

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 ≥ 1 unit/year from 0 to 24 months), 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 POLyarthrites Indifférenciées Récentes (ESPOIR). Calprotectin serum concentrations were assessed according to manufacturer method (Hycult, Frontstraat, Netherlands; standard range from 1.6 to 25 ng/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,² 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.

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Table 1 Univariate analyses and multivariate analyses—risk factors of van der Heijde modified Sharp score (SHS) progression in the first 3 years

| N = 615 | No radiological progression, n=290 | Radiological progression, n=325 | Univariate analysis HR (95% CI) | P value | Multivariate analysis HR (95% CI) | P value |
|----------------------------|------------------------------------|---------------------------------|---------------------------------|---------|-----------------------------------|---------|
| Female gender (%) | 79.3% (230) | 76.9% (250) | 0.95 (0.73 to 1.23) | 0.696 | – | – |
| CRP (mg/dL) | 7 (4 to 18) | 12 (5 to 28) | 1.03 (1 to 1.06) | 0.047 | Not selected | |
| ACPA (IU) | 0 (0 to 256) | 121 (0 to 572) | 1.01 (1 to 1.01) | 0.040 | 1.01 (1 to 1.01) | 0.093 |
| DAS-28 | 5.2 \pm 1.22 | 5.3 \pm 1.2 | 1.07 (0.98 to 1.17) | 0.148 | – | – |
| Age (years) | 48.7 (38 to 56.3) | 52.4 (41.1 to 58.4) | 1.01 (1 to 1.02) | 0.082 | – | – |
| Current smoking | 48.3% (140) | 46.8% (152) | 1.04 (0.84 to 1.29) | 0.732 | – | – |
| DMARDs (%) | 77.2% (224) | 86.8% (282) | 1.50 (1.09 to 2.07) | 0.013 | 1.36 (0.99 to 1.89) | 0.060 |
| Calprotectin (μ g/cL) | 3.2 (1.88 to 4.8) | 3.8 (2.3 to 5.3) | 1.06 (1.01 to 1.12) | 0.027 | 1.06 (1 to 1.11) | 0.045 |

Univariate and multivariate analyses: Cox model; HR (95% CI).

Percentage (number); mean \pm SD or median (25th, 75th centiles) where appropriate.

ACPA, anti-citrullinated protein/peptide antibody; CRP, C reactive protein (mg/dL); DAS-28, Disease Activity Score-28; DMARDs, disease-modifying antirheumatic drugs, that is, methotrexate ≥ 7.5 mg/week, leflunomide at the visit before radiological evolution or at the last follow-up visit; IU, international unit; Not selected, outcome was excluded from multivariate Cox model because P value for model entry was >0.5 or P value for model retention was >0.10 . Radiological progression was defined as an increase ≥ 5 of the total SHS score.

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