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LETTER

Serum calprotectin levels do not predict subsequent relapse in rheumatoid arthritis in remission: a post-hoc analysis of STRASS study

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Dear Editor,

Calprotectin (MRP8/14 or S100A8/A9 protein) is an alarmin intensely released by neutrophils and macrophages in the site of inflammation such as the synovitis. Samantha Louise Smith *et al* showed in a large cohort of patients with active rheumatoid arthritis (RA) that calprotectin is a biomarker of RA disease activity which does not predict, beyond the use of C-reactive protein (CRP), the response to tumour necrosis factor inhibitor (TNFi).[1] Interestingly, a decrease in calprotectin levels at the month 1 and month 3 on TNFi was associated with a moderate-to-good response.[1] The persistence of higher calprotectin level while the patient is in sustained remission may indicate poor control of synovial inflammation, which may lead to subsequent relapse, especially on treatment tapering. Some studies reported that calprotectin in patients with RA in remission could be a useful biomarker to predict change of treatment over 5 years and future relapse.[2 3] The performance of calprotectin to predict clinical response after disease-modifying antirheumatic drugs tapering is still controversial.[4 5]

We conducted a post-hoc analysis of the Spacing of TNF-blocker injections in Rheumatoid ArthritiS Study (STRASS) (NCT 00780793).[6] Briefly, patients with RA fulfilling the 1987 American College of Rheumatology criteria, in remission Disease Activity Score 28 (DAS28)<2.6) for more than 6 months with stable joint damage and stable dosage of etanercept or adalimumab for at least 1 year were randomised into two treatment strategies, continue TNFi at a stable dose (maintenance strategy) or injection spacing (spacing strategy). We included all patients with serum samples available and performed a calprotectin dosage at baseline (IDK Calprotectin ELISA Kit). Relapse during the 18 months was defined as a DAS28>2.6 with DAS28 increase >0.6 compared with the previous visit. The objective was to evaluate if calprotectin serum level during sustained RA remission under TNFi could be associated with the risk of at least one relapse within 18 months of follow-up. T-test, spearman correlation (Rs) and Cox regression analyses were performed. A p value<0.05 was considered statistically significant.

One hundred and twenty-nine patients were included. Sixty-eight were in the maintenance arm and 61 in the spacing arm. One hundred patients (77.5%) were women, mean age was 55.3 (±11.5) years, 87 were anti-citrullinated protein antibody (78.4%) and 78 (69.6%) rheumatoid factors positive (online supplemental table 1). Levels of baseline calprotectin were modestly correlated with CRP (Rs=0.26, 95% CI 0.06 to 0.40) but not with pain Numeric Rating Scale (NRS), disease activity NRS, erythrocyte sedimentation rate, tender joints count and DAS28-CRP. We did not observe difference in serum calprotectin levels between patients who relapsed during 18 months of follow-up (mean±SD, 1564.6±995.8) and those who did not (1460.2±1113.7 ng/mL, p=0.59) (figure 1). We also did not find any difference in calprotectin levels in relapsers according to the treatment protocol: maintenance strategy (relapser mean±SD 1397.8±838.3 vs 1423.2±872.7 ng/mL, p=0.90)) or spacing strategy (relapser mean±SD 1677.0±1083.5 vs 1549.1±1585.7 ng/mL, p=0.77) (figure 1). There was also no difference in calprotectin levels when we study the occurrence of earlier relapse at 3, 6, 9 and 12 months. Calprotectin

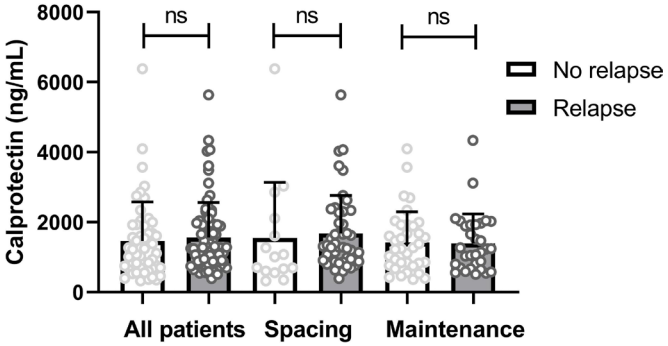

Figure 1 Serum calprotectin levels at baseline in patients with rheumatoid arthritis in sustained remission who relapsed or did not during 18 months of follow-up after continuing the tumour necrosis factor inhibitor at a stable dose (maintenance strategy) or spacing the injections (spacing strategy). Each dot represents one patient. Dark grey dots represent patients with relapse and light grey dots represent patients who do not relapse. Mean±SD, t-test.

levels at baseline were not associated with risk of relapse even after adjustment for potential confounders (online supplemental table 2). The main limitation of this post-hoc analysis is the limited number of patients included, which raises a power issue to demonstrate a small mean difference in calprotectin level, which may have contributed to a false-negative result.

Hence, even if we observed that calprotectin was associated with disease activity parameters, we found that calprotectin did not add any information to predict the risk of early or late relapse in patients with RA in sustained remission on TNFi regardless of the treatment strategy used.

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Contributors XR, MC and MVC collected the data and performed the calprotectin assay. XR and MC were responsible for data analysis. XR and MC wrote the first draft of the manuscript. MVC, MHP, BF and AB contributed to the conception and study design. BF provided and cared for the study patients. All authors contributed substantially to the interpretation of the data and critically reviewed the work for important intellectual content. All authors approved the final version.

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