Calprotectin is not independent from baseline erosion in predicting radiological progression in early rheumatoid arthritis. Comment on ‘Calprotectin as a marker of inflammation in patients with early rheumatoid arthritis’ by Jonsson et al.

We have read with great interest the article by Jonsson et al that was recently published online in ARD,1 which suggested that calprotectin, also known as S100A8/S100A9 heterodimer, was associated with radiographic progression in early rheumatoid arthritis (RA). Calprotectin correlates significantly with inflammatory markers and disease activity score.2 Besides correlations between baseline calprotectin levels, Clinical Disease Activity Index and ultrasonography power Doppler, the authors showed that baseline calprotectin levels correlated with van der Heijde modified Sharp score (SHS) progression (defined as an increase ≥5 of the total SHS score/year), independently of age, gender, Clinical Disease Activity Index, erythrocyte sedimentation rate (ESR), C reactive protein (CRP) levels and rheumatoid factor positivity.1

We analysed the initial serum calprotectin among patients with early RA fulfilling American College of Rheumatology/European League Against Rheumatism 2010 of the French observational cohort Etude et Suivi des Polyrheumatis Indifferencées Récentes (ESPOIR). Calprotectin serum concentrations were assessed according to manufacturer method (Hycult, Frontstraat, Netherlands; standard range from 1.6 to 25 mg/mL). Univariate and multivariate risk Cox models with a backward stepwise were constructed for 615 patients with early RA for whom radiological data were available. Outcome measures included in the analysis were gender, CRP, anti-citrullinated peptide antibody (ACPA), Disease Activity Score, age, smoking status, calprotectin, disease-modifying antirheumatic drugs (DMARDs) treatment and typical initial erosion. The radiological progression was defined as an increase ≥5 of the total SHS score/year.

CRP, ACPA, DMARD treatment and calprotectin were significantly associated with structural evolution in the univariate analysis. When baseline erosion was removed from the multivariate analysis, calprotectin was the only predictor of the structural evolution over 3 years (HR 1.06, 95% CI (1.00 to 1.11), P=0.045, table 1). These results confirmed that calprotectin predicts radiological progression in a large cohort of early RA. When the presence of baseline typical erosion was combined in the multivariate Cox model, calprotectin was not an independent predictor of structural evolution anymore (HR 1.03, 95% CI (0.97 to 1.10), P=0.297).

Calprotectin, which is predominantly expressed by myelomonocytic cells and constitutes 40% of the polymorphonuclear neutrophil cytosolic proteins,3 was identified as a marker of RA in the synovial fluid and in the serum, with serum concentrations differentiating RA from other rheumatic diseases.4 Besides their intracellular functions,5 calprotectin has been introduced as an important proinflammatory factor mainly secreted by activated neutrophils. A direct role in radiological damage has been suggested because of the activation of matrix metalloproteases by S100 proteins.6

We acknowledge the putative role of new biomarkers,7 such as calprotectin, in early RA management. Jonsson et al showed that calprotectin is a better predictor of structural progression than ESR or CRP. In order to know whether calprotectin should be implemented in daily practice, it is critical to determine whether calprotectin is also independent from major predictors of structural evolution in RA, such as ACPA and baseline erosion.7 In ESPOIR cohort, calprotectin is no more associated with structural damage when baseline erosion is considered.

Maxime Chevreau,1 Marie-Hélène Paclet,2,3 Xavier Romand,1,2 Jean-Louis Quesada,1,3 Olivier Vittecoq,2 Philippe Dieude,1 Bertrand Toussaint,4 Philippe Gaudin,1,2 Athan Baillet1,2

1 Department of Rheumatology, Grenoble Alpes University Hospital, Grenoble, France
2 Univ Grenoble Alpes, GREP-UCA EA7408, Grenoble, France
3 Lab. Biochimie des Enzymes et des Protéines, Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France
4 INSERM, Clinical Investigation Center CIC P 1406, Grenoble University Hospital, Grenoble, France
5 Scientific Department of the Clinical Research Delegation, Grenoble Alpes University Hospital, Grenoble, France
6 Department of Rheumatology, Rouen Hospital, Bois-Guillaume, France
7 Department of Rheumatology, Bichat Hospital, Paris, France
8 Laboratoire TIMC-IMAG-TheREx, UMR 5525 Centre National de la Recherche Scientifique, Univ Grenoble Alpes, Grenoble, France

Correspondence to Dr Athan Baillet, Rheumatology, Grenoble Alpes University Hospital, Université Grenoble Alpes, Echirroles 38434 Cedex, France; abaillet@chu-grenoble.fr

Acknowledgements We wish to thank Nathalie Rincheval (CHU Montpellier and EA 2415) 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 Cartagrel, Toulouse; B Combe, Montpellier; D Bougeret, Grenoble; J-J Schmitz, Strasbourg; A-B Huc, Besancon; A Eaves, Lyon; C Seguela, Lille; T Tauber, Nantes; C Masson, Mantes) and all the investigators who recruited and followed the patients (F Berenbaum, Paris-Saint Antoine; MC Boissier, Paris-Bobigny; A Cartagrel, Toulouse; B Combe, Montpellier; D Bougeret, Grenoble; J-J Schmitz, Strasbourg; A-B Huc, Besancon; A Eaves, Lyon; C Seguela, Lille; T Tauber, Nantes; C Masson, Mantes) and all the investigators who recruited and followed the patients (F Berenbaum, Paris-Saint Antoine; MC Boissier, Paris-Bobigny; A Cartagrel, Toulouse; B Combe, Montpellier; D Bougeret, Grenoble; J-J Schmitz, Strasbourg; A-B Huc, Besancon; A Eaves, Lyon; C Seguela, Lille; T Tauber, Nantes; C Masson, Mantes).
Correspondence

M Dougados, Paris-Cochin; P Fardelone et P Bourrier, Amiens; B. Fautrel, Paris-La Pitié; RM Flipo, Lille; Ph Goupille, Tours; F Liote, Paris-Lariboisière; O Vittecoq, Rouen; X Mariette, Paris Bicêtre; O Meyer et Ph Dieude, Paris Bichat; A Saraux, Brest; Th Schaeverbeke, Bordeaux; J Sibilia, Strasbourg). We thank V Devauchelle and C Lukas for expert X-ray reading and S Martin (Paris Bichat) who did all the central dosages of Creactive protein, IgA rheumatoid factor and IgM rheumatoid factor and anti-citrullinated protein antibodies. The authors thank Ms Sylvie Papacatsis for her contribution to this study.

Contributors MC, M-HP, XR, J-LQ and AB have made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. OV, PD, BT and PG have revised the draft critically for important intellectual content and have approved the final version published.

Funding An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years. Two additional grants from Institut national de la santé et de la recherche médicale (INSERM) were obtained to support part of the biological database. The French Society of Rheumatology, Pfizer, Abbvie and Roche-Chugai also supported the Etude et Suivi des POlyarthrites Indifférenciées Récentes INSERM (ESPOIR) cohort study. This study was funded by the Scientific Department of the Clinical Research Delegation (DRCI), Grenoble Alpes University Hospital.

Competing interests None declared.

Ethics approval The Montpellier ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

To cite Chevreau M, Paclet M-H, Romand X, et al. Ann Rheum Dis 2018; 77: e84. Received 8 December 2017 Accepted 15 December 2017 Published Online First 10 January 2018

REFERENCES