Response to: 'Calprotectin is not independent from baseline erosion in predicting radiological progression in early rheumatoid arthritis' by Chevreau *et al*

We appreciate the additional data regarding calprotectin and radiographic progression provided by Chevreau *et al*[1] as an eLetter addressing our published research paper.[2] It is important to explore new biomarkers in different cohorts of patients with early and established rheumatoid arthritis (RA). Calprotectin levels have previously been shown to be associated with joint damage in established RA.[3 4] Hammer *et al*[5] have shown that calprotectin was an independent predictor of radiographic joint damage after 10 years of follow-up. Chevreau *et al* present data on baseline calprotectin as a predictor of rapid radiographic progression (defined as an increase of ≥5 van der Heijde Sharp score units/year) in a large cohort of patients with early RA, and did not find calprotectin to be associated with structural damage when baseline erosions were considered.[1]

In order to address the issues raised by Chevreau *et al*[1] we performed additional statistical analyses. When introducing baseline van der Heijde modified Sharp erosion score in the multivariate model (including erythrocyte sedimentation rate, C reactive protein, age, gender, Clinical Disease Activity Index and rheumatoid factor (RF)), baseline erosion score was a significant predictor of radiographic progression (OR 1.14, 95% CI 1.02 to 1.28; table 1). Importantly, calprotectin in the highest quartile remained a significant independent predictor of radiographic damage in the multivariate model (OR 3.52, 95% CI 1.15 to 10.72; table 1). RF was a stronger predictor than anticitrullinated peptide antibody (ACPA) in univariate models; thus, we chose to include RF in our initial model.[2] When assessing the multivariate model including ACPA instead of RF, both calprotectin and baseline erosions remained significant independent predictors of radiographic progression, while ACPA was not a significant predictor (OR 1.27, 95% CI 0.52 to 3.08, p=0.60).

Comparison between cohorts should be done with caution, and the Aiming for Remission in Rheumatoid Arthritis: a Randomized Trial Examining the Benefit of Ultrasonography in a Clinical TIght Control Regimen (ARCTIC)[6] and Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohorts[7] are different. Serologically, 44% vs 39% of patients were positive for RF-IgM and ACPA in the ESPOIR cohort compared with 71% and 82% in the ARCTIC cohort. Treatment strategies were different in the two cohorts; in ESPOIR there were no protocol-based treatment strategies, as opposed to ARCTIC with a structured, aggressive tight control algorithm aiming for remission. In the ARCTIC cohort, 41% of disease-modifying antirheumatic drug-naïve patients with early RA progressed radiographically during the 2 years of follow-up, with radiographic progression defined as ≥1 unit/year from 0 to 24 months.[2] However, rapid radiographic progression was rare, occurring in only 11 out of the 230 patients included in the full analyses set.

In modern RA care, patients are identified at an early stage and often before radiographic damage is evident. In such a setting, our results indicate that calprotectin may be an independent predictor of radiographic damage, but the role of calprotectin needs to be further investigated in different cohorts before being fully implemented in routine care.

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Table 1 Predictors of radiographic progression ≥1 unit/year from 0 to 24 months (n=215)

	Univariate		Multivariate	
Baseline variables	**OR**	**p value**	**OR**	**p value**
Age	**1.04 (1.02 to 1.07)**	**<0.001**	1.02 (1.00 to 1.05)	0.09
Gender (female)	0.61 (0.35 to 1.07)	0.09	0.71 (0.36 to 1.37)	0.30
Calprotectin quartile (range)				
First quartile (186–556 µg/L)	Ref	Ref	Ref	Ref
Second quartile (567–1028 µg/L)	1.51 (0.66 to 3.46)	0.33	1.55 (0.60 to 4.01)	0.37
Third quartile (1045–2158 µg/L)	1.39 (0.61 to 3.20)	0.44	0.97 (0.36 to 2.60)	0.94
Fourth quartile (2235–48079 µg/L)	**6.06 (2.62 to 14.02)**	**<0.001**	**3.62 (1.20 to 10.93)**	**0.02**
ESR, quartile (range)				
First quartile (1–10 mm/hour)	Ref	Ref	Ref	Ref
Second quartile (11–18 mm/hour)	1.07 (0.47 to 2.43)	0.87	0.80 (0.31 to 2.04)	0.64
Third quartile (19–31 mm/hour)	1.26 (0.55 to 2.86)	0.59	0.82 (0.30 to 2.19)	0.69
Fourth quartile (32–110 mm/hour)	**3.74 (1.64 to 8.52)**	**0.002**	0.99 (0.29 to 3.35)	0.99
CRP, quartile (range)				
First quartile (0.3–2.8 mg/L)	Ref	Ref	Ref	Ref
Second quartile (3–6 mg/L)	0.69 (0.29 to 1.64)	0.41	0.41 (0.15 to 1.09)	0.07
Third quartile (7–16 mg/L)	1.29 (0.54 to 3.04)	0.57	0.75 (0.25 to 2.19)	0.59
Fourth quartile (18–117 mg/L)	**2.85 (1.20 to 6.76)**	**0.02**	0.89 (0.24 to 3.22)	0.85
CDAI (0-76)	1.02 (1.00 to 1.04)	0.08	1.01 (0.98 to 1.04)	0.50
RF positivity	1.86 (0.99 to 3.48)	0.053	1.92 (0.91 to 4.06)	0.09
vdHS erosion score (0–280)	**1.18 (1.07 to 1.29)**	**0.001**	**1.14 (1.01 to 1.27)**	**0.03**

P values <0.05 in bold.
CDAI, Clinical Disease Activity Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; h, hour; L, liter; mg, milligram; mm, millimeter; OR, odds ratio; Ref, reference category (lowest quartile as reference); RF, rheumatoid factor; µg, microgram; vdHS, van der Heijde modified Sharp.

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