RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Serum biochemical marker of synovial tissue turnover, C1M, predicts radiological progression in early rheumatoid arthritis

Patrick Garnero ,[1] Sofie Falkenløve Madsen,[2] Florent Eymard ,[3] Jérémie Sellam,[4] Roland Chapurlat,[1] Anne-C Bay-Jensen[2]

To cite: Garnero P, Falkenløve Madsen S, Eymard F, *et al*. Serum biochemical marker of synovial tissue turnover, C1M, predicts radiological progression in early rheumatoid arthritis. *RMD Open* 2025;**11**:e005501. doi:10.1136/rmdopen-2025-005501

Received 27 January 2025
Accepted 3 June 2025

[1]Unit 1033, INSERM, Lyon, France
[2]Rheumatology, Nordic Bioscience, Herlev, Denmark
[3]Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Lariboisière, Fédération de Rhumatologie, Université Paris 7 Denis Diderot, Paris, France
[4]Rheumatology, INSERM UMRS_938, Sorbonnes Université UPMC Univ Paris 06, St-Antoine Hospital, DHU i2B, Paris, France

Correspondence to
Dr Patrick Garnero;
patrick.garnero@inserm.fr

ABSTRACT

Objectives To investigate whether serum C1M and C2M, biochemical markers of synovial and cartilage tissue destruction, were associated with progression of joint damage in patients with early arthritis.

Methods 813 early arthritis patients (<6 months of symptoms, 82% with rheumatoid arthritis, 18% undifferentiated arthritis) from the prospective ESPOIR study were followed for 5 years. Radiographic progression was assessed using the van der Heijde Sharp score, and progression was defined as an increase of 1 or 5 unit(s) between baseline and 1 year or 5 years. Associations between baseline C1M and C2M and progression were assessed by logistic regression.

Results Increased baseline continuous serum C1M levels were associated with the risk of progression at 1 year, after adjustment for age, gender and body mass index (BMI). Patients with levels in the highest quartile of C1M had an OR (95% CI) of total joint damage progression of 2.75 (1.70–4.45) compared with patients in the lowest quartile. When disease activity score 28, C reactive protein and anticyclic citrullinated peptide 2 antibodies positivity were included in the model, high C1M remained significantly associated with progression with an OR (95% CI) of 2.12 (1.06–4.23). At 5 years, C1M was significantly associated with the risk of total joint damage progression after adjustment for age, gender and BMI. There was no significant association of C2M with progression at 1 year or 5 years.

Conclusions High baseline serum C1M, but not C2M, is associated with increased radiographic progression in early arthritis, independently of classical risk factors. C1M, in conjunction with other risk factors, may help identify patients at higher risk of joint damage.

WHAT IS ALREADY KNOWN ON THE TOPIC:

⇒ Identifying high-risk early rheumatoid arthritis (RA) patients remains challenging with the current diagnostic tests. Serum C1M and C2M are biochemical markers of synovium and cartilage collagen turnover, respectively.

WHAT THIS STUDY ADDS

⇒ Increased C1M, but not C2M, is associated with a higher risk of progression in early RA at 1 year and 5 years, independently of conventional risk factors such as anticyclic citrullinated peptide 2 antibodies, disease activity score 28 and C reactive protein at 1 year.

HOW THIS STUDY MIGHT AFFECT RESEARCH PRACTICE OR POLICY

⇒ Biochemical markers of synovium turnover such as serum C1M may be used to identify early RA patients at higher risk of progression, together with conventional risk factors.

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory disease characterised by synovial inflammation, cartilage degradation and subchondral bone erosion.[1 2] The mechanisms leading to joint damage are not yet fully understood, although the secretion of proinflammatory cytokines, such as interleukin 1 and tumour necrosis factor, proteolytic enzymes including matrix metalloproteases (MMPs) and other catabolic factors by the synovial tissue, is one of the earliest and most important events involved in this process.[1–4]

The prognosis of RA is highly variable across patients and difficult to predict with usual risk factors such as disease activity parameters, autoantibodies, C reactive protein (CRP) and radiological scores, especially in early arthritis.[5 6] The availability of specific biochemical markers of the remodelling of the extracellular matrix (ECM) of the synovium, cartilage and bone may have a role in predicting disease progression and monitoring treatment efficacy.[7–13] Because the ECM of joint tissues is mainly composed of fibrillar collagens which are degraded by MMPs, MMP-mediated catabolic fragments of

these molecules are among the most promising biochemical markers in RA. Recently, immunoassays for serum MMP-mediated biochemical markers of type I (C1M) and type II (C2M) collagen degradation have been developed. Type I collagen is, with type III collagen, the major constituent of synovium tissue, whereas type II is the main protein of the cartilage matrix and is almost exclusively distributed in cartilage.[14] Although type I collagen is widely distributed in body tissues, its degradation products in biological fluids including serum and urine reflect mainly the remodelling of tissues with high turnover, that is, bone and synovium in patients with active RA. The degradation of type I collagen in bone tissue is mainly mediated by the cysteine protease cathepsin K, whereas in other connective tissues, MMPs are the main collagenolytic enzymes.[15] Thus, in RA, MMP-mediated degradation products of type I collagen such as C1M are a sensitive non-invasive biological marker of synovium tissue, although the contribution of other soft tissue degradation to the systemic C1M levels cannot be excluded. Conversely, fragments of type II collagen, such as C2M, reflect almost exclusively cartilage matrix degradation. A few studies performed in active patients with long-standing disease participating in randomised clinical trials showed that baseline serum C1M levels were associated with radiological progression over a period of 1 year or less, although it remains unclear whether this association was independent of CRP.[9 16 17] One small study including 38 consecutive patients with early RA (disease duration <1 year) showed a modest association of high baseline C2M with erosion at 2 years, although this analysis did not control for potential confounding variables and conventional risk factors of progression.[18]

The aim of this study was to investigate the association between baseline measurements of serum C1M and C2M and the radiographic progression of joint damage in a large cohort of patients with early arthritis participating in the ESPOIR prospective study over a 5-year follow-up period with extensive clinical and biological evaluations.

PATIENTS AND METHODS

Patients with early arthritis

The ESPOIR cohort (in French, the study and follow-up of early undifferentiated arthritis, referenced NCT03666091) is a multicentre early arthritis cohort described in detail elsewhere.[19] With the approval of the Montpellier University (France) ethical committee, 16 university hospital rheumatology departments enrolled patients, covering a large part of the country. Clinical, laboratory and imaging data were collected at baseline, then every 6 months for the first 2 years, then once a year. One biological resources centre (Sarah Tubiana, Paris-Bichat) oversaw centralising and managing biological data collection.

The inclusion criteria were the following: patients aged 18–70 years provided signed informed consent, had two or more swollen joints, with a duration >6 weeks and <6 months, used no previous disease-modifying drugs and no steroids and had no definite diagnosis of a disease other than RA or undifferentiated arthritis. Thus, the ESPOIR cohort consists of both early undifferentiated inflammatory arthritis and recently developed RA. At baseline, an exhaustive data collection was performed according to recommendations in early arthritis.[19] These include, but are not limited to, the demographical variables age, gender, body weight and height and symptom duration, full clinical examination for the determination of the disease activity score 28 using erythrocyte sedimentation rate (DAS28-ESR) score[20] and the biological variables CRP and anticyclic citrullinated peptide 2 antibodies (ACPA) tested by ELISA (DiaSorin, Antony, France; positive if ≥50 units/mL) measured in a central laboratory (S. Martin, Immunology Department, Bichat Hospital, Paris, France). The diagnosis of RA was based on the American College of Rheumatology-European League Against Rheumatism 2010 criteria for RA at inclusion.[21] At baseline, fasting morning blood samples were collected, and serum was stored at a temperature below −70°C until analysis. Collection of baseline blood samples was done from 2002 to 2005 and assays of C1M and C2M were performed in 2022.

Data analysed in the present study pertain to baseline, 12 months and 5 years of follow-up in all the 813 subjects who had serum available at baseline to measure C1M and C2M.

Radiographic evaluation

Radiographs of the hands, wrists and feet in the posteroanterior view were taken for each patient at baseline, 12 months and 5 years. Images were centralised and scored according to the van der Heijde modified Sharp score (mSS)[22] by two experienced rheumatologists who were blinded to the patient's other data, knowing the chronological sequence. For each patient, an erosion score, a joint space narrowing (JSN) score and a total radiographic score were assessed. Based on the reproducibility of the radiographic scoring, the smallest detectable change (SCD) was calculated at 1.0 mSS unit. Progression was defined by an increase from baseline in the mSS score of at least one point for progression at 12 months and five points (corresponding to an increase of 1 mSS unit/year) for progression at 5 years. These cut-off values corresponding to the SCD (1 unit/year) of the radiographic assessment have been previously used in this cohort for other analyses.[23 24]

Serum C1M and C2M measurements

C1M levels were measured using a manual ELISA (NordicC1M, Nordic Bioscience). The assay was performed according to the manufacturer's instructions.[13] Briefly, samples were measured in duplicate, including two kit controls. The mean value of duplicates was used for the analyses. Intravariation and intervariation acceptance criteria were set at <20%; 43 samples were rerun and met the criteria in the second run. 58

samples measured below the lower limit of quantification (LLOQ <11.8 ng/mL) and were given the value of the LLOQ.[13]

C2M levels were measured using the automated open ISYS-I10 platform using the NordicC2M assay (Nordic Bioscience). The assay was performed according to the manufacturer's instructions.[13] Briefly, samples were measured in singles as the assay is automatic with high intra-assay precision, including two kit controls which were run in duplicate. The intra-assay variation ranged from 0.1–9.2% and the interassay coefficients of variation (CVs) of the two controls <15%. Five samples had insufficient sample volume and were not measured for C2M. All samples measured above the LLOQ (4.0 ng/mL).

Statistical analyses

Results are shown as mean±SD and/or median for quantitative variables, as indicated. Because both C1M/C2M and radiographic progression data were not normally distributed, non-parametric tests were used. The comparison between groups of serum C1M and C2M values was performed using the Mann-Whitney test. The correlation of serum C1M and C2M levels with baseline clinical, biological and radiographic variables was analysed by Spearman rank correlations with no adjustment for multiple tests. The relationships between baseline serum C1M and C2M values and radiographic progression at 1 year and 5 year were assessed by logistic regression with baseline demographic variables that were significantly associated with raw values of C1M and/or C2M as covariates, that is, age, body mass index (BMI) and gender. These covariables, which may affect both biochemical marker levels and progression, are commonly used in studies investigating biochemical markers in arthritis studies, including a recent investigation in the same cohort.[24] To assess whether serum C1M and C2M provided prognostic information independent from major classical risk factors, further logistic regression analyses were performed by including ACPA positivity, baseline DAS28-ESR score and baseline CRP levels (in addition to age, BMI and gender) in the model. These covariables were also used in a previous publication on a similar topic.[24] In logistic regression models, serum C1M and C2M levels were considered either as a continuous variable or dichotomised in centiles. The strength of the association was expressed in OR and 95% CI. The comparison of the proportion of patients with progression and no progression in the different quartiles of baseline C1M/C2M levels was analysed using the Pearson χ^2 test. Statistical analysis was performed with SAS/STAT V.9.04.01. SAS Institute in Cary, North Carolina, USA.

RESULTS

Baseline characteristics and cross-sectional associations in patients with early arthritis

Table 1 shows the baseline characteristics of the patients with early arthritis included in the study. 82% of patients had a confirmed diagnosis of RA at baseline. Age, gender distribution and disease activity data were those commonly found in a population of early arthritis patients with a median symptom duration of 4.9 months. 39% of patients were ACPA positive. The radiological scores were low as expected in such populations.

Table 1 Baseline characteristics of the 813 patients with early arthritis

Variables	Mean (SD)	Median (5–95 pct)
Patients diagnosed with RA (n, %)	651 (82%)	
Age (years)	48.1 (13)	50 (25–66)
Women (n, %)	610 (76%)	
BMI (kg/cm^2)	25.0 (4.7)	24.3 (19.0–33.7)
Symptom duration (month)	7.1 (8.5)	4.9 (1.6–24)
DAS28-ESR	5.11 (1.31)	5.08 (2.93–7.43)
C reactive protein (mg/mL)	20.3 (33)	9 (0–83)
ACPA positive patients (n, %)	311 (39%)	
Erosion mSS	0.63 (2.27)	0 (0–4)
Narrowing mSS	2.62 (4.00)	1 (0–12)
Total mSS	3.22 (5.19)	1.5 (0–12)
Serum C1M (ng/mL)	69.2 (54.2)	50.2 (23.6–175)
Serum C2M (ng/mL)	20.6 (5.1)	19.7 (15.1–29.4)

ACPA, anticitrullinated protein antibodies; BMI, body mass index; DAS28-ESR, disease activity score 28 using erythrocyte sedimentation rate; mSS, van der Heidje modified Sharp score; RA, rheumatoid arthritis.

Serum C1M values were on average higher in men than women (+28%, p<0.0001). Serum C1M correlated significantly with BMI and C2M with age, although r values are very low (table 2). Serum C1M levels were significantly correlated with DAS 28 and CRP. C2M was also significantly associated with these two parameters, but with very low Spearman rank correlation coefficients (table 2).

There was no significant correlation of serum C1M or C2M levels with radiological joint scores (table 2).

Association between baseline serum level of C1M and C2M and radiographic progression

Of the 788 patients included in the study, 735 (93%) had valid radiographic data at baseline. 629 patients had both baseline and 1-year radiographic values, whereas at 5 years progression data were available for 445 subjects.

1-year progression

Baseline values of serum C1M—but not C2M—were 42% higher in patients with progression of total joint damage than in patients with no progression (median: 68 ng/mL vs 48 ng/mL, p<0.0001). As shown in table 3, when analysed as a continuous variable, baseline serum C1M levels were significantly associated with the 1-year risk of

Table 2 Correlation of baseline C1M and C2M with baseline RA clinical, biological and radiological parameters

Baseline parameters	Spearman r value, p value	
	C1M	C2M
Age	0.025, 0.49	0.09, 0.01
BMI	0.12, 0.0009	−0.0028, 0.94
DAS 28	0.77, p<0.0001	0.09, 0.014
CRP	0.43, p<0.0001	0.12, 0.002
Erosion score	0.05, 0.20	−0.0004, 0.99
JSN score	0.07, 0.07	0.058, 0.12
Total joint score	0.06, 0.11	0.06, 0.14

BMI, body mass index; CRP, C reactive protein; DAS 28, disease activity score 28 using erythrocyte sedimentation rate; JSN, joint space narrowing; RA, rheumatoid arthritis.

erosion, JSN and total damage progression. After additional adjustments for ACPA, DAS 28 and CRP, the association of serum C1M—used as a continuous variable in the logistic regression model—with progression was no longer significant. There was no significant association between baseline C2M and progression of erosion, JNS or total damage (table 3).

Next, patients were categorised in quartiles of baseline serum C1M levels. The percentage of patients with total joint score progression increased from quartile 1 to quartile 4 of baseline C1M levels (Pearson χ^2 test, p<0.0001 for distribution of progression and no progression across quartiles). For example, among patients with baseline C1M levels in Q1, 31% did progress at 1 year whereas there were 54% of patients with baseline C1M levels in Q4 who progressed (table 4). There was also an increased risk of progression with increased baseline C1M quartiles (age-sex-BMI adj. OR (95% CI): 1.34 (1.16 to 1.54), p<0.0001 for each quartile increase of baseline C1M). Patients with baseline C1M in the highest quartile had an age-sex-BMI OR (95% CI) of progression of 2.75 (1.70 to 4.45), p<0.0001 compared with patients with C1M in the lowest quartile (table 4). When baseline DAS 28, CRP and ACPA positivity were considered, the OR of total joint progression associated with C1M in the highest quartile decreased but remained significant (OR: 2.12 (1.06 to 4.23), p=0.03). When progression was defined by an increase in bone erosion score, there was also a significant increase in the percentage of patients with progression with increased baseline quartile of C1M (Pearson χ^2 test, p<0.0001) (table 5). The risk of progression increased with higher baseline C1M levels (table 5). For example, the age-sex-BMI adjusted OR (95% CI) of progression of bone erosion for the highest quartile of C1M was 4.59 (2.25 to 9.39), p<0.0001, which decreased but remained significant when DAS 28, CRP and ACPA positivity were included in the logistic regression model (OR (95% CI): 3.80 (1.48 to 9.74), p=0.005).

There was no significant association between quartiles of baseline C2M levels and the risk of 1 year progression in total joint damage, erosion or JSN (data not shown).

5-year progression

Patients with progression of total damage at 5 years had 33% (p=0.0037) higher median baseline serum C1M levels than patients with no progression. There was no significant difference in baseline C2M levels between patients with progression and no progression regardless of the radiological score considered (data not shown). After adjustment for age, gender and BMI, each ng/ml increase of baseline C1M was significantly associated with higher risk of total joint progression (OR (95% CI): 1.004 (1.0008 to 1.008), p=0.016). When the variables ACPA positivity, DAS28 and CRP were further included in the model, the association of C1M with progression was no longer significant (p=0.74). There was no significant association of serum C2M with radiological progression regardless of the type of Sharp score considered.

When the analyses were restricted to patients with RA at baseline, very similar results were obtained for both C1M and C2M at both 1 year and 5 years (data not shown).

Table 3 Baseline continuous serum levels of C1M and C2M and the 1-year risk of progression in patients with early arthritis analysed by logistic regression analysis

1-year progression	OR (95%) for each ng/ml increase in baseline C1M/C2M							
	Adjusted for age-gender and BMI				Additional adjustments for DAS 28, CRP and ACPA			
	C1M	P value	C2M	P value	C1M	P value	C2M	P value
Erosion	**1.004 (1.001–1.007)**	**0.010**	0.992 (0.952–1.033)	0.686	1.004 (0.998–1.010)	0.162	0.974 (0.935–1.024)	0.343
JSN	**1.003 (1.001–1.006)**	**0.028**	1.016 (0.986–1.047)	0.309	1.002 (0.999–1.007)	0.420	1.008 (0.976–1.004)	0.634
Total damage	**1.004 (1.001–1.007)**	**0.014**	1.020 (0.990–1.052)	0.197	1.002 (0.997–1.007)	0.435	1.001 (0.978–1.005)	0.529

Data shown in bold style are statistically significant results
ACPA, anticitrullinated protein antibodies; BMI, body mass index; CRP, C reactive protein; DAS28, disease activity score 28 using erythrocyte sedimentation rate; JSN, joint space narrowing.

Table 4 Number and percentage of patients with progression and no progression of total joint damage at 1 year by quartiles of baseline C1M

Quartile of baseline C1M	N (%) of patients with no progression	N (%) of patients with progression	Age-sex-BMI adjusted OR (CI) versus Q1
Q1	108 (69%)	48 (31)	–
Q2	92 (58%)	66 (42%)	1.50 (0.93 to 2.42)
Q3	93 (59%)	65 (41%)	1.62 (0.99 to 2.63)
Q4	72 (46%)	85 (54%)	2.75 (1.70 to 4.45)

OR of progression for each quartile of C1M was obtained by logistic regression using quartile 1 as a reference.

DISCUSSION

This study performed in a large and well-characterised population of patients with early arthritis followed prospectively for 5 years showed that the measurement of baseline serum C1M, a biochemical marker of synovial collagen tissue turnover, was significantly associated with the short-term and long-term risk of radiological progression. In contrast, serum C2M, a biochemical marker of cartilage collagen destruction, was not significantly associated with progression. These findings suggest that early in the arthritis disease, synovial activity plays a more important role than cartilage turnover in mediating joint damage progression.

In RA management, one of the main clinical challenges is the identification, early in the disease, of patients who are likely to progress more rapidly to target the use of biologic treatments to high-risk patients who need to have the tightest control management. Because classical risk factors including systemic unspecific biological parameters of inflammation, for example, CRP, clinical disease activity scores, autoantibodies or radiological parameters, lack sensitivity in early disease,[5] we speculate that dynamic biochemical markers of joint tissues turnover may help. To address this issue, we measured at baseline serum C1M and C2M in a large well-characterised prospective study of patients with early RA and investigated their association with short-term and long-term radiological progression.

At baseline, serum C1M was positively correlated with DAS28-ESR and CRP, which are validated indices of disease activity. The correlation coefficients, however, were modest, suggesting that C1M reflects biological processes which are not fully captured by these conventional risk factors of progression.

In logistic regression models including age, gender and BMI as potential confounding variables, we found that baseline serum C1M levels considered as a continuous variable were associated with the progression of total joint damage at both 1 year and 5 years. The ORs were significant but very low because they represent an increase in risk for a change of only 1 ng/mL of C1M levels, although median levels in patients with RA were 50.2 ng/mL and levels varied between 3 ng/mL and 500 ng/mL in this population. Thus, analysing the association of biochemical markers with progression as a continuous variable with an increment of 1 unit may not be the most useful and relevant for clinical uses. In various clinical conditions, including arthritis, several studies have classified patients in centiles of markers to define patients at risk.[9 12 16 24 25] Using this approach, we found that patients with baseline levels of C1M in the highest quartile had a 2.75 higher risk of total joint progression at 1 year compared with patients with C1M values in the lowest quartile, after adjustments for age, gender and BMI. The risk was even more important when progression was assessed as an increase of bone erosion score with a corresponding OR of 4.59. Interestingly, when DAS 28, CRP and ACPA were included in the prediction model, high C1M levels remained significantly associated with an increased risk of progression, although the OR was lower because C1M correlated with CRP and DAS 28 at baseline. Thus, C1M contributed to radiological progression in part independently of classical variables used to identify patients with RA at risk. At 5 years, raw

Table 5 Number and percentage of patients with progression and no progression of bone erosion at 1 year by quartiles of baseline C1M

Quartile of baseline C1M	N (%) of patients with no progression	N (%) of patients with progression	Age-sex-BMI adjusted OR (CI) versus Q1
Q1	144 (92%)	12 (8 %)	–
Q2	131 (83%)	27 (17%)	2.20 (1.06 to 4.61)
Q3	130 (82%)	28 (18%)	2.34 (1.12 to 4.88)
Q4	116 (74%)	41 (26%)	4.59 (2.25 to 9.39)

OR of progression for each quartile of C1M was obtained by logistic regression using quartile 1 as a reference.

levels of serum C1M remained a significant predictor of total joint damage progression after adjustments for age, gender and BMI. However, because the number of subjects who could be evaluated for progression was substantially lower than at 1 year, a reliable analysis in quartiles could not be performed.

Contrasting with the positive relationships of C1M with disease activity and progression, this study showed no significant association of C2M with these parameters. Thus, in early RA, this biochemical marker of cartilage destruction is not useful to identify patients at high risk, although in established disease, biochemical markers of type II collagen degradation were shown to be associated with disease progression.[9] Because, in early RA, the extent of joint tissue damage is very limited, biochemical markers of cartilage turnover may lack sensitivity.

This study has strengths and some limitations. The population was large, prospectively recruited and rigorously investigated over a long-term follow-up. All patients had a homogeneous stage of early disease with no treatment at baseline that may have influenced the levels of serum C1M and C2M. The progression at 1 year was available for the vast majority of patients included in the study, joint damage was evaluated by state-of-the-art radiography assessment, and the major risk factors have been measured at baseline. However, at 5 years, only 60% of patients with baseline radiological data were available for progression analysis. Thus, results at 5 years may not be as robust as the 1 year findings. We did not analyse the relationships of C1M and C2M and clinical progression using DAS 28. We also did not consider the influence of treatment groups during follow-up, because the primary objective of this study was to specifically evaluate whether baseline markers may help to predict joint damage progression, regardless of treatment. These valuable analyses should be the topic of further studies. The results may not apply to treated patients with established RA. We could also not compare the performance of serum C1M and C2M to other joint tissue remodelling markers including urinary crosslinked type II collagen C-telopeptide (CTX-II), the current most established cartilage turnover marker in arthritis,[9 12] because urine samples were not available in the study. Finally, because samples were stored for about 20 years before being assayed for C1M and C2M, potential degradation may have influenced C1M and/or C2M concentration. However, C1M and C2M are collagen fragments which are believed to be highly stable in serum stored at −80°C. Comparison of average values with historical fresh samples did not show major changes in absolute concentrations of C1M/C2M. We cannot, however, exclude that possible alterations of C1M and C2M data during storage may have some influence in the findings, probably by decreasing the true association of these markers with progression.

In summary, serum measurements of C1M, but not C2M, were associated with the risk of radiographic progression in patients with early arthritis, independently of the major currently validated clinical and biological risk factors at short-term. This biological marker may be combined with other biomarkers of disease activity to improve the identification of patients with early arthritis at high risk for progression.

X Anne-C Bay-Jensen @ACBayJensen

Acknowledgements We wish to thank Nathalie Rincheval (Montpellier) who did expert monitoring and data management and all the investigators who recruited and followed the patients (F. Berenbaum, Paris-Saint Antoine, MC. Boissier, Paris-Bobigny, A. Cantagrel, Toulouse, B. Combe, Montpellier, M. Dougados, Paris-Cochin, P. Fardellone et P. Boumier Amiens, B. Fautrel, Paris-La Pitié, RM. Flipo, Lille, Ph. Goupille, Tours, F. Liote, Paris- Lariboisière, O. Vittecoq, Rouen, X. Mariette, Paris Bicetre, P. Dieude, Paris Bichat, A. Saraux, Brest, T. Schaeverbeke, Bordeaux, J. Sibilia and Strasbourg).

Contributors PG: conception and design of the study, analysis and interpretation of data, drafting the article and final approval of the version to be submitted. SFM: collection of the data, data interpretation, critical revision of the article and final approval. FE: critical revision of the article and final approval of the manuscript. JS: critical revision of the article and final approval of the manuscript. RC: critical revision of the article and final approval of the manuscript. ACBJ: critical revision of the article and final approval of the manuscript. Guarantor: PG.

Funding An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years. Two additional grants from INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Pfizer, Abbvie, Lilly, and more recently Fresenius and Biogen also supported the ESPOIR cohort study.

Competing interests ACBJ is an employee of and own stocks in Nordic Biosciences. All the other authors declare no conflict of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Montpellier University (France) ethical committee Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All authors, where ethically possible, agree to publicly release all data.

ORCID iDs
Patrick Garnero http://orcid.org/0000-0003-0939-5099
Florent Eymard http://orcid.org/0000-0003-2758-5216

REFERENCES

1 Harris ED. Rheumatoid arthritis. Pathophysiology and implications for therapy. *N Engl J Med* 1990;322:1277–89.
2 McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med* 2011;365:2205–19.
3 Hitchon CA, El-Gabalawy HS. The synovium in rheumatoid arthritis. *Open Rheumatol J* 2011;5:107–14.
4 Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016;388:2023–38.
5 Scott DL. Prognostic factors in early rheumatoid arthritis. *Rheumatology (Oxford)* 2000;39 Suppl 1:24–9.
6 Fex E, Jonsson K, Johnson U, *et al*. Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. *Br J Rheumatol* 1996;35:1106–15.
7 Garnero P, Geusens P, Landewé R. Biochemical markers of joint tissue turnover in early rheumatoid arthritis. *Clin Exp Rheumatol* 2003;21:S54–8.
8 Landewé RBM, Geusens P, van der Heijde DMFM, *et al*. Arthritis instantaneously causes collagen type I and type II degradation in patients with early rheumatoid arthritis: a longitudinal analysis. *Ann Rheum Dis* 2006;65:40–4.
9 Garnero P, Landewé R, Chapurlat RD. The role of biochemical markers of joint tissue remodelling to predict progression

and treatment efficacy in inflammatory rheumatic diseases. *Rheumatology (Oxford)* 2020;59:1207–17.
10 Freeston JE, Garnero P, Wakefield RJ, *et al*. Urinary type II collagen C-terminal peptide is associated with synovitis and predicts structural bone loss in very early inflammatory arthritis. *Ann Rheum Dis* 2011;70:331–3.
11 Syversen SW, Landewe R, van der Heijde D, *et al*. Testing of the OMERACT 8 draft validation criteria for a soluble biomarker reflecting structural damage in rheumatoid arthritis: a systematic literature search on 5 candidate biomarkers. *J Rheumatol* 2009;36:1769–84.
12 Garnero P, Landewé R, Boers M, *et al*. Association of baseline levels of markers of bone and cartilage degradation with long-term progression of joint damage in patients with early rheumatoid arthritis: the COBRA study. *Arthritis Rheum* 2002;46:2847–56.
13 Drobinski PJ, Bay-Jensen AC, Karsdal MA, *et al*. Connective tissue remodelling is differently modulated by tocilizumab versus methotrexate monotherapy in patients with early rheumatoid arthritis: the AMBITION study. *Arthritis Res Ther* 2021;23:13.
14 Gelse K, Pöschl E, Aigner T. Collagens--structure, function, and biosynthesis. *Adv Drug Deliv Rev* 2003;55:1531–46.
15 Fields GB. Interstitial collagen catabolism. *J Biol Chem* 2013;288:8785–93.
16 Siebuhr AS, Bay-Jensen AC, Leeming DJ, *et al*. Serological identification of fast progressors of structural damage with rheumatoid arthritis. *Arthritis Res Ther* 2013;15:R86.
17 Bay-Jensen AC, Platt A, Jenkins MA, *et al*. Tissue metabolite of type I collagen, C1M, and CRP predicts structural progression of rheumatoid arthritis. *BMC Rheumatol* 2019;3:3.
18 Maijer KI, Gudmann NS, Karsdal MA, *et al*. Neo-Epitopes--Fragments of Cartilage and Connective Tissue Degradation in Early Rheumatoid Arthritis and Unclassified Arthritis. *PLoS One* 2016;11:e0149329.
19 Combe B, Benessiano J, Berenbaum F, *et al*. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. *Joint Bone Spine* 2007;74:440–5.
20 Prevoo MLL, Van'T Hof MA, Kuper HH, *et al*. Modified disease activity scores that include twenty-eight-joint counts development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
21 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
22 van der Heijde DM, van Riel PL, Nuver-Zwart IH, *et al*. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989;1:1036–8.
23 Mouterde G, Lukas C, Logeart I, *et al*. Predictors of radiographic progression in the ESPOIR cohort: the season of first symptoms may influence the short-term outcome in early arthritis. *Ann Rheum Dis* 2011;70:1251–6.
24 Garnero P, Gineyts E, Rousseau JC, *et al*. A new serum biochemical marker of synovium turnover predicts radiographic progression in patients with early arthritis. *Rheumatology (Oxford)* 2024;63:874–81.
25 Combe B, Landewe R, Lukas C, *et al*. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007;66:34–45.