepancies

Figure 1 Receiver operating characteristic (ROC) curves: rapid radiographic progression prognosis by anticyclic citrullinated peptides generation 2 antibodies (anti-CCP2), antimutated citrullinated vimentine antibodies (anti-MCV) and antihuman citrullinated fibrinogen antibodies (AhFibA) tests. ROC curves built on the ability of each test (for anti-CCP2, anti-MCV and AhFibA) to predict 1-year rapid radiographic progression. Area under the curve values are expressed as continuous variables.

Table 2 One-year RRP and baseline ACPA titres (anti-CCP2, anti-MCV, AhFibA)

	Number of patients with RRP (%)	OR (95% CI)	p Value (χ^2)
Anti-CCP2			
Negative	53 (18.0)	1	–
Low titre (≤3N)	5 (45.5)	3.80 (1.11 to 13.10)	0.0226
High titre (>3N)	87 (33.5)	2.30 (1.54 to 3.43)	<0.0001
p Value (OR trend)	2.90 10^{-5}		
Anti-MCV			
Negative	51 (19.0)	1	–
Low titre (≤3N)	7 (13.7)	0.68 (0.29 to 1.59)	NS
High titre (>3N)	87 (35.2)	2.31 (1.54 to 3.48)	<0.0001
p Value (OR trend)	2.96 10^{-5}		
AhFibA			
Negative	47 (17.3)	1	–
Low titre (≤3N)	10 (33.3)	2.39 (1.04 to 5.49)	0.0332
High titre (>3N)	88 (33.3)	2.39 (1.58 to 3.62)	<0.0001
p Value (OR trend)	2.08 10^{-5}		

>3N, 3 times the cut-off; ≤3N, ≤3 times the cut-off.
p Value, χ^2 test, comparisons of the percentages of patients with negative, low and high titres of antibodies, with negative as the reference.
p Value (OR trend) = test of trend.
ACPA, anticitrullinated peptide antibodies; AhFibA, antihuman citrullinated fibrinogen antibodies; anti-CCP2, anticyclic citrullinated peptides generation 2 antibodies; anti-MCV, antimutated citrullinated vimentine antibodies; RRP, rapid radiographic progression.

between studies may be explained by differences in inclusion criteria and treatment regimen across studies. Only few studies compared ACPA specificities in terms of radiographic outcome.

In our cohort, low anti-MCV titres were not associated with 1 year RRP, as compared with high ACPA titres. The threshold of 3N was more discriminating to predict the risk of RRP among patients with a positive anti-MCV test, which was not the case with two other tests. In multivariate analysis, the erosive burden brought by ACPA positivity was associated with high anti-MCV titre but not with the other two tests titres. Thus, the anti-MCV titre was discriminating to predict the evolution towards 1 year RRP unlike the other two tests titres.
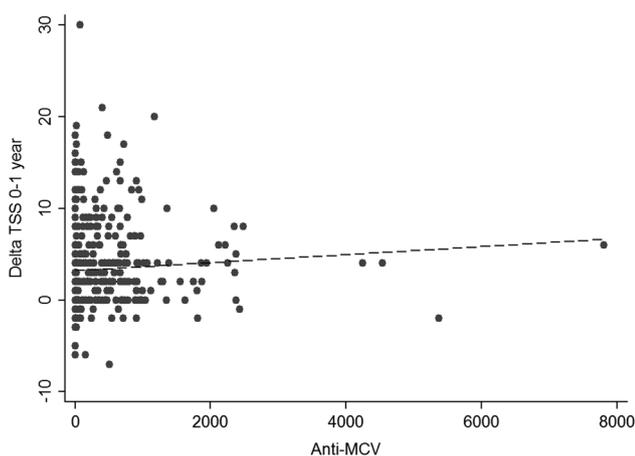

Figure 2 Spearman correlation between anticitrullinated peptide antibodies (ACPA) titres and total modified sharp score (mTSS): antimutated citrullinated vimentine antibodies (anti-MCV) test.

Syversen et al[21 22] were among the first to show that high anti-CCP2 and high anti-MCV (ELISA, Orgentec) titres added information to the radiographic outcome when compared to ACPA positivity. The observation concerning anti-MCV test supports our results. In these studies, high ACPA corresponded to the third tertile (>253 U/mL) for anti-MCV test and >200 U/mL for anti-CCP2 test. It seems important to consider that: high ACPA titres in these papers are higher than our cut-off (3 times the positivity threshold ie, 75 U/mL for anti-CCP2 and >60 U/mL for anti-MCV) and populations studied were not comparable.

In the current work, one weakness is the small sample size for patients with low anti-MCV positivity (51 patients). Most of the patients with rapid RRP had high ACPA titres (approximately 60%) and only a few (<10%) had low+ ACPA. We cannot exclude the fact that a lack of power could explain the absence of observed 1 year RRP risk in the low+ anti-MCV group. However, even with small sample size for patients with low anti-CCP2 positivity and low AhFibA positivity, we observed an overrisk of 1 year RRP. These results need to be confirmed on other cohorts of early RA.

Studies assessing prognostic relevance of anti-CCP levels often evaluated 'radiographic progression'. We assessed the correlation with the 'rapid radiographic progression' (RRP), with a different definition from 'radiographic progression'. The change in the radiographic outcome may influence the results.

Considering the anti-CCP2 test, we did not make the same observation as with the anti-MCV test, and the 3N threshold did not seem discriminating for identifying RRP RA. The wide antigen specificity of the anti-CCP2 test could also 'attenuate' the radiographic discriminating properties of some ACPA specificity titres.

Table 3 One-year RRP in regard to the shared epitope and ACPA status

	RRP+ (n)	RRP+ and ACPA+ (n)	RRP− (n)	RRP− and ACPA+ (n)	OR (95% CI)	p Value (χ^2)
Anti-CCP2						
Shared epitope +	87	62	205	126	1.55 (0.88 to 2.80)	NS
Shared epitope −	51	25	198	46	3.18 (1.59 to 6.32)	0.0003
Anti-MCV						
Shared epitope +	87	65	205	132	1.63 (0.91 to 3.02)	NS
Shared epitope −	51	24	198	64	1.86 (0.94 to 3.64)	0.0496
AhFibA						
Shared epitope +	87	66	205	132	1.74 (0.96 to 3.24)	NS
Shared epitope −	51	27	198	56	2.85 (1.44 to 5.63)	0.0009

ACPA, anticitrullinated peptide antibodies; AhFibA, antihuman citrullinated fibrinogen antibodies; anti-CCP2, anticyclic citrullinated peptides generation 2 antibodies; anti-MCV, antimutated citrullinated vimentine antibodies; N, number of patients; NS, not significant; p, results of χ^2 test; RRP, patients with rapid radiographic progression.

We analysed patients with serodiscordance between the three ACPA tests. There were only a few patients displaying serodiscordance and subgroup size was too small to draw any firm conclusion. This concordance between the three ACPA tests suggests that they detected 'similar' autoantibodies. This concordance also suggests that, to improve our knowledge of the link between autoantibodies fine specificities and radiographic outcome in RA, assessment of tests with lower concordance is needed.

Our results should be interpreted with regard to the qualitative aspect of the ACPA test used. The commercial anti-CCP2 kit uses a mix of synthetic citrullinated peptides. Thus discussion about the fine specificities of ACPA and radiographic outcome is inappropriate with this test owing to its wide specificities. This kind of report cannot be made with home-made tests such as AhFibA. Although it is justifiable to wonder about the performances of home-made tests, the AhFibA test proved it was a reliable test for RA diagnosis with similar performances to those of anti-CCP2 and anti-MCV tests when used on a large scale on the ESPOIR cohort.[11]

We assessed the relationship between SE carriage, ACPA positivity and radiographic outcome. ACPA positivity was associated with an increased RRP risk, but only in the SE negative subgroup. This result suggests an

Table 4 Multivariate analysis of variables associated with 1 year RRP

	OR	95% CI	p Value
Model 1: assessing anti-CCP2			
AUC 0.6496 (95% CI 0.5979 to 0.7003)			
Anti-CCP2 positivity	2.15	1.43 to 3.21	<0.001
CRP level (>10 mg/L)	1.73	1.15 to 2.58	0.007
Erosions at baseline	1.50	1.00 to 2.25	0.049
Model 2: assessing anti-MCV			
AUC 0.6304 (95% CI 0.5784 to 0.6825)			
Anti-MCV positivity	Discarded during logistic regression		
RF positivity	2.12	1.40 to 3.20	<0.001
CRP level (>10 mg/L)	1.80	1.21 to 2.67	0.004
Model 3: assessing AhFibA			
AUC 0.6536 (95% CI 0.6018 to 0.7055)			
AhFibA positivity	2.39	1.57 to 3.63	<0.001
CRP level (>10 mg/L)	1.68	1.13 to 2.51	0.011
Age at RA onset	1.02	1.00 to 1.04	0.031
Model 4: assessing high ACPA titre (>3N)			
AUC 0.6480 (95% CI 0.5958 to 0.7003)			
High anti-CCP2 or AhFibA titres	Discarded during logistic regression		
High anti-MCV titres	2.17	1.45 to 3.24	<0.001
CRP level (>10 mg/L)	1.69	1.13 to 2.53	0.010
Erosions at baseline	1.50	1.00 to 2.25	0.049

Models included baseline ACPA status, age, erosive status, CRP level and RF status.
ACPA, anticitrullinated peptide antibodies; AhFibA, antihuman citrullinated fibrinogen antibodies; anti-CCP2, anticyclic citrullinated peptides generation 2 antibodies; anti-MCV, antimutated citrullinated vimentine antibodies; AUC, area under (the receiver operating characteristic) curve; CRP, C reactive protein; RA, rheumatoid arthritis; RF, rheumatoid factor; RRP, rapid radiographic progression.

interaction between the SE and the ACPA status with a redundancy. This interaction could explain why we did not find an association between SE carriage and RRP in our multivariate analysis models including ACPA status. Similar results were reported in a paper by Scherer *et al.*[5] In their study, concerning patients with RA from the Leiden Early Arthritis Clinic and EURIDISS cohorts, SE alleles were associated with RRP. This association was not observed in the ACPA-positive subgroup.

Concerning comparability on therapy, we assessed the rapid RRP in different groups of patients depending on their treatment (data not shown). Baseline steroids and 1 year steroids use did not influence the 1 year RRP status. DMARDs use at year 1 influenced the radiographic course. Biologics use during the first year did not seem to influence the rapid RRP. But it is important to take into account that the inclusions were incorporated between 2002 and 2005 and that only 40 patients used biologics during the first year. Thus we cannot draw any conclusion concerning biologics. We cannot exclude the fact that some of our results could be explained, at least in part, by the treatment or the population size. We analysed the 'treatment with DMARD at year 1' as a variable (data not shown). About 83% of the patients were treated with any DMARD at year 1. Although associated with protection against rapid RRP in univariate analysis, this variable was not associated in our multivariate analysis, and keeping this variable in the three ACPA tests multivariate models did not change the results observed.

Our data concerning the anti-MCV test and the recent report of better radiographic outcome for patients with anti-MCV seronegativation[20] support the point that, among ACPA tests, the anti-MCV test may predict RRP. The anti-MCV test is specific for the diagnosis of RA; we showed that anti-MCV titres may also be informative to predict 1 year RRP.

Author affiliations
[1]Rheumatology Center, Purpan University Hospital, Toulouse, France
[2]UMR 1043, INSERM, CPTP, Toulouse, France
[3]Rheumatology Department, La Cavale Blanche Hospital, Brest, France
[4]Laboratory of Epidermis Differentiation and Rheumatoid Autoimmunity, UMR CNRS 5165, INSERM 1056, Toulouse, France
[5]Laboratory of Cell Biology and Cytology, Purpan University Hospital, Toulouse, France
[6]Rheumatology Department, Pellegrin University Hospital, Bordeaux, France
[7]INSERM U1173, UFR des Sciences de la Santé, University Versailles Saint Quentin, Montigny-Le-Bretonneux, France
[8]UF Immunology Autoimmunity & Hypersensitivity, Bichat-Claude Bernard Hospital, APHP, Paris, France
[9]UMR 1027, INSERM, University Paul Sabatier Toulouse III, Toulouse, France

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