Serum Calprotectin (S100A8/A9): A Promising Biomarker in Diagnosis and Follow-up in Different Subgroups of Juvenile Idiopathic Arthritis

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Abstract

Background

Management of juvenile idiopathic arthritis (JIA) lacks of diagnostic and prognostic biomarkers. Therefore, this study was designed to assess the use of serum calprotectin (sCal) as a marker of disease activity and its monitoring, and as a classification and prognosis tool of response to treatment or risk of flares in patients with JIA.

Methods

Eighty-one patients with JIA from the CAP48 multicentric cohort were included in this study, as well as 11 healthy controls. Enzyme-linked immunosorbent assay (ELISA) method was used to quantify sCal with a commercial kit. Mann-Whitney tests were used to compare results, correlations were assessed with Spearman's rank correlation coefficients and Receiver Operating Characteristic curves were also generated to evaluate serum calprotectin as a prognostic tool.

Results

Patients with an active disease compared to healthy controls and to patients with inactive disease showed an 8-fold and a 2-fold increased level of sCal respectively. sCal was found to be correlated with the CRP and even more strongly with the ESR. Evolution of DAS28 scores correlated well with evolution of sCal, as opposed to evolution of CRP. As for the CRP, sCal could differentiate forms with active oligoarthritis from polyarthritis or systemic forms. However, sCal brought an added value compared to the CRP as a prognosis marker. Indeed, patients with active disease and good responder to treatment (pediACR > 30) at 6 months following the sample test had higher sCal levels, while patients with inactive disease had higher sCal levels in case a flare was observed up to 3 to 9 months following the sample test.

Conclusions

This study confirms the potential uses of serum calprotectin as a biomarker in diagnosis and follow-up in JIA.

Background

Juvenile idiopathic arthritis (JIA) represents a very heterogeneous disease and is divided in 7 sub-groups according to the International League of Associations for Rheumatology (ILAR) classification: oligoarthritis, rheumatoid factor (RF)-positive and -negative polyarthritis, enthesitis-related arthritis, psoriatic arthritis, systemic arthritis and undifferentiated arthritis (1). JIA can be associated with a significant morbidity and mortality and represents an important cause of short-term and long-term disability (2, 3).

Immune pathogenesis of JIA is still incompletely understood. Disease probably results, as for most autoimmune diseases, from a combination of genetic susceptibility, with identified susceptibility genes (HLA and non HLA-related), triggered by environmental factors, and causing over-activation of innate and adaptive (T-cell or B-cell) immunity (3).

The course of the disease is characterized by alternating periods of flares and remission. Some predictors of poor outcome have been identified (presence of RF, early radiographic changes, symmetrical disease, extension of arthritis at onset, positivity of antinuclear antibodies [ANA]), but lack of precise and reliable prognosis factors remains a major problem in JIA (2, 3).

Serum calprotectin (sCal), also known as myeloid-related protein (MRP) 8/14, is part of the S100 proteins family (with pro-inflammatory effects) and is formed by a stable heterodimer of S100A8 and S100A9 subunits (4). It has been described in many studies involving numerous inflammatory diseases (Crohn's disease, cystic fibrosis, sepsis, etc.) (5–7), including rheumatologic diseases (rheumatoid arthritis, systemic lupus erythematosus, etc.) (8–10).

In JIA, sCal was shown to be elevated in patients with active disease, particularly in the systemic form, notably helping to distinguish them from patients with infections or malignant disease (which can present as a hard differential diagnosis at first) (11–13). It has also shown promising results as a biomarker predicting disease relapse after stopping NSAIDs (14), methotrexate (15, 16) or etanercept (17) treatment.

In this study, we intended to measure sCal in a Belgian population of JIA patients among the CAP48 cohort and to correlate its level with regard to the different clinical subgroups of JIA, disease activity and outcome (evaluate the response to treatment in patients with active disease or the risk of flares in inactive disease).

Methods

Study design

Eighty-one patients were enrolled from an observational multicentric study (CAP48 cohort) and followed for a duration of 2 years at the time of this study. The cohort was divided in 2 subgroups: patients with an established disease (already treated with a DMARD) or naïve of any treatment at time of inclusion. The patients were followed every 3 months during first year of follow-up, then every 6 months. Details of this study are described elsewhere.

Definitions

The inclusion criterion was a diagnosis of JIA according to the ILAR criteria.

The disease activity was followed by DAS28-CRP and JADAS10-CRP scores (18, 19). The disease inactivity was defined according to the American College of Rheumatology (ACR) criteria revised in 2011

(20), while remission was defined as a persistent inactivity for 6 months under stable treatment.

Response to treatment was assessed by pediACR scores (21), which comprise the variation of 6 core outcome parameters (physician global assessment of disease activity on a 10-cm Visual Analogue Scale [VAS], patient/parent assessment of overall wellbeing on a 10-cm VAS, functional ability based on the Childhood Health Assessment Questionnaire (CHAQ), number of joints with active arthritis, number of joints with limited range of motion and erythrocyte sedimentation rate [ESR]). Therefore in our study, the patients were considered as responders if reaching a pediACR $\geq$ 30 at 6 months and/or an inactive disease. Finally, the definition of flare was based on the criteria developed in 2002, and characterized by worsening of 2 core outcome variables (COV) by $\geq$ 40% without concomitant improvement of more than one of the remaining COV by $\geq$ 30% (22).

Serum calprotectin measurements

Serum calprotectin was measured at baseline in all 81 patients (active or inactive). The serum samples were frozen and stored at -80 °C. The levels of sCal were measured by ELISA method with a commercial kit (Bühlmann Laboratories AG, Schönenbuch, Switzerland), chosen after review of literature, that would theoretically deliver more consistent results. The intra-assay coefficient of variability was 5%.

Statistical analysis

The statistical analyses were made using SPSS v23.0 (IBM®, Armonk, New York, USA) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA). Comparisons were done with parametric t tests when the number of samples was superior to 25 (assuming they followed a Gaussian distribution) and with a Mann-Whitney test when it was inferior to 25. Correlations between measures were assessed with Spearman's rank correlation coefficient. Receiver operating characteristic (ROC) curves were also generated to appraise sensitivity and specificity of measuring serum calprotectin as a prognostic tool.

Results

Demographic data at baseline

The patients had a median age of 12.6 years, with a predominance of female (F:M sex ratio of 1.9:1). The disease duration was 2.1 and 5.0 years in the naïve and established cohort respectively. Thirty-six patients had an active disease at baseline (of whom 35 started a new treatment at baseline), while 45 patients were in a state of disease inactivity or remission. More detailed information about their baseline parameters are available in an additional table file [see Additional file 1].

The control population had a median age of 26.2 years, with a predominance of female (F:M sex ratio of 1.7:1).

Levels of serum calprotectin according to disease activity and clinical and biologic parameters

The levels of sCal were significantly higher in patients with an active disease than in patients with an inactive disease illustrated by a 2-fold increased level of sCal (11403 ng/mL compared to 6555 ng/mL) (Fig. 1). They were also very significantly higher than in healthy controls, measured at 1737 ng/mL.

Furthermore, the serum calprotectin also correlates with some clinical (tender joint counts [TJC] and CHAQ) and biological (ESR and C-reactive protein [CRP]) markers of disease activity. It correlates even more with ESR ($r = 0.79$, $p < 0.001$) than with CRP ($r = 0.45$, $p < 0.05$). Moreover, the evolution of DAS28 score over time correlated strongly with the evolution of sCal over the same period of time ($r = 1$, $p < 0.05$), but not with the CRP.

Levels of serum calprotectin according to clinical subgroups

Systemic arthritis differs significantly from polyarthritis, enthesitis-related arthritis and oligoarthritis with regard to levels of sCal and CRP (Fig. 2). When all forms of oligoarthritis (enthesitis-related arthritis [ERA], persistent and extended) are grouped, their levels of sCal (7515 ng/mL) also differ significantly from polyarthritis (14714 ng/mL) and systemic arthritis (26976 ng/mL). Enthesitis-related arthritis was associated with the lowest levels of sCal and CRP.

Levels of serum calprotectin according to the response to treatment

Among the 35 patients with active disease at baseline and starting a new treatment, 74.3% will be considered as responders with a pediACR > 30 at 6 months (or 9 months if lack of follow-up data at 6 months). Those patients did not differ from patients who will not respond to treatment in any clinical or laboratory parameters at baseline, except for higher levels of sCal, whereas CRP did not allow similar discrimination (Table 1, Fig. 3A).

Table 1
– Clinical and biologic parameters among responders and non-responders patients after 6 months

	Responders at 6 months (n = 26)	**Non-responders at 6 months (n = 9)**	**p-value**
Age at disease onset, years median (range)	9.5 (1.1–15.8)	12.0 (2.8–16.7)	ns
Disease duration, years mean (SEM)	3.9 (0.8)	3.6 (0.9)	ns
Female sex n (%)	14 (53.8)	3 (33.3)	ns
ANA+ n (%)	7 (26.9)	1 (11.1)	ns
Number of DMARDs used mean (SEM)	1.5 (0,2)	2 (0.3)	ns
TJC mean (SEM)	1.8 (0.5)	0.8 (0.3)	ns
SJC mean (SEM)	2.1 (0.9)	0.8 (0.3)	ns
Physician VAS mean (SEM)	21.7 (4.1)	22.3 (5.3)	ns
Patient/parent VAS mean (SEM)	22.7 (6.7)	15.0 (6.1)	ns
CHAQ mean (SEM)	0.4 (0.1)	0.2 (0.1)	ns
CRP, mg/L mean (SEM)	13.0 (3.3)	12.0 (4.0)	ns

ANA, antinuclear antibody; TJC, tender joint count; SJC, swollen joint count; VAS, disease evaluation on a visual analogue scale; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; sCal, serum calprotectin; [1], the systemic forms were excluded (JADAS score is not validated for these forms); ns, not significant (significant results are written in bold).

	Responders at 6 months (n = 26)	Non-responders at 6 months (n = 9)	p-value
ESR, mm/h mean (SEM)	25.2 (9.2)	28.0 (2.9)	ns
DAS-28CRP mean (SEM)	2.6 (0.3)	2.3 (0.3)	ns
JADAS10-CRP[1] mean (SEM)	8.2 (2.0)	4.7 (1.4)	ns
sCal, ng/mL mean (SEM)	12625 (2079)	4304 (975)	**0.03**

ANA, antinuclear antibody; TJC, tender joint count; SJC, swollen joint count; VAS, disease evaluation on a visual analogue scale; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; sCal, serum calprotectin; [1], the systemic forms were excluded (JADAS score is not validated for these forms); ns, not significant (significant results are written in bold).

With a threshold fixed at 3127 ng/mL, the ROC curves obtained a sensitivity of 84% and a specificity of 44%, with a likelihood ratio of 1.51 and an area under the curve (AUC) of 0.74 (Fig. 3B).

Levels of serum calprotectin according to the risk of flares

Within the 45 patients in remission at baseline, 8.9% will experience a flare in the following 3 to 9 months. They had significantly higher levels of sCal at baseline than patients who stay in prolonged remission under stable treatment (Table 2, Fig. 4A). That difference was not observed with CRP.

Table 2
– Serum calprotectin and C-reactive protein levels according to risk of flares among patients in remission

	Flare within 3 to 9 months (n = 4)	No flare within 3 to 9 months (n = 41)	p-value
sCal, ng/mL mean (SEM)	26073 (5295)	7066 (1126)	**0.001**
CRP, mg/L mean (SEM)	0.6 (0.5)	1.2 (0.2)	ns

sCal, serum calprotectin; CRP, C-reactive protein; ns, not significant.

The analysis of ROC curves identified a threshold fixed at 10285 ng/mL associated with a sensitivity of 100%, a specificity of 78% and a likelihood ratio of 4.56 (Fig. 4B). The AUC was in this case of 0.95.

Discussion

Levels of sCal were significantly higher in AJI patients than healthy controls, and even higher according to disease activity, as found before by other teams (11, 13, 23). Serum calprotectin is correlated to TJC and can also be a reflection of disease severity (CHAQ), as reported previously by some authors (11, 23). We confirm its correlation with inflammatory markers (CRP and ESR) (13, 23) but interestingly point out a high variability of sCal for normal values of CRP.

Our data show that sCal has the same faculty as CRP to differentiate oligoarthritis forms from polyarthritis or systemic forms, and confirm results described in systemic forms by Frosch et al (12). Enthesitis-related arthritis forms also tended to have lower levels of sCal compared to the other forms, and polyarthritis forms tended to present intermediate levels of sCal situated between systemic and oligoarthritis forms.

One major interest of this study consists of the confirmation of sCal as a predictive marker of good response to treatment (all types of treatment confounded), as mentioned in 2 recent cohorts studies treated specifically by methotrexate or TNF-inhibitors (17, 24). Importantly, cut-off obtained from the ROC curve does not offer perfect prediction, so that decision of treatment cannot be based solely on sCal levels and must take into account other clinical factors. Moreover, current medical practice points to an increasingly personalized medicine. Thereby, more and more studies, like ours, are investigating molecules of interest that can guide the therapeutic process, often derived from promising studies in the large field of rheumatoid arthritis (25–27) that could inspire other future studies in JIA. Furthermore, sCal was recently shown to be easily and rapidly detected in blood with a test based on lateral flow immunoassay (LFIA) technology, which could provide a useful point-of-care testing (13).

The second key point of this study underlines the utility of sCal as a very significant predictive marker of relapse when measured in patients in remission, as outlined by other teams (14–17, 23, 28). Serum calprotectin could therefore represent a marker of residual disease activity, even with no clinical or biological sign of persistent inflammation. It could thereby play a role in the monitoring of patients, helping to identify patients in remission under treatment who will probably stay in a prolonged remission and discuss discontinuation or tapering of treatment without risk of future relapses. More recently, Hinze et al did not find similar results when following patients with a polyarticular course and treated with TNF-inhibitors, but this prospective study evaluated the predictive interest of sCal levels measured at baseline in patients with clinically inactive disease under anti-TNF therapy and followed for a period of 6 months, and then at the time long-term treatment was discontinued (29), while our study evaluated the use of sCal to predict risk of flares under maintained treatment during the 9-months follow-up. The outcomes were thus not comparable and the time of follow-up under stable treatment was not identical. Our study underlines thus a group of patients at risk of relapse who could benefit from a more frequent monitoring during a longer period of time, even if in a seemingly reassuring remission state. Another recent study could not find a relationship between sCal and the prediction of response to treatment and flare; this study excluded systemic forms (which could be more inflammatory and aggressive, thus maybe more

related to variations of sCal) and comprised two very different cohorts (30). Overall, it underlines the fact that JIA is a very heterogeneous disease that translates into few comparable studies.

A prospective non-randomized clinical trial studying stratified therapeutic approaches based on biomarkers in patients with a polyarticular course has just completed recruitment and results are awaited for December 2020 (ISRCTN 69963079). In light of recent results (29, 30), it could also be interesting to study sCal in oligoarticular and systemic forms to evaluate its efficacy as a prognosis marker in other specific subgroups of patients (results from Hinze et al tended to show that dosage of sCal under stable treatment could be discriminating in extended oligoarthritis and seropositive polyarthritis, but not in seronegative polyarthritis). Evaluating levels of sCal in patients tapering their treatment without discontinuing it totally could also be of interest.

One of our limitations would be our control cohort comprising of young adults, instead of children comparable to our patients. However, levels of serum calprotectin measured in previous controlled-studies did not significantly differ with regard to age or sex distribution of the control cohort (11, 14, 31). It should also be noted that patients under anti-TNF therapy could theoretically present modified secretion of sCal because of the decrease in TNF levels following treatment and thus the potential downregulation of the S100 proteins inflammatory pathway (32). In our study, 18% of patients were under anti-TNF therapy, while the vast majority (89% of patients) was under methotrexate treatment (which would less affect the S100 proteins pathway). Another limitation consists of a potential selection bias with regards to the patients included from specialized centers and thus potentially with a more severe disease, requiring more treatment. Heterogeneity of the spectrum of JIA also leads to a more strenuous analysis in subgroups. Finally, the partial retrospective collection of data can also misrepresent some results.

Conclusions

This study confirms the interest of sCal as a diagnostic tool and an activity marker. Particularly, it could represent a predictive marker of response to treatment or maintenance of inactive disease which could be used in routine. This protein is indeed relatively stable and easily measured in the serum.

This study was approved by ethic comities of each hospital involved. Informed consent was obtained from each patient and parents.

Abbreviations

ACR
American College of Rheumatology
ANA
antinuclear antibodies
AUC
area under the curve

CHAQ
childhood health assessment questionnaire
COV
core outcome variables
CRP
C-reactive protein
ERA
enthesitis-related arthritis
ESR
erythrocyte sedimentation rate
ILAR
International League of Associations for Rheumatology
JIA
juvenile idiopathic arthritis
LFIA
lateral flow immunoassay
MRP
myeloid-related protein
RF
rheumatoid factor
ROC
receiver operating characteristic
sCal
serum calprotectin
TJC
tender joint counts
VAS
visual analogue scale

Declarations

Ethics

This study complies with the Declaration of Helsinki and was approved by the ethics comities of each hospital involved. Informed consent has been obtained from each patient and parents.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interest

The authors declare that they have no competing interests.

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Authors' contributions

CL performed the ELISA tests, analyzed and interpreted all data, and wrote the manuscript. All authors made substantial contributions to the acquisition of data. All authors read and approved the final manuscript.

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Figures

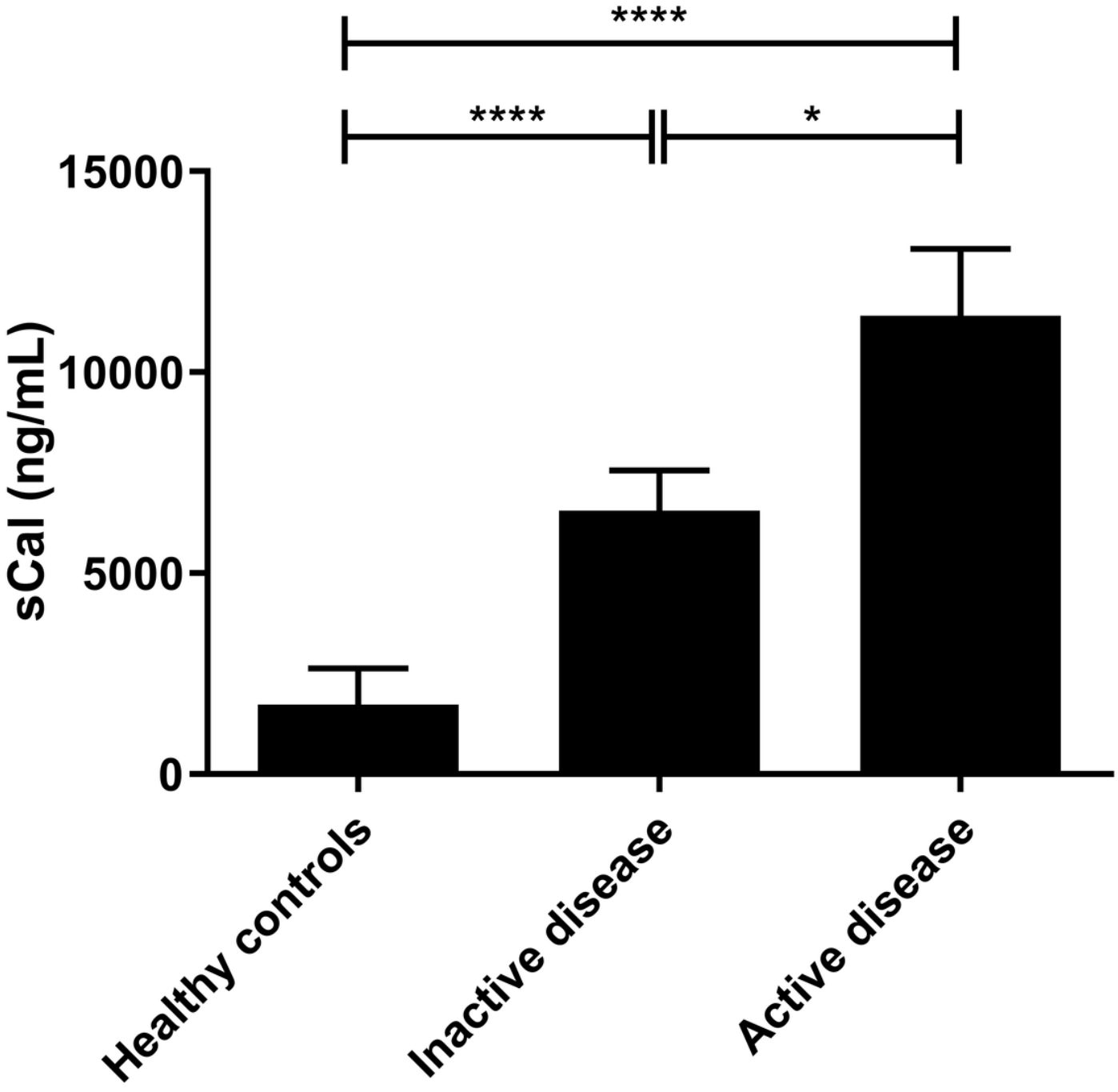

Figure 1

Levels of serum calprotectin according to disease activity. sCal, serum calprotectin; *, p<0.05; ****, p<0.0001.

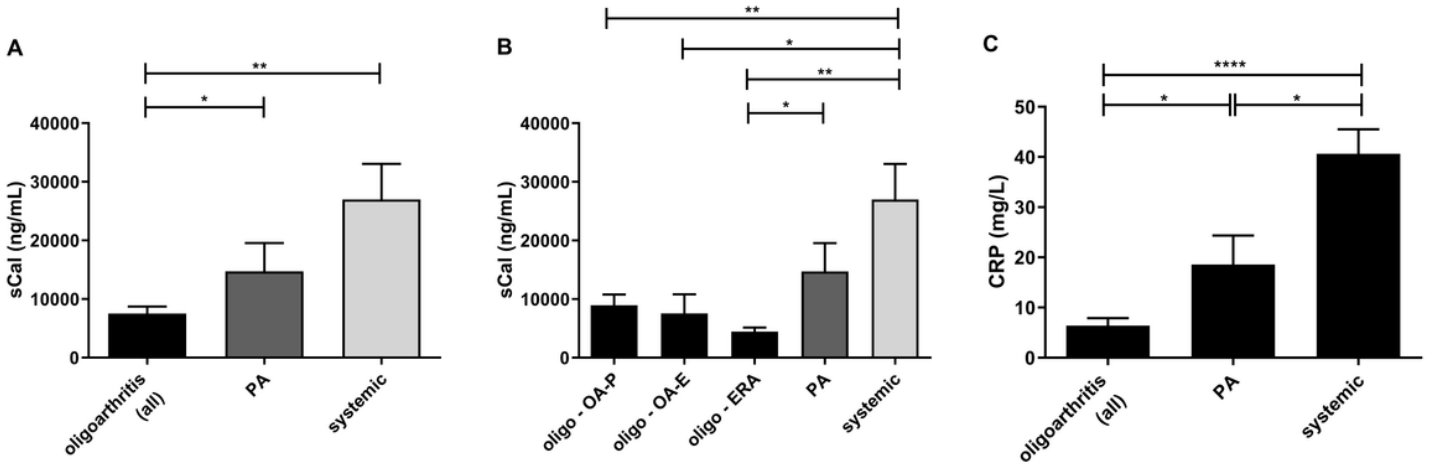

Figure 2

Levels of serum calprotectin or C-reactive protein according to clinical subgroups. (A-B) Levels of serum calprotectin according to clinical subgroups, with all forms of oligoarthritis grouped (A) or separated according to their categories (B). (C) Levels of C-reactive protein according to clinical subgroups. sCal, serum calprotectin; PA, polyarthritis; OA-P, persistent form of oligoarthritis; OA-E, extended form of oligoarthritis; ERA, enthesitis-related arthritis; CRP, C-reactive protein; *, p<0.05; **, p<0.01; ****, p<0.0001.

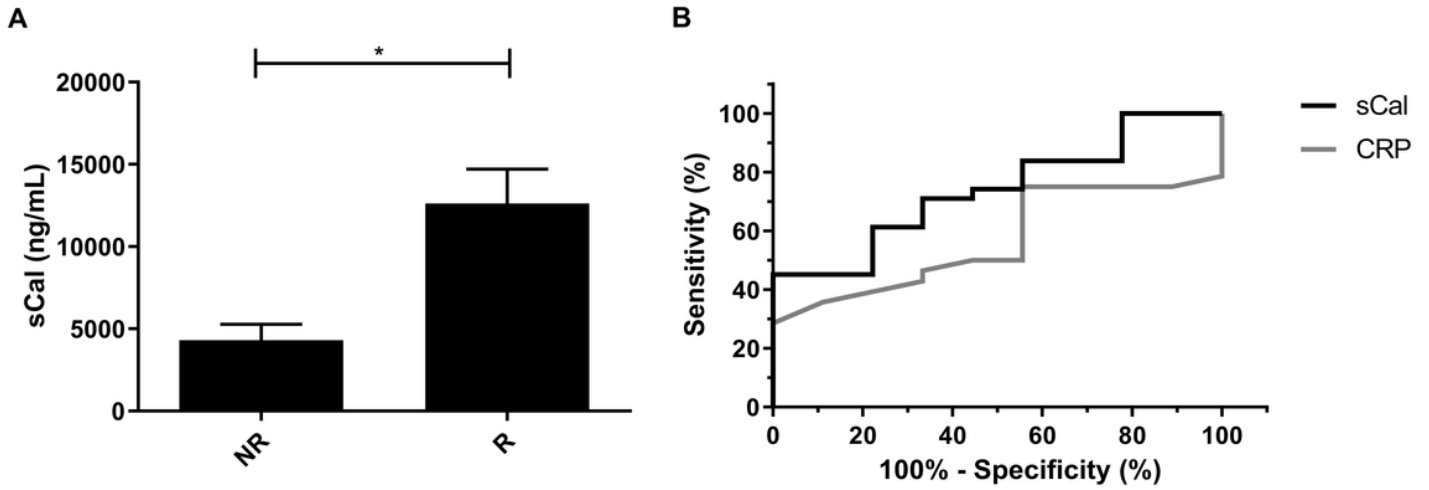

Figure 3

Levels of serum calprotectin according to the response to treatment. (A) Levels of serum calprotectin in patients with an active disease and starting a new treatment, according to the response to treatment. (B) ROC curves of response to treatment according to serum calprotectin or C-reactive protein. NR, non-responders; R, responders; sCal, serum calprotectin; CRP, C-reactive protein; *, p<0.05.

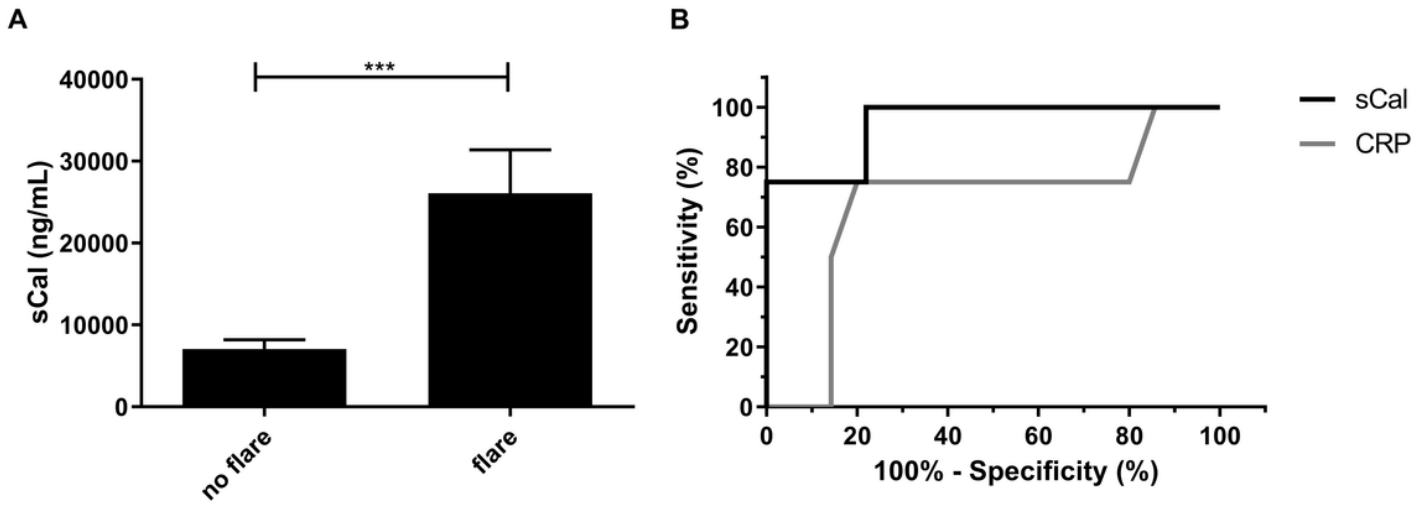

Figure 4

Levels of serum calprotectin according to the risk of flares. (A) Levels of serum calprotectin according to the risk of flare among patients in remission. (B) ROC curves of risk of flares according to serum calprotectin or C-reactive protein. sCal, serum calprotectin; CRP, C-reactive protein; ***, p<0.001.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1.docx