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ORIGINAL RESEARCH

Impending radiographic erosive progression over the following year in a cohort of consecutive patients with inflammatory polyarthritis: prediction by serum biomarkers

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ABSTRACT

Background/Purpose To evaluate biomarkers as predictors of impending erosion progression.

Methods Variables were measured at baseline and annually up to 5 years in patients with recent-onset polyarthritis treated to zero swollen joints. Erosive status was defined as ≥5 Units in Sharp/van der Heijde Erosion Score; Rapid Erosive Progression (REP) was defined as an increase ≥5 Units in Erosion Scores between consecutive visits. Generalised estimating equations (GEEs) evaluated the effect on REP of positive anticyclic citrullinated peptides (ACPAs) and/or rheumatoid factor (RF), C-reactive protein >8.0 mg/L (High-CRP) and 14-3-3η protein ≥0.50 ng/mL (High-14-3-3η), alone and in combinations.

Results Out of 2155 evaluations in 749 consecutive patients, REP occurred after 186 (8.6%) visits, including 13 (2.2%) in patients recruited since 2010. Only 18/537 (3.4%; 6/411 (1.5%) in non-erosive vs 12/126 (9.5%) in patients already erosive) visits without any positive biomarker were followed by REP; at least one biomarker was positive prior to REP in 168/186 (90.3%) visits. Being positive for all four biomarkers conferred a positive predictive value (PPV) of 30.0% (RR 21.8) in patients non-erosive at the visit versus 35.5% (RR 3.07) in those already erosive. High-14-3-3η increased REP only in visits with High-CRP (eg, RR 2.5 to 3.9 when ACPA also positive) and in patients with non-erosive status (eg, RR from 4.3 to 9.4 when also High-CRP).

Conclusions Adding High-14-3-3η to positive antibodies and CRP improves prediction of impending REP. Although REP is becoming rarer, signatures of biomarkers might help to adapt treatment strategies in at-risk individuals, even those already erosive.

Key messages

What is already known about this subject?

- Rapid erosive progression (REP) still occurs in some RA patients. CRP, RF, ACPA and the 14-3-3η protein are widely used in clinical practice as biomarkers of disease severity. Their stability over time and combined impact in real-life data remains unclear.

What does this study add?

- Over 5 years of follow- up in 749 consecutive patients (2155 evaluations) treated to zero swollen joints, ACPAs were very stable and CRP very responsive to disease control; variability of RF and 14-3-3η was intermediate and similar.
- At a given evaluation, the risk for REP was 3.4% (1.5% in non-erosive and 9.5% in erosive patients) when all four biomarkers were negative, and one in three (RR >7.5) when all four were positive.
- ACPA and RF contributed similarly to REP risk, independently of CRP status. Elevated levels of 14-3-3η contributed independently to REP risk, but only in those patients with elevated CRP and in patients not already erosive at the visit.

How might this impact on clinical practice or future developments?

- Signatures of biomarkers help stratify risk for REP and might help to adapt treatment strategies in at-risk RA individuals. Their combined impact is major in visits of non-erosive patients (RR 20.0; PPV 30.0%; NPV 98.5%), but still significant in those already erosive at the visit (RR 3.1; PPV: 35.5%; NPV: 90.5%).

At 0.5% to 1%, rheumatoid arthritis (RA) is the most prevalent chronic autoimmune inflammatory joint disease in adults.[1] Current strategies combining early and intensive treatment control disease activity and reduce erosive progression in most, but not all, patients.[2] Unlike joint thinning that may result from non-inflammatory processes such as osteoarthritis, erosive joint damage results from the local recruitment of osteoclasts and represents the hallmark of rheumatoid disease. Biomarkers such as antibodies, mostly anticitrullinated peptide/protein antibodies (ACPAs) and rheumatoid factor (RF), and

C-reactive protein (CRP), only explain part of the joint damage.[3] Modifiable biomarkers such as CRP can be used to monitor disease and assess the change in prognostic risk that occurs after the institution of treatment. On the contrary, ACPA and RF provide stratification as seropositive or negative, but are not useful in the longitudinal assessment of prognostic risk. Serum 14-3-3η is a recent biomarker highly specific for RA.[4] When added to high C-reactive protein (High-CRP; >8.0 mg/L), elevated (≥0.19 ng/mL) 14-3-3η serum levels identified significantly more RA patients with radiographic progression.[5 6] Patients who reverted from positive to negative 14-3-3η levels had better clinical response than patients who remained positive at 1 year.[5] We previously found that a higher 14-3-3η cut-off at 0.50 ng/mL was optimal to predict more adverse clinical and radiographic outcomes in early RA.[6] We also observed that baseline 14-3-3η levels, CRP levels, age and antibodies in recent-onset polyarthritis represented independent predictors of subsequent joint damage over 5 years.[6]

Several models predictive of rapid radiographic progression (RRP) in early RA patients have been published using randomised clinical trial data (ASPIRE, BEST),[7 8] or registries (ESPOIR).[9] These models have been updated using pooled data from five sources, including the three listed above, suggesting that swollen joint count (SJC), CRP, RF and erosion at inclusion are the best predictors of RRP over the following year.[10] However, SJC, CRP, RF and even erosion status do change over follow up. We postulated that, rather than using baseline values, use of combinations (or signatures) of biomarkers assessed at each visit could improve the assessment of imminent risk of radiographic erosive progression.

The objective of the current study was to determine the potential of longitudinal assessments at each visit of combinations of biomarkers with independent prognostic contribution to erosion development and to predict impending severe erosive progression over the following year in consecutive patients with recent-onset inflammatory polyarthritis treated to a target of zero swollen joints and observed over 5 years.

METHODS

Patient cohort

The longitudinal Early Undifferentiated PolyArthritis (EUPA) cohort was previously described.[6,11–13] Recruitment started in 1998 and is still ongoing. We included consecutive adult patients with at least three swollen joints for 1 to 12 months evaluated by a Centre Hospitalier Universitaire de Sherbrooke (CHUS) rheumatologist. Patients with bacterial or crystal induced arthritis or with a defined connective tissue disease or systemic vasculitis according to ACR criteria[14] were excluded. Patients were treated at the rheumatologist's discretion, who aimed at sustained remission defined by consensus from the onset of the cohort as 0 swollen out of 66 joints.[2 15] Blood samples were drawn, coded and stored, and hands and feet radiographs performed at baseline and at each scheduled follow-up visit. Patients provided written informed consent and the Ethics Review Board of the CHUS approved the study (ClinicalTrials.gov ID: NCT00512239).

No patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes, interpret the results or contribute to the writing or editing of this document for readability or accuracy.

Disease variables

A rheumatologist performed joint counts, and a trained coordinator collected patient information at inclusion and at follow-up visits that were scheduled at 18, 30, 42 and 60 months after onset. Time of onset was self-reported as the day or week during which symptoms/signs of inflammatory arthropathy appeared. Variables assessed included demographics; 68 tender joint count (TJC) and 66 SJC; drug use at and between visits; modified Health Assessment Questionnaire (mHAQ)[16]; serum CRP (upper normal limit: 8.0 mg/L); components of the Simplified Disease Activity Index (SDAI); and RA-associated antibodies (see below). Joint space narrowing and erosions were scored according to the Sharp/van der Heijde (Sharp) method, with a maximum score of 448 units, including 280 units for the Erosion component alone.[17] Radiographs were read in known time sequence by two blinded assessors, one of whom was a study investigator (GB). Under these conditions, the smallest detectable change (SDC) was previously defined as <5 units.[18]

RA-associated antibodies

IgM RF was measured using RapiTex RF, Dade Behring Inc, Newark DE (positive (RF) ≥40 IU/mL); anti-CCP2 antibodies using QuantaLite, Inova Diagnostics, San Diego CA, according to the manufacturer's instructions (positive (ACPA) >20.0 U/mL) or, since 2009, using EuroImmun assay (positive >5.0 U/mL). The two assays use the same antigen plates, and their results are easily interconvertible using a logarithmic equation.

Serum 14-3-3η measurements

Serum 14-3-3η levels were measured by the manufacturer, blinded to patient data, using the 14-3-3η ELISA (JOINTstat), according to the manufacturer's protocol (Augurex Life Sciences Corp, Vancouver, Canada). Samples with levels below the reportable range were assigned a concentration of 0.0 ng/mL; those with levels above the upper limit were defined as levels ≥20 ng/mL. Positive 14-3-3η was defined at ≥0.19 ng/mL; high positive (High-14-3-3η) was defined at ≥0.50 ng/mL.[6]

Outcomes

Erosive progression (EP) was defined by a positive (≥1) difference between the erosion component of the Sharp/van der Heijde Score over two consecutive annual visits. Rapid erosive progression (REP) was defined by

a difference ≥5 (eg, above the SDC) in Erosion Scores over two consecutive visits. Erosive status at a given visit was defined as a score ≥5 in the erosion component. Remission was defined as SDAI ≤3.3.[19]

Statistical methods

Quantitative variables were presented as mean (SD) or as median and 25th–75th percentiles (IQR). Categorical variables were presented with frequencies and percentages. Generalised estimated equations (GEEs) with random effect were computed to evaluate individual and combined effects of positive antibodies (RF and/or ACPA), High-CRP and High-14-3-3η at a given visit on radiographic erosive progression (REP and EP) over time. Subanalyses were performed on patients with normal or High-CRP and on patients with non-erosive (Sharp Erosion Score <5) or erosive (Sharp Erosion Score ≥5) status at a given visit. Multivariate GEEs on REP were performed using demographic, clinical, biomarker and treatment variables at the previous visit, except for age, gender and ACPA for which baseline values were used. Variables with p<0.1 in univariate analysis were included. All interactions were evaluated and those that were non-significant were excluded one by one until the smallest Quasi-likelihood under the Independence model Criterion (QIC) was reached. All analyses used only available data without imputation, since <5% of values for each variable were missing, except for Sharp Scores missing in 7.6% of visits. Statistical analysis was performed using SAS software version 9.4 and GraphPad Prism Software version 7.00 for Windows. The false discovery rate correction of Benjamini and Hochberg was used for multiple comparisons.[20] A corrected p value <0.05 denoted statistical significance.

RESULTS

Baseline patient characteristics

As of May 2018, from the 834 patients then recruited in the EUPA cohort, 33 never met inclusion criteria or developed exclusion criteria, and 52 did not have 14-3-3η values available at baseline (figure 1). In the 749 remaining patients, at baseline, the mean age was 59.9 years, 450 (60.1%) were women, median symptom duration was 3.5 months and 91.4% fulfilled 1987/2010 classification criteria for RA (table 1). Disease activity was moderate to high: median (IQR) SDAI: 29.4 (19.5–43.8); median (IQR) M-HAQ 0.8 (0.4–1.4). Baseline joint damage was low, with median total Sharp (IQR) of 3 (0–7) and median Erosion Sharp (IQR) of 1 (0–3). Patients rapidly received disease-modifying antirheumatic drug (DMARD) treatments (26.4% before inclusion and 96% between baseline and the 18-month visit), usually methotrexate alone or in combination with other DMARDs.

Prevalence of positive biomarkers at baseline

At baseline, High-CRP was present in 57.7%, while ACPA and RF were present in 34.7% and 37.9% of patients, respectively; either antibody was present in 43.7% (table 1). High-14-3-3η (≥0.50 ng/mL) identified a similar number of patients (33.6%), while 60.9% reached the lower manufacturer-recommended cut-off (0.19 ng/mL). Prevalence of antibodies (RF or ACPA) and of High-14-3-3η (≥0.50 ng/mL) among the 679 (91.4%) RA patients was 47.6% and 58.7%, respectively; their specificity for RA in the cohort was 98.4% and 82.8%, respectively. Prevalence and specificity for RA of 14-3-3η (≥0.19 ng/mL) were 73.2% and 43.8%, respectively. As previously reported,[6] the 0.50 ng/mL cut-off for 14-3-3η (High-14-3-3η) best correlated with radiographic outcomes and was thus used for further analyses.

Stability of biomarkers over time and progression of bone erosions

Samples from each visit were serially tested, allowing the evaluation of the stability of each biomarker (Online supplementary table 1). Baseline status of negative antibodies was quite stable over follow-up (93.3% for negative ACPA, 92.6% for negative RF), while normal CRP (74.5%) and 14-3-3η (61.5%) were more variable. Baseline ACPA remained positive in 86.5%, while RF remained stably positive in 53.5%, but only half of RF reverters to negative (24.5% of patients) remained stably negative during follow-up. High-14-3-3η status reverted to negative at least once in 61.2%. Baseline High-CRP status became negative at least once in 86.4%. High-CRP and High-14-3-3η thus had similar highly variable patterns, ACPA was very stable, and positive RF was intermediate. As not all patients were tested up to 5 years, these values represent the upper limits of biomarker stability.

Within the group of initially High-14-3-3η-positive patients, REP between baseline and 18 months was more frequent in patients who remained High-14-3-3η than in those who became negative (24.8% vs 10.7%, p=0.016) (Online supplementary figure). This difference decreased but remained significant (RR (95% CI)=2.77 (1.46 to 5.26), p=0.0019) over follow-up, during which 51% of those turning negative at 18 months again became positive at least once. This suggested that, similar to CRP, the status of High-14-3-3η at a given visit might impact radiographic progression over the following period.

Biomarkers and prediction of erosive damage progression over the following year

Baseline biomarkers, including 14-3-3η levels, failed to correlate with joint narrowing and functional limitations (data not shown). These observations reflect different pathogenic pathways for joint erosions and narrowing, as well as previous reports of a better correlation of function with joint narrowing than with erosions.[21]

Progression by ≥1 erosion (EP) occurred after 903 (41.2%) visits, including 149 (25.3%) in patients recruited since 2010. Individual biomarkers and their combinations were statistically associated with EP, but with low RR (<2 even with four positive biomarkers) (Online supplementary table 2). As the SDC in Sharp/van der Heijde score was about 5, low associations of biomarkers with EP were likely due to variability in the assessment of erosion scores.

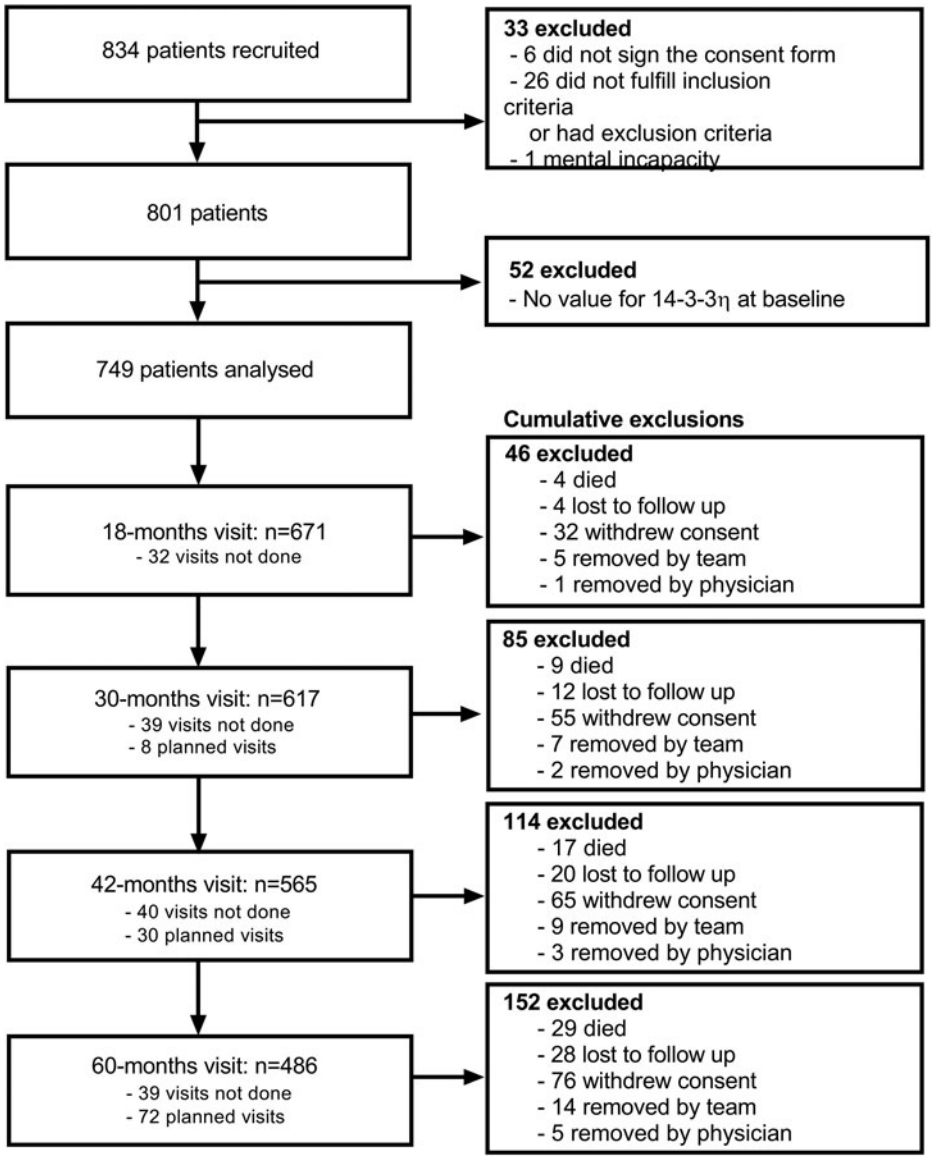

Figure 1 Flowchart of patient enrollment process. Patients were excluded when alternative diagnoses such as microcrystalline arthritis or a defined connective tissue disease became apparent over follow-up. Patients were removed by the team during follow-up, when repeatedly not compliant or too sick (usually from associated comorbidities) to come to their follow-up appointments. A few patients were also removed by the treating rheumatologist when their disease was no longer active and follow-up was not felt to be clinically justified. 'Visits not done' refer to missed visits at that specific evaluation, while 'planned visits' refer to visits to be done after the report date.

REP represents a change in the Erosion Score ≥5 units over two consecutive visits, larger than SDC. REP occurred after 186 (8.5%) of the 2194 visits, in 118 (17.8%) of 663 patients; 77 (41.4%) of REP occurred following inclusion visits. Of note, REP occurred in 10.8% of the visits of patients included between 1998 and 2010 and became rare (13/588 visits, 2.2%, 9 following baseline) in patients recruited since 2010.

Complete information on all four biomarkers was available before 164 of the 186 REP episodes. Only 18 (3.4%) visits negative for all four biomarkers were followed by REP, only 2 since 2010. At least one biomarker was positive in 90.3% visits followed by REP. When analysed individually, High-14-3-3η, ACPA, RF and High-CRP were all significantly associated with REP at the subsequent visit (range of RR=1.56 to 2.52) (table 2). Each individual biomarker had similarly poor positive predictive value (PPV: 12.8–15.1%) and excellent negative predictive value (NPV: 93.1–94.9%).

Combining biomarkers improved PPV. For example, relative to being negative, being positive for both ACPA and High-CRP (RR (95% CI)=5.24 (3.46 to 7.94)) increased PPV to 24.3% and NPV to 96.6%. Adding High-14-3-3η to ACPA and High-CRP increased PPV to 31.2% and NPV to 96.5% (RR=6.29 (3.92–10.10)). Similar results were obtained using RF (instead of ACPA) in

Table 1 Baseline descriptive characteristics

	n	Value
Age (years)	749	59.9±15
Women	749	450 (60.1)
Body mass index (kg/m^2)	706	26.5 (23.2–29.9)
Current smokers	728	129 (17.7)
Ever smokers		327 (44.92)
Symptom duration (months)	749	3.5 (2–6)
Fulfilling 1987 or 2010 sets of criteria for rheumatoid arthritis	743	679 (91.4)
14-3-3η protein levels, ng/mL	749	0.3 (0.1–1.1)
14-3-3η≥0.19 ng/mL	749	456 (60.9)
14-3-3η≥0.50 ng/mL (High-14-3-3η)	749	252 (33.6)
Anticyclic citrullinated peptide 2 (CCP2), IU/mL	748	3.2 (1.2–48.9)
Anti-CCP2>5 IU/mL (positive; ACPA)	748	260 (34.8)
Rheumatoid factor (RF), IU/mL	749	0 (0–160)
RF≥40 IU/mL (positive; RF)	749	284 (37.9)
RF and/or ACPA positive	748	327 (43.7)
RF and/or ACPA positive and/or 14-3-3η≥0.19 ng/mL	748	538 (71.9)
RF and/or ACPA positive and/or 14-3-3η≥0.50 ng/mL	748	414 (55.4)
Erythrocyte sedimentation rate, mm/h	748	28 (16–5)
Erythrocyte sedimentation rate >20 mm/h	748	475 (63.5)
C-reactive protein (CRP), mg/L	749	11 (4–28.1)
CRP >8.0 mg/L (High; High-CRP)	749	432 (57.7)
Modified Health Assessment Questionnaire (M-HAQ)	714	0.8 (0.4–1.4)
Swollen joint count (66 joints; SJC66)	748	11 (6–17.5)
Tender joint count (68 joints; TJC68)	745	12 (5–19)
Patient's general health (0–100 mm; PtVAS)	724	55 (33.5–77)
Physician's global assessment of disease activity (0–100 mm; MDVAS)	749	43 (28–64)
Disease Activity Score 28 joints using CRP (DAS28-CRP)	721	5.0 (4.1–6.1)
Simple Disease Activity Index (SDAI)	721	29.4 (19.5–43.8)
Total Sharp/van der Heijde (Sharp) Score	692	3 (0–7)
Total Sharp/van der Heijde (Sharp) positive (≥5)	692	249 (36.1)
Sharp/van der Heijde (Sharp) Erosion Score	692	1 (0–3)
Sharp/van der Heijde (Sharp) erosion positive (≥5)	692	108 (15.7)
Sharp/van der Heijde (Sharp) Narrowing Score	692	1 (0–4)
Sharp/van der Heijde (Sharp) narrowing positive (≥5)	692	146 (21.1)
Treatment received before inclusion		
Disease-modifying antirheumatic drugs (DMARD)	749	198 (26.4)
Methotrexate	749	129 (17.2)
Hydroxychloroquine	749	131 (17.5)
Other DMARD	749	12 (1.6)
Oral corticosteroids	749	231 (30.8)
Biologic DMARD	749	3 (0.4)

Continuous variables presented with mean ±SD or median (IQR: 25th–75th); categorical variables with frequencies (%).

combination with High-CRP and High-14-3-3η: PPV: 31.7% and NPV 95.7%. Following ACPA, RF and High-CRP visits (in the absence of 14-3-3η values), REP occurred in 27.2% (RR 7.77 (4.88–12.37); NPV: 97.3%). With all four positive biomarkers, including High-14-3-3η, the RR for REP remained similar at 7.62 (4.63–12.56), but PPV increased to 32.8% and NPV remained at 96.6%.

Table 2 Impact of positive status for 14-3-3η, rheumatoid factor (RF), anticyclic peptide antibodies (ACPA) and C-reactive protein (CRP) at each visit on prediction of rapid erosive progression (REP) at the subsequent annual visit

	Visits	Rapid erosive progression (REP; ΔErosions ≥5 between two visits)		
Variables at previous visit	**Total**	**n (%)**	**RR (95% CI)**	**P value**
Individual variables				
High-14-3-3η	695	89 (12.8)	1.56 (1.16–2.10)	0.0034
ACPA positive	727	103 (14.2)	2.50 (1.77–3.53)	<0.0001
RF positive	762	115 (15.1)	2.52 (1.79–3.55)	<0.0001
High CRP	721	108 (15.0)	2.23 (1.66–3.00)	<0.0001
RF, ACPA	(n=1938)			
Both negative	1059	45 (4.2)	1	
One positive	353	35 (9.9)	2.15 (1.36–3.42)	0.0012
Both positive	526	85 (16.2)	3.52 (2.35–5.27)	<0.0001
RF, CRP	(n=2155)			
Both negative	957	32 (3.3)	1	
One positive	917	85 (9.3)	2.11 (1.45–3.09)	0.0001
Both positive	281	69 (24.6)	5.14 (3.37–7.85)	<0.0001
ACPA, CRP	(n=1945)			
Both negative	822	28 (3.4)	1	
One positive	864	74 (8.6)	2.10 (1.48–2.99)	<0.0001
Both positive	259	63 (24.3)	5.24 (3.46–7.94)	<0.0001
14-3-3η, RF	(n=2083)			
Both negative	1070	61 (5.7)	1	
One positive	593	44 (7.4)	1.38 (0.94–2.02)	0.1049
Both positive	420	80 (19.0)	2.78 (1.88–4.12)	<0.0001
14-3-3η, ACPA	(n=1881)			
Both negative	903	44 (4.9)	1	
One positive	627	59 (9.4)	1.84 (1.31–2.59)	0.0005
Both positive	351	61 (17.4)	2.93 (1.93–4.45)	<0.0001
14-3-3η, CRP	(n=2090)			
Both negative	935	48 (5.1)	1	
One positive	914	78 (8.5)	1.37 (0.97–1.92)	0.073
Both positive	241	59 (24.5)	3.49 (2.39–5.12)	<0.0001
14-3-3η, RF, CRP	(n=2083)			
All negative	721	31 (4.3)	1	
One positive	752	48 (6.4)	1.37 (0.88–2.13)	0.1693
Two positive	449	55 (12.2)	2.35 (1.49–3.70)	0.0002
All positive	161	51 (31.7)	5.59 (3.53–8.84)	<0.0001
14-3-3η, ACPA, CRP	(n=1880)			
All negative	593	21 (3.5)	1	
One positive	745	53 (7.1)	1.72 (1.18–2.49)	0.0044
Two positive	401	46 (11.5)	2.63 (1.66–4.16)	<0.0001
All positive	141	44 (31.2)	6.29 (3.92–10.10)	<0.0001
14-3-3η, RF, ACPA	(n=1874)			
All negative	822	40 (4.9)	1	
One positive	411	22 (5.4)	1.28 (0.82–2.01)	0.2803
Two positive	347	45 (13.0)	2.54 (1.59–4.04)	<0.0001

Continued

Table 2 Continued

Variables at previous visit	Visits Total	Rapid erosive progression (REP; ΔErosions ≥5 between two visits) n (%)	RR (95% CI)	P value
All positive	294	57 (19.4)	3.60 (2.30–5.64)	<0.0001
RF, ACPA, CRP	(n=1938)			
All negative	713	19 (2.7)	1	
One positive	597	46 (7.7)	2.38 (1.57–3.60)	<0.0001
Two positive	422	44 (10.4)	3.32 (2.05–5.36)	<0.0001
All positive	206	56 (27.2)	7.77 (4.88–12.37)	<0.0001
14-3-3η, RF, ACPA, CRP	(n=1874)			
All negative	537	18 (3.4)	1	
One positive	583	37 (6.3)	1.68 (1.08–2.61)	0.0221
Two positive	339	25 (7.4)	2.13 (1.27–3.58)	0.0043
Three positive	293	44 (15.0)	3.66 (2.17–6.17)	<0.0001
All positive	122	40 (32.8)	7.62 (4.63–12.56)	<0.0001

Values for 14-3-3η, ACPA, RF and CRP were available at 185, 165, 186 and 186 visits preceding a REP episode, respectively.

We previously reported that 14-3-3η and CRP levels are not correlated, while High-14-3-3η correlates only moderately with RF and ACPA positivity.[6] As CRP and erythrocyte sedimentation rate (ESR) are the only highly modifiable biomarkers in current practice, we assessed the impact of concomitant RF, ACPA and High-14-3-3η on subsequent radiographic progression following a visit when CRP was normal or high (table 3). The much lower RR observed when biomarkers are combined in the presence of a normal CRP supports the importance of inflammation in erosive progression. In the presence of a normal CRP, High-14-3-3η levels were not correlated with REP nor did they significantly increase the relative risks conferred by RF and ACPA. On the contrary, in the presence of High-CRP, High-14-3-3η levels significantly increased the relative risks for REP, whether antibodies were positive or not (table 3).

Because the presence of erosions is a very strong predictor of damage progression in several predictive models,[7–10] we also evaluated the impact of positive biomarkers in patients that were either non-erosive or already erosive at a given visit (Table 4). We again defined erosive as an erosion component of the Sharp/van der Heijde Score ≥5.

Among non-erosive patients, each of the four biomarkers positive at a given visit significantly increased the RR for REP, from 2.78 (High-14-3-3η) to 4.31 (High-CRP), and each biomarker acted synergistically with the others. For example, being positive for both ACPA and High-CRP increased the RR to 14.1. Similarly, adding High-14-3-3η to ACPA and High-CRP increased RR to 21.8, higher than adding RF to ACPA and High-CRP (RR 18.1). Having all four biomarkers positive yielded an RR of 20.0. In non-erosive visits, being negative for all four biomarkers appeared protective (only 1.5% of such visits associated with REP), while being positive for all four was highly predictive of REP (PPV 30.0%; NPV 98.5%).

Among erosive patients, the risk of REP in the absence of any biomarker was 8.5% and that in the presence of all four biomarkers was 35.5%. Each of High-CRP (RR 1.7), RF (RR 1.9) and ACPA (RR 1.6) individually increased the RR of REP, while High-14-3-3η failed to do so. High-CRP, ACPA and RF interacted numerically in these erosive patients, yielding a maximal RR of 3.65 when all three were positive.

The detection of High-14-3-3η thus amplified by 20% the PPV for REP conferred by positive ACPA, RF and High-CRP (from 27.2% to 32.8%) and by 50% (from 20.2% to 30%) the PPV conferred by ACPA, RF and High-CRP in patients with non-erosive status. On the contrary, detection of 14-3-3η did not appear useful in patients with normal CRP levels nor in patients already erosive at the visit.

Multivariate analysis of variables at each visit to predict Rapid Erosive Progression

To determine the independent role of biomarkers, multivariate predictive models using continuous and dichotomous 14-3-3η and significant variable interactions at each visit were evaluated in relation to REP (table 5). Multivariate GEE analysis with repeated measures of continuous 14-3-3η (Model 1) showed that increasing age, swollen (SJC66) and tender (TJC68) joint counts, ACPA and High-CRP positivity, as well as the interactions of High-CRP with both 14-3-3η levels and SJC were each independently significantly associated with REP. In multivariate GEE analysis with repeated measures using dichotomous 14-3-3η and significant variable interactions (Model 2), independent predictors of REP over the following year were age, SJC66, ACPA and interactions of High-CRP with High-14-3-3η and SJC and interactions of High-14-3-3η with SJC and TJC.

Table 3 Impact of positive status for 14-3-3η ≥0.50 ng/mL (High-14-3-3η), positive rheumatoid factor (RF) and positive anti-CCP2 (ACPA) on prediction of rapid erosive progression (REP; ≥5 erosion units between two successive visits) according to normal (≤8.0 mg/L) or high C-reactive protein (High-CRP) at a given visit

	Visits	REP (ΔErosions ≥5 between 2 visits)		
	Total	n (%)	RR (95% CI)	P value
Normal CRP (≤8.0 mg/L)				
Individual variables				
High 14-3-3η	453	30 (6.6)	1.15 (0.72–1.85)	0.5627
ACPA positive	468	40 (8.5)	2.51 (1.59–3.98)	<0.0001
RF positive	481	46 (9.6)	2.75 (1.70–4.47)	<0.0001
RF, ACPA	(n=1284)			
Both negative	713	19 (2.7)	1	
One positive	251	20 (8)	2.97 (1.65–5.35)	0.0003
Both positive	320	29 (9.1)	3.48 (1.99–6.10)	<0.0001
14-3-3η, RF	(n=1383)			
Both negative	721	31 (4.3)	1	
One positive	403	18 (4.5)	1.15 (0.63–2.09)	0.6497
Both positive	259	29 (11.2)	2.37 (1.35–4.17)	0.0026
14-3-3η, ACPA	(n=1238)			
Both negative	593	21 (3.5)	1	
One positive	435	30 (6.9)	1.86 (1.14–3.05)	0.0138
Both positive	210	17 (8.1)	2.21 (1.18–4.15)	0.0130
14-3-3η, RF, ACPA	(n=1233)			
All negative	537	18 (3.4)	1	
One positive	298	15 (5)	1.52 (0.81–2.84)	0.1922
Two positive	226	18 (8)	2.38 (1.26–4.50)	0.0076
All positive	172	17 (9.9)	2.93 (1.54–5.57)	0.0011
High CRP (>8.0 mg/L)				
Individual variables				
High 14-3-3η	241	59 (24.5)	2.23 (1.54–3.22)	<0.0001
ACPA positive	259	63 (24.3)	2.52 (1.60–3.97)	<0.0001
RF positive	281	69 (24.6)	2.43 (1.57–3.75)	<0.0001
RF, ACPA	(n=654)			
Both negative	346	26 (7.5)	1	
One positive	102	15 (14.7)	1.85 (0.95–3.59)	0.0703
Both positive	206	56 (27.2)	3.22 (1.96–5.27)	<0.0001
14-3-3η, RF	(n=700)			
Both negative	349	30 (8.6)	1	
One positive	190	26 (13.7)	1.8 (1.12–2.9)	0.0154
Both positive	161	51 (31.7)	3.52 (2.2–5.64)	<0.0001
14-3-3η, ACPA	(n=642)			
Both negative	310	23 (7.4)	1	
One positive	191	29 (15.2)	2.18 (1.31–3.65)	0.0029
Both positive	141	44 (31.2)	3.93 (2.30–6.73)	<0.0001
14-3-3η, RF, ACPA	(n=641)			
All negative	285	22 (7.7)	1	
One positive	113	7 (6.2)	1.14 (0.58–2.24)	0.7084
Two positive	121	27 (22.3)	3.18 (1.71–5.90)	0.0003
All positive	122	40 (32.8)	4.31 (2.46–7.56)	<0.0001

Table 4 Impact of positive status for High-14-3-3η, rheumatoid factor (RF), anticyclic peptide antibodies (ACPA) and high C-reactive protein (CRP) at each visit on prediction of rapid erosive progression (REP) according to low (<5) (table 4A) or high Sharp Erosion Score (≥5) (table 4B) at a given visit

	Visits	REP (ΔErosions ≥5 between 2 consecutive visits)		
	Total	n (%)	RR (95% CI)	P value
A				
Non-erosive status at the visit (Sharp Erosion Score <5)				
Individual variables				
14-3-3η	437	37 (8.5)	2.78 (1.75–4.4)	<0.0001
ACPA positive	457	41 (9)	3.64 (2.19–6.03)	<0.0001
RF positive	461	40 (8.7)	3.19 (1.98–5.14)	<0.0001
CRP	485	46 (9.5)	4.31 (2.65–7.01)	<0.0001
RF, ACPA	(n=1388)			
Both negative	816	16 (2)	1	
One positive	264	17 (6.4)	3.29 (1.69–6.39)	0.0005
Both positive	308	31 (10.1)	5.1 (2.81–9.26)	<0.0001
RF, CRP	(n=1505)			
Both negative	725	12 (1.7)	1	
One positive	615	26 (4.2)	2.52 (1.3–4.87)	0.0062
Both positive	165	30 (18.2)	10.62 (5.56–20.3)	<0.0001
ACPA, CRP	(n=1392)			
Both negative	636	8 (1.3)	1	
One positive	601	28 (4.7)	3.71 (1.74–7.93)	0.0007
Both positive	155	28 (18.1)	14.06 (6.62–29.85)	<0.0001
14-3-3η, RF	(n=1443)			
Both negative	796	21 (2.6)	1	
One positive	416	15 (3.6)	1.36 (0.72–2.56)	0.347
Both positive	231	31 (13.4)	4.99 (2.9–8.6)	<0.0001
14-3-3η, ACPA	(n=1335)			
Both negative	688	13 (1.9)	1	
One positive	454	25 (5.5)	2.88 (1.51–5.51)	0.0014
Both positive	193	25 (13)	6.75 (3.51–12.96)	<0.0001
14-3-3η, CRP	(n=1446)			
Both negative	682	15 (2.2)	1	
One positive	624	22 (3.5)	1.58 (0.84–2.98)	0.1567
Both positive	140	30 (21.4)	9.41 (5.25–16.86)	<0.0001
14-3-3η, RF, CRP	(n=1443)			
All negative	540	12 (2.2)	1	
One positive	544	12 (2.2)	0.99 (0.45–2.16)	0.9814
Two positive	275	19 (6.9)	3.07 (1.53–6.17)	0.0016
All positive	84	24 (28.6)	12.47 (6.47–24.03)	<0.0001
14-3-3η, ACPA, CRP	(n=1334)			
All negative	456	6 (1.3)	1	
One positive	547	18 (3.3)	2.48 (1.01–6.06)	0.0464
Two positive	260	18 (6.9)	5.21 (2.13–12.75)	0.0003
All positive	71	21 (29.6)	21.85 (9.3–51.34)	<0.0001
14-3-3η, RF, ACPA	(n=1331)			
All negative	627	13 (2.1)	1	

Continued

Table 4 Continued

	Visits	REP (ΔErosions ≥5 between 2 consecutive visits)		
	Total	n (%)	RR (95% CI)	P value
One positive	317	9 (2.8)	1.37 (0.6–3.11)	0.4504
Two positive	233	19 (8.2)	3.91 (1.96–7.79)	0.0001
All positive	154	22 (14.3)	6.81 (3.49–13.3)	<0.0001
RF, ACPA, CRP	(n=1388)			
All negative	552	6 (1.1)	1	
One positive	457	18 (3.9)	3.61 (1.48–8.79)	0.0047
Two positive	260	16 (6.2)	5.7 (2.29–14.17)	0.0002
All positive	119	24 (20.2)	18.11 (7.7–42.61)	<0.0001
14-3-3η, RF, ACPA, CRP	(n=1331)			
All negative	411	6 (1.5)	1	
One positive	450	13 (2.9)	1.96 (0.77–5.02)	0.158
Two positive	234	8 (3.4)	2.34 (0.85–6.5)	0.1015
Three positive	176	18 (10.2)	6.95 (2.83–17.03)	<0.0001
All positive	60	18 (30)	19.99 (8.39–47.64)	<0.0001
B				
Erosive status at the visit (Sharp Erosion Score ≥5)				
Individual variables				
14-3-3η	258	52 (20.2)	1.08 (0.75–1.55)	0.6827
ACPA positive	270	62 (22.3)	1.6 (1.06–2.42)	0.0245
RF positive	301	75 (24.9)	1.93 (1.31–2.84)	0.0009
CRP	236	62 (26.3)	1.67 (1.19–2.34)	0.0029
RF, ACPA	(n=550)			
Both negative	243	29 (11.9)	1	
One positive	89	18 (20.2)	1.48 (0.79–2.74)	0.2192
Both positive	218	54 (24.8)	2.09 (1.3–3.35)	0.0022
RF, CRP	(n=650)			
Both negative	232	20 (8.6)	1	
One positive	302	59 (19.5)	2 (1.25–3.2)	0.004
Both positive	116	39 (33.6)	3.17 (1.87–5.35)	<0.0001
ACPA, CRP	(n=553)			
Both negative	186	20 (10.8)	1	
One positive	263	46 (17.5)	1.58 (1.05–2.37)	0.0299
Both positive	104	35 (33.7)	2.58 (1.57–4.26)	0.0002
14-3-3η, RF	(n=640)			
Both negative	274	40 (14.6)	1	
One positive	177	29 (16.4)	1.32 (0.85–2.06)	0.2145
Both positive	189	49 (25.9)	1.65 (1.04–2.64)	0.0344
14-3-3η, ACPA	(n=546)			
Both negative	215	31 (14.4)	1	
One positive	173	34 (19.7)	1.26 (0.84–1.88)	0.2667
Both positive	158	36 (22.8)	1.45 (0.91–2.33)	0.1204
14-3-3η, CRP	(n=644)			
Both negative	253	33 (13)	1	
One positive	290	56 (19.3)	1.28 (0.86–1.89)	0.2222
Both positive	101	29 (28.7)	1.85 (1.19–2.89)	0.0063

Continued

Table 4 Continued

	Visits	REP (ΔErosions ≥5 between 2 consecutive visits)		
	Total	n (%)	RR (95% CI)	P value
14-3-3η, RF, CRP	(n=640)			
All negative	181	19 (10.5)	1	
One positive	208	36 (17.3)	1.64 (0.95–2.84)	0.0784
Two positive	174	36 (20.7)	1.83 (1.05–3.19)	0.0316
All positive	77	27 (35.1)	2.86 (1.58–5.19)	0.0005
14-3-3η, ACPA, CRP	(n=546)			
All negative	137	15 (10.9)	1	
One positive	198	35 (17.7)	1.45 (0.95–2.23)	0.0875
Two positive	141	28 (19.9)	1.69 (0.99–2.87)	0.0535
All positive	70	23 (32.9)	2.42 (1.4–4.21)	0.0017
14-3-3η, RF, ACPA	(n=543)			
All negative	195	27 (13.8)	1	
One positive	94	13 (13.8)	1.02 (0.55–1.91)	0.9491
Two positive	114	26 (22.8)	1.69 (0.97–2.92)	0.0625
All positive	140	35 (25)	1.78 (1.05–3.03)	0.0336
RF, ACPA, CRP	(n=550)			
All negative	161	13 (8.1)	1	
One positive	140	28 (20)	1.94 (1.18–3.19)	0.0091
Two positive	162	28 (17.3)	2.16 (1.25–3.72)	0.0055
All positive	87	32 (36.8)	3.65 (2.1–6.37)	<0.0001
14-3-3η, RF, ACPA, CRP	(n=543)			
All negative	126	12 (9.5)	1	
One positive	133	24 (18)	1.63 (0.94–2.84)	0.0847
Two positive	105	17 (16.2)	1.71 (0.93–3.14)	0.0841
Three positive	117	26 (22.2)	2.22 (1.2–4.1)	0.0111
All positive	62	22 (35.5)	3.07 (1.64–5.75)	0.0005

DISCUSSION

In this real-world large cohort of consecutive recent-onset polyarthritis (>91% RA) patients observed over a mean of 4.9 years (IQR 3–7), measuring four serum biomarkers contributed incremental information to identify over 90% of visits with impending REP over the following year. By combining these four biomarkers, we identified subsets of patients that had up to a one in three risks for REP, with RR>7.5 in the whole cohort and RR~20 in patients not already erosive at the visit. Adding positive RF to a combination of High-CRP, ACPA and High-14-3-3η delivered a lower increase in PPV for REP (31.2% vs 32.8%) than adding High-14-3-3η to the three others (27.2% vs 32.8%). This likely results from the strong correlation between RF and ACPA, while High-14-3-3η lacks correlation with High-CRP and is only moderately correlated with seropositivity.

Elevated CRP and previous erosive status represent major mediators of erosion progression in RA patients.[10] We thus performed subset analyses according to these two predictors to better define the role of each biomarker in specific clinical situations.

Stratifying patients according to CRP levels, the rate of REP was 3.4% when all four biomarkers were negative, 7.7% when only High-CRP was positive and 9.1% when only RF and ACPA were both positive. Seropositive RF and/or ACPA contributed moderately (RR 3.2 to 3.5 when both positive) on their own in patients with and without High-CRP. For its part, High-14-3-3η provided an independent contribution to risk prediction only in patients with High-CRP.

Similarly, in subset analyses according to erosive status, in the absence of any positive biomarker, the rate of REP after visits where patients were still non-erosive was 1.5%, and 8.5% after visits of already erosive ones. This difference in rate gives an estimation of the independent contribution of an erosive status to predict REP, when all four assessed biomarkers are negative. Fort their part, each positive biomarker contributed individually and synergistically to RR for REP (up to 20.0 in visits of non-erosive patients), while in already erosive patients, all biomarkers

Table 5 General estimating models of rapid erosive porogression (REP) (increase in the Erosion Score ≥5 between two consecutive visits) using biomarkers at each preceding visit and their interactions

	REP (increase in Erosion Score ≥5 between 2 visits)					
	Univariate model		Multivariate Model 1		Multivariate Model 2	
	RR (95% CI)	P value	RR (95% CI)	P value	RR (95% CI)	P value
			QIC=1140.2735		QIC=1114.8320	
14-3-3η, ng/mL	1.03 (1.01–1.05)	**0.0041**	0.99 (0.96–1.02)	0.4949	—	—
High-14-3-3η (≥0.50 ng/mL)	1.61 (1.19–2.17)	**0.0021**	—	—	0.83 (0.51–1.33)	0.4352
Age (years)	1.02 (1.00–1.03)	**0.0222**	1.02 (1.00–1.04)	**0.0100**	1.02 (1.01–1.04)	**0.0082**
Women gender	0.61 (0.42–0.89)	**0.0101**	1.09 (0.58–2.05)	0.7955	1.12 (0.59–2.14)	0.7212
SJC66	1.04 (1.03–1.05)	**<0.0001**	1.03 (1.00–1.06)	**0.0233**	1.06 (1.02–1.09)	**0.0013**
TJC68	1.04 (1.03–1.05)	**<0.0001**	1.02 (1.00–1.05)	**0.0475**	1.00 (0.97–1.03)	0.8292
M-HAQ	1.49 (1.19–1.87)	**0.0005**	0.86 (0.66–1.12)	0.2731	0.88 (0.67–1.17)	0.3754
ACPA positive	2.56 (1.75–3.76)	**<0.0001**	3.91 (2.17–7.04)	**<0.0001**	3.96 (2.18–7.18)	**<0.0001**
High-CRP (>8.0 mg/L)	2.31 (1.72–3.12)	**<0.0001**	1.89 (1.20–2.98)	**0.0062**	1.59 (0.95–2.68)	0.0794
Biologic	0.53 (0.24–1.16)	0.1114	—	—	—	—
Methotrexate	0.58 (0.44–0.77)	**0.0002**	0.88 (0.61–1.28)	0.5012	0.87 (0.61–1.24)	0.4339
Sulfasalazine	0.94 (0.57–1.53)	0.7913	—	—	—	—
Hydroxychloroquine	0.70 (0.53–0.93)	**0.0140**	1.00 (0.64–1.56)	0.9988	0.97 (0.63–1.50)	0.8853
Other conventional DMARD	0.15 (0.00–7.68)	0.3414	—	—	—	—
14-3-3η×High-CRP			1.04 (1.00–1.08)	**0.0333**	—	—
High-14-3-3η× High-CRP			—	—	1.87 (1.03–3.40)	**0.0407**
High-14-3-3η×SJC66			—	—	0.96 (0.92–1.00)	**0.0310**
High-14-3-3η×TJC66			—	—	1.04 (1.00–1.08)	**0.0295**
Women× ACPA positive			0.50 (0.23–1.06)	0.0704	0.49 (0.23–1.04)	0.0628
SJC66×High-CRP			0.97 (0.94–0.99)	**0.0140**	0.97 (0.94–1.00)	**0.0388**
TJC68×Hydroxychloroquine			1.02 (1.00–1.04)	**0.0467**	1.03 (1.00–1.05)	**0.0204**

Model 1 used continuous 14-3-3η levels and Model 2 used High-14-3-3η status. Multivariate generalised estimating equations on REP were performed using demographic, clinical, biomarker and treatment variables at the previous visit, except for age, gender and ACPA status for which baseline values were used.
ACPA, anticyclic citrullinated peptide antibodies; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic dru; M-HAQ, Modified Health Assessment Questionnaire; SJC66, swollen joint count in 66 joints; TJC, tender joint count in 68 joints.
Bold is when p values are below 0.05; an underlined value means that the p value is between 0.05 and 0.10 (ie, indicates a trend)

but 14-3-3η also increased the RR for REP (up to 3.6). In both erosive and non-erosive patients, the PPV for REP of four positive biomarkers was close to one in three (30.0% in non-erosive and 35.5% in already erosive patients).

High-14-3-3η (≥0.50 ng/mL) thus appears to play the role of an amplifier interacting with High-CRP (and inflamed joints), consistent with the proposed role of extracellular 14-3-3η as an enhancer for the release of proteolytic enzymes and proinflammatory cytokines, such as TNFα.[22 23] As activation of osteoclasts causing bone erosions may result from multiple direct and indirect mechanisms, the direct impact of 14-3-3η may be blunted in the presence of existing definite erosions. Our results also support the interest of identifying novel variable RA biomarkers not correlated with current lines of division of RA, such as seropositivity or inflammation.

Our data confirm the stability (>85%) of baseline anti-CCP2 status and of negative RF status, but show the potential for at least temporary reversion of positive RF in 50% of very early RA patients treated to remission. We also observed that only half of those tested early into disease remain stable at the same High-14-3-3η status (positive or negative). Those patients remaining High-14-3-3η positive early on had more subsequent erosive progression over 5 years than patients reverting to negative. Evaluating for the persistency of High-14-3-3η levels at least 1 year apart in early RA patients thus appears reasonable, especially early in disease.

Our study has numerous strengths. First, the prospective nature of data, sera and Sharp Scores collection over a 5-year period following the onset of disease allowed us to determine the variables' relative contribution to radiographic progression observed longitudinally. Second, we followed a large number of consecutive recent-onset polyarthritis patients, with minimal selection bias and variability of evaluation, which were rapidly treated-to-target after symptom onset (with DMARDs and biologics then available), similar to currently recommended strategies.

The vast majority (>91%) fulfilled the classification criteria for RA at baseline. Third, we concentrated on erosion prediction rather than on total Sharp/van der Heijde Scores. In our cohort, none of the assessed biomarkers at a given visit was statistically associated with progression of joint space narrowing over the following year. Pooling narrowing and erosion scores could dilute correlations between variables and erosion progression. Fourth, we aimed to predict the risk of REP based on biomarkers present at each visit, not on baseline biomarkers as in most previous studies.[7–10] As many predictors vary over time (eg, CRP, SJC and to some degree RF and erosive status), models based on baseline predictors may perform less well when applied at a specific visit during clinical follow-up. Furthermore, the PPV of fixed positive variables such as erosive status or ACPA will decrease over long-term follow-up, as most positive patients will not experience consecutive REP episodes, while their NPV will decrease as REP appears in previously non-erosive or ACPA-negative patients. Finally, our patients had minimal missing data, and therefore no imputations were needed.

Limitations first include the lack of uniform treatment. Although the aim remained a state of zero swollen joints, the rate of EP and REP declined markedly over the 20 years of observation. This was largely due to the availability of new and effective therapeutic options, the use of higher doses of methotrexate (frequently parenteral) and stricter treat-to-target strategies. Second, we concentrated on joint erosion prediction, and one can contest the clinical relevance of this outcome. For sure, the incidence of severe erosive progression markedly decreased over the years, but bone erosions remain the most explicit characteristics of severe RA. Of note, minimal erosive damage still developed in 25% of our patients recruited since 2010. Furthermore, REP still occurs in some patients, despite current treat-to-target approaches, especially soon after diagnosis or during disease flares over follow-up. As RA is a lifelong disease persisting over decades, and the half-life of our current conventional, biologic or targeted DMARDs is about 5 years, informed use of biomarker predictors of damage may be helpful to complement clinical expertise. Inversely, some damage progression may occur in patients in clinical remission. Because of their excellent NPV (typically above 98%), biomarker signatures may help identify patients in remission for which decreasing treatment appears appropriate. Third, we used a higher threshold than the manufacturer's upper limit of normal for 14-3-3η (≥0.50 vs ≥0.19 ng/mL). As for antibodies, higher levels of 14-3-3η present better prognostic properties.[6] Fourth, the optimal prognostic use of signatures of biomarkers will require validation in multiple cohorts. Fifth, although we identified subsets of patients at a one in three risk for REP by using combinations of four positive biomarkers, 18 (11.0%) REP events still occurred in patients with no positive biomarkers and 37 (22.6%) more with a single positive one. This suggests that other variables not yet identified or included in this analysis contribute to a patient's risk of severe erosive damage. Additional variables may explain why only one-third of patients with all four positive biomarkers at a given visit developed REP over the following year. Whether these factors are biomarkers, treatment-related or patient-related variables remain to be determined. Finally, due to the observational design of our study, we cannot infer that more intensive targeted drug therapy in patients at high risk would have prevented the progression of joint damage. However, identifying patients at very high impending risk of rapid erosive damage in practice as well as in clinical trials is now possible.

CONCLUSION

In patients treated to remission early into disease, High-CRP, positive RA-associated antibodies and High-14-3-3η levels at a specific visit were predictive of impending rapid erosion progression over the following year. The addition of High-14-3-3η was only significant in patients with elevated CRP and in those with non-erosive status at a given visit. In multivariate analyses, High-CRP and antibodies had the most significant impact, but an independent contribution of 14-3-3η, a modifiable biomarker, interacting with CRP and joints counts was shown to predict erosive progression. Using a signature of serum biomarkers along the disease course may thus inform therapeutic strategies tailored to halt rapid erosive joint damage progression in the most susceptible patients.

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Competing interests Norma Biln is an Augurex Life Sciences Inc employee. None of the other authors reports any conflict of interest related to this manuscript, except that the 14-3-3η measurements were performed free of charge by Augurex Life Sciences Inc, Augurex remaining totally blinded to clinical data.

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Ethics approval The Ethics Review Board of the CHUS approved the EUPA study (registered at ClinicalTrials.gov ID: NCT00512239).

Data sharing statement Individual participant data that underlie the results reported in this article will be available after deidentification, beginning 9 months and ending 36 months after article publication, to researchers providing a methodologically sound research proposal. Study proposal, statistical analytic plan and analytic code will also be available to achieve aims in the approved proposal. Proposals should be sent to gilles.boire@usherbrooke.ca. To gain access, researchers will need to sign a data access agreement.

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