# CXCL-13 serum levels in patients with rheumatoid arthritis treated with abatacept

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## Abstract

### Objective

*C-X-C motif chemokine 13 (CXCL-13), which is expressed by synovial follicular dendritic cells and activated mature antigen-experienced T-helper cells, has been described as a surrogate marker of lymphoid phenotype of synovitis in rheumatoid arthritis (RA). A preferential response to anti-interleukin-6 receptor (IL-6R) as compared to anti-tumour necrosis factor alpha (TNFα) monotherapy has been described in patients with increased levels of CXCL-13. We hypothesised that serum levels of CXCL-13 could be used as a biomarker of response to treatment with abatacept (ABA), a T-cell co-stimulation blocker.*

### Methods

*Serum levels of CXCL-13 and of soluble intracellular adhesion molecule 1 (sICAM-1) (a putative marker of the myeloid subtype of synovitis) were measured by indirect solid-phase enzyme immunoassays, before (T0) and after 6 months of therapy with ABA (T6) in 63 patients with RA. Circulating T follicular helper cells and B cell subpopulations were identified by flow-cytometry.*

### Results

*At T0, CXCL-13 serum levels were higher in RA patients than in healthy controls ($p=0.0001$) and correlated with disease activity, while no difference between the two groups was observed as far as sICAM-1 levels. Serum levels of CXCL-13 levels decreased after therapy with ABA both in patients who achieved a clinical response ($p<0.01$) and in non-responders ($p=0.01$), whereas sICAM-1 levels did not significantly change. When comparing RA patients who responded to ABA with non-responders no significant difference of baseline serum levels of CXCL-13 was observed.*

### Conclusion

*CXCL-13 serum levels are raised in RA patients and decrease after therapy with ABA. We were not able to demonstrate that serum CXCL-13 levels predict the clinical response to ABA in RA patients.*

**Key words**

rheumatoid arthritis, abatacept, CXCL-13, biomarkers

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## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. The cellular elements and the soluble components of both the innate and adaptive immune system play important pathophysiological roles in the disease process (1). Although a wide array of effective therapeutic agents is nowadays available for the treatments of patients with RA, for each single agent, or class of agents, there is a proportion of patients who do not respond to them. Precision medicine is therefore one of the major unmet needs in the management of RA, and biomarkers who can predict clinical response to individual therapeutic modalities and guide treatment decisions are still needed (2).

Studies of rheumatoid synovitis demonstrated its complexity, and it has been hypothesised that different response to differently targeted drug might be explained by synovial tissue heterogeneity (2). Classification of synovial tissue based on RNA sequencing was shown to be superior to that based on immunohistochemical analysis to stratify patients' response to different drugs (3). However, as synovial biopsies are not routinely obtained from RA patients, serum biomarkers surrogating synovial subtypes have been proposed for this purpose (4).

Indeed, C-X-C motif chemokine 13 (CXCL-13), which is expressed by synovial follicular dendritic cells and activated mature antigen-experienced helper T-cells, acts as B-cell chemoattractant, and controls the organisation of B cells within follicles of lymphoid tissues (4). In patients with RA, serum CXCL-13 is correlated with synovial CXCL-13 measured at a single joint (5); raised CXCL-13 serum levels were reported to be associated with a lymphoid synovial phenotype (4).

On the other hand, soluble intercellular adhesion molecule (sICAM-1), the product of a gene which is upregulated in synovial fibroblasts and vascular endothelial cells in response to tumour necrosis factor alpha (TNF-α), was described to be associated with a myeloid subtype of synovitis (4, 6).

Interestingly, it was reported that baseline serum levels of these two biomarkers were differentially associated with clinical response to biological agents: RA patients with low sICAM-1 and high CXCL-13 levels had high response rate to anti-interleukin-6 receptor (IL-6R) and low to anti-TNF-α treatment, and *vice versa* (4).

Surprisingly, no information is available on the utility of dosing serum levels of CXCL-13 and sICAM-1 in predicting the response to the T-cell co-stimulation blocker abatacept (ABA; CTLA4-Ig) in RA patients. Experimental models show that ABA can block the generation of follicular helper T-cells (TFH) (7), the cells who, interacting with B-cells in germinal centers, can promote the production of autoantibodies in RA. Notably, TFH are characterised by expression of CXCR5, the receptor of CXCL-13, on their surface. Indeed, in patients with RA the number of circulating TFH (cTFH) is higher as compared to healthy controls (HC), but it can be reduced by treatment with ABA (8, 9). The specific role of CXCL-13 in the generation of follicle-like structures and in the interaction between TFH and B-cells (4), events which are likely to be targeted by ABA (7-9), lead us to the hypothesis that clinical response to ABA might be associated with high levels of CXCL13. In the present study, serum levels of CXCL-13 and sICAM-1 were therefore measured, before and after therapy with ABA, in 63 consecutive patients with RA. Correlation with disease activity, cTFH and circulating B cell subpopulations were also evaluated.

## Materials and methods

### *Patients and controls*

Sixty-three consecutive patients with RA, treated with ABA for at least 6 months, were enrolled in the study. Their main clinical and demographic characteristics are shown in Table I. Data on cTFH of 32 of them were already described (9). The study was approved by the Institution Ethics Committee (NP 2495), and patients' written consent, according to the Declaration of Helsinki, was obtained. Clinical disease activity and the response to the treatment were evaluated respectively with the 28-joint Disease Activity Score (DAS28) (based on CRP), and

the European League Against Rheumatism (EULAR) Criteria of Response to the treatment (10). Anti-carbamylated protein antibodies (anti-CarP) were evaluated as previously described (11). Twenty-two sex and age-matched HC (17 female, 77.3%); median age: 56 [10th–90th percentile: 38–67]) were also evaluated.

*Serum CXCL-13 and sICAM-1 level analysis*

Serum samples were collected and stored at -80°C immediately before the first administration of ABA (T0) and then after 6 months (T6). CXCL-13 and sICAM-1 levels were dosed by commercial indirect solid-phase enzyme immunoassays (R&D Systems Inc., Minneapolis, MN, USA, and Thermo Fisher Scientific Inc., Waltham, MA, USA), with sensitivity limits of 0.43 pg/mL, and 2.17 ng/mL, and intra-assay CV% of 4.7% and 8.8%, respectively. The analysis was carried out simultaneously on all serum samples at the end of the study.

*Flow cytometry*

T- and B-cell counts were determined by flow cytometry (Cytomic Navios, Beckman Coulter Inc., Fullerton, CA, USA). Briefly, 100 µl of fresh whole blood were stained for 20 min at 4°C with combinations of monoclonal antibodies (Beckman Coulter Inc.: IgD-FITC, CD3-FITC, CD38-PE, CD19-PC5, CD4-PC5, CD24-APC, CD8-PC7, CD27-PC7, CD45-ECD, ICOS-APC; R&D Systems Inc.: CXCR5-AF500); naive B-cells were defined as CD19+CD27-IgD+, transitional B-cells as CD19+CD24highCD38high, switched memory B-cells as CD19+ CD27+IgD-, unswitched memory B-cells as CD19+CD27+IgD+, and cTFH as CD3+CD4+CXCR5+ICOS+ lymphocytes, as previously described (9, 12, 13) (Supplementary Fig. S1). Absolute cell count was determined by single-platform analysis. Data analysis was performed using the FlowJo software 9.9.6 (Tree Star, Ashland, OR, USA).

*Statistics*

Data are expressed as the median (10th–90th percentile). Differences between groups were evaluated by Mann-Whitney U-test. Wilcoxon-signed rank test was applied to assess variations with in paired quantitative variables. The correlations between variables were evaluated by Spearman rank correlation test.

**Table I.** Baseline demographic, serological and clinical features of 63 RA patients.

| Features at baseline | Patients (n=63) |
|---|---|
| Gender: M/F, n (%) | 12/51 (19.0/81.0) |
| Age, years | 60.0 (41.0-71.6) |
| BMI, kg/m$^2$ | 23.2 (17.7-30.5) |
| Smokers, n (%) | 13 (20.6) |
| RF positivity, n (%) | 32 (50.8) |
| Anti-CCP positivity, n (%) | 51 (81.0) |
| Anti-CarP positivity, n (%)* | 16 (30.2) |
| CRP, mg/L | 6.4 (1.1-24.0) |
| ESR, mm/h | 28.0 (7.2-42.5) |
| DAS28-CRP | 4.66 (3.28-5.80) |
| HAQ | 0.75 (0.12-2.25) |
| Disease duration, months | 96.0 (22.4-297.6) |
| Currently treated with corticosteroid, n (%) | 57 (90.5) |
| Daily dose (Prednisone equivalent mg) | 4.3 (2.9-11.2) |
| Previous csDMARDs, n (%) | 2 (1-3) |
| Currently treated with csDMARD(s), n (%) | 52 (82.5) |
| Currently treated with MTX, n (%) | 46 (73.0) |
| MTX weekly dose, mg | 15.0 (10.0-15.5) |
| Naive to bDMARD, n (%) | 31 (49.2) |
| Previous bDMARDs, n (%) | 1 (0-2) |

BMI: Body Mass Index; RF: rheumatoid factor; Anti-CCP: anti-cyclic citrullinated peptide antibodies; Anti-CarP: anti-carbamylated proteins antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: 28-joints Disease Activity Score; HAQ: Health Assessment Questionnaire; DMARD: disease modifying anti-rheumatic drugs, conventional synthetic (cs), and biologics (b); MTX: Methotrexate; n: number of subjects. *available for 53 patients. Data showed as median (10th-90th percentile), if not otherwise explained.

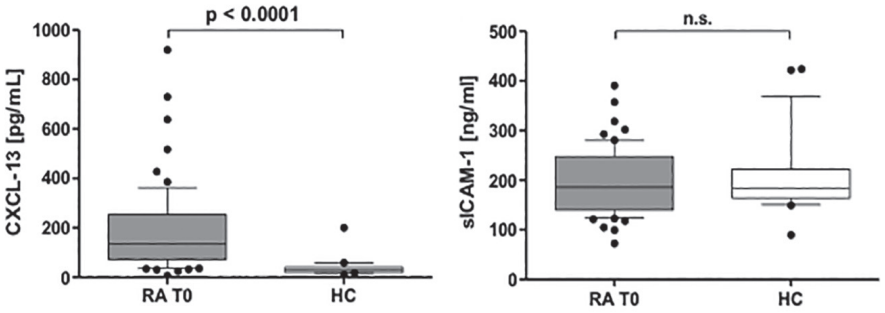


**Fig. 1.** CXCL-13 and sICAM-1 serum levels' comparison between rheumatoid arthritis (RA) patients at baseline (T0) and healthy controls (HC). n.s.=not significant. Data are presented as box plot (median, 25–75th percentile) with whiskers (10-90th percentile), and outliers (single dots).

## Results

*Analysis at baseline*

At baseline, CXCL-13 serum levels were higher in RA patients than in HC [136 (42–325) *vs*. 32 (19-58) pg/ml; $p<0.0001$], while no difference between the two groups was observed as far as sICAM-1 levels [186 (125–276) *vs*. 184 (153–246) ng/ml; $p=0.99$] (Fig. 1).

In patients with RA, CXCL-13 levels were correlated with CRP levels ($p=0.002$) and DAS28-CRP ($p=0.05$), whereas sICAM-1 levels were correlated with CRP levels ($p=0.04$), but not with DAS28-CRP (Fig. 2). No significant correlations between CXCL-13 and THF or B-cell subpopulations were observed, whereas sICAM-1 levels were significantly correlated with the absolute numbers of circulating B-cells (R=0.41; $p=0.02$), of switched memory B-cells (R=0.38; $p=0.03$), and of transitional B-cells (R=0.46; $p=0.009$).

No significant difference of CXCL-13 and sICAM-1 serum levels between anti-CCP+ and anti-CCP-, or anti-CarP+ and anti-CarP-, patients was found (data not shown).

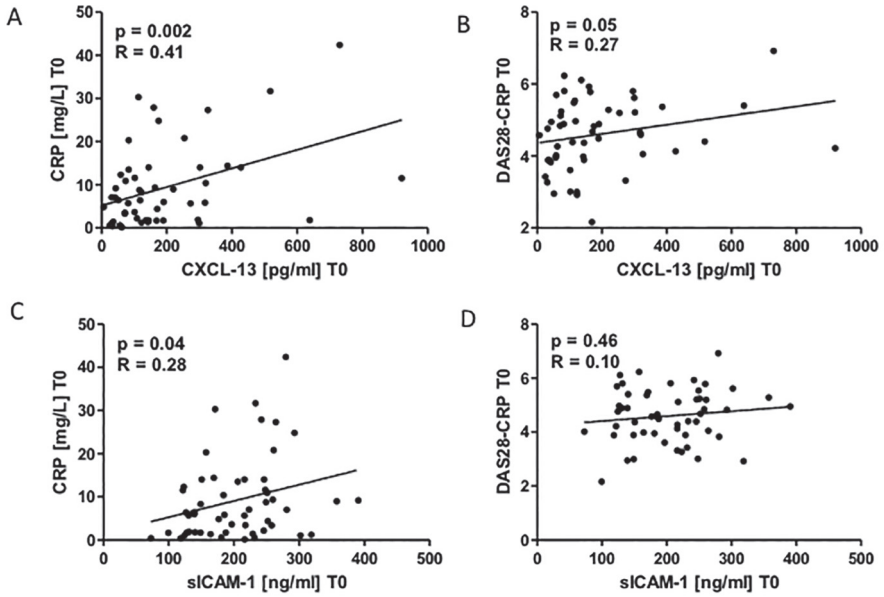


**Fig. 2.** Correlation between CXCL-13 serum levels and CRP (**A**)/DAS28-CRP (**B**) and between sICAM-1 serum levels and CRP (**C**)/DAS28-CRP (**D**) at baseline (T0).
CRP: C-reactive protein; DAS28: 28-joint Disease Activity Score.

**Table II.** Clinical and laboratory parameters variations after 6 months of therapy with abatacept.

| Clinical and laboratory parameters | T0 | T6 | *p*-value |
|---|---|---|---|
| CRP, mg/L | 6.4 1.1-24.0) | 2.0 (0.6-12.2) | <0.0001 |
| ESR, mm/h | 28.0 (7.2-42.5) | 19.5 (3.7-32.3) | 0.01 |
| DAS28-CRP | 4.66 (3.28-5.80) | 2.85 (2.06-4.20) | <0.0001 |
| HAQ | 0.75 (0.12-2.25) | 0.62 (0.00-1.63) | 0.02 |
| cTFH (% of CD3+ CD4+ cells)** | 0.6 (0.0-4.5) | 0.1 (0.0-3.2) | 0.04 |
| Switched Memory B cells (% of CD19+ cells)*** | 16.0 (7.6-33.0) | 12.1 (5.7-25.5) | 0.0005 |

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire; cTFH: circulating follicular helper T-cells. **available for 33 patients. ***available for 35 patients.

*Analysis after 6 months of treatment with ABA*

Reduction of disease activity and improvement of function were observed after 6 months of treatment with ABA (Table II). Moreover, reduction of the percentage of switched memory B-cells ($p$=0.0005) and of cTFH ($p$=0.04) were observed (Table II).

In 51 evaluable patients, serum levels of CXCL-13 levels decreased after therapy with ABA ($p$<0.0001), whereas sICAM-1 levels did not significantly change (Fig. 3A). The reduction of CXCL-13 levels was observed both in patients who achieved a EULAR response (Fig. 3B) [n: 37; $p$=0.0001] and in non-responders [n: 14; $p$=0.01]. At T6, a significant inverse correlation was found between CXCL-13 and the absolute number of total B-cells (R=-0.69; $p$=0.02), naive (R=-0.70; $p$=0.02) and switched memory (R= -0.70; $p$=0.02) B-cells. Considering the trend with time, T0-T6 variations of CXCL-13 serum levels were found to be directly correlated with T0–T6 variations of naive B-cells frequency (R=0.35; $p$=0.04) (Suppl. Fig. S2).

*Comparison between RA patients, responders or non-responders to ABA*

When we compared CXCL-13 and sICAM-1 serum levels at baseline in RA patients who responded to ABA with those observed in non-responders, to evaluate whether these parameters might be used as predictors of response to ABA, we did not find any significant difference (Fig. 3B). No difference in these biomarkers levels was observed between responders and non-responders at T6, too (Fig. 3B). Moreover, the CXCL-13/sICAM-1 ratio was not different between the two groups, neither at baseline nor at T6 (data not shown). No difference in the rate of EULAR response was found when creating subgroups defined as low (below pre-treatment median), or high (equal to or greater than pre-treatment median), for each of the two biomarkers (4) (data not shown).

Finally, the variations of CXCL-13 and sICAM-1 serum levels between T0 and T6 were not different between the two groups (data not shown).

## Discussion

Our data confirmed that serum levels of the B-cell chemoattractant CXCL-13 are elevated in patients with RA (4, 14-16), and directly correlated with disease activity (15-17). We could not confirm that anti-CCP are associated with higher levels of CXCL-13 (15), but this observation might be explained by the very low numbers of anti-CCP-negative RA patients included in our study.

Some previous longitudinal studies reported reduction of CXCL-13 serum levels in patients treated with biological disease modifying anti-rheumatic drugs (DMARDs), particularly rituximab and anti-IL6R (4, 5, 15), but also, though less constantly, after therapy with TNF-blocking agents (4, 15, 18-20), while in patients treated with conventional DMARDs, high levels of CXCL-13 were associated with a reduced probability of achieving low disease activity (15).

Surprisingly, to the best of our knowledge, no information was available on the effect of ABA, a T-cell costimulation blocker, on CXCL-13 serum levels in patients with RA. In our longitudinal study, we demonstrated that ABA therapy induces a decrease of CXCL-13 serum levels. Moreover, T-cell costimulation blockade by ABA decreases phenotypic signs of B-cell hyperactivity, and the number of cTFH (9, 12). The reduced production of CXCL-13 and these changes in the phenotype of circulating lymphocytes might be explained by T-cell co-

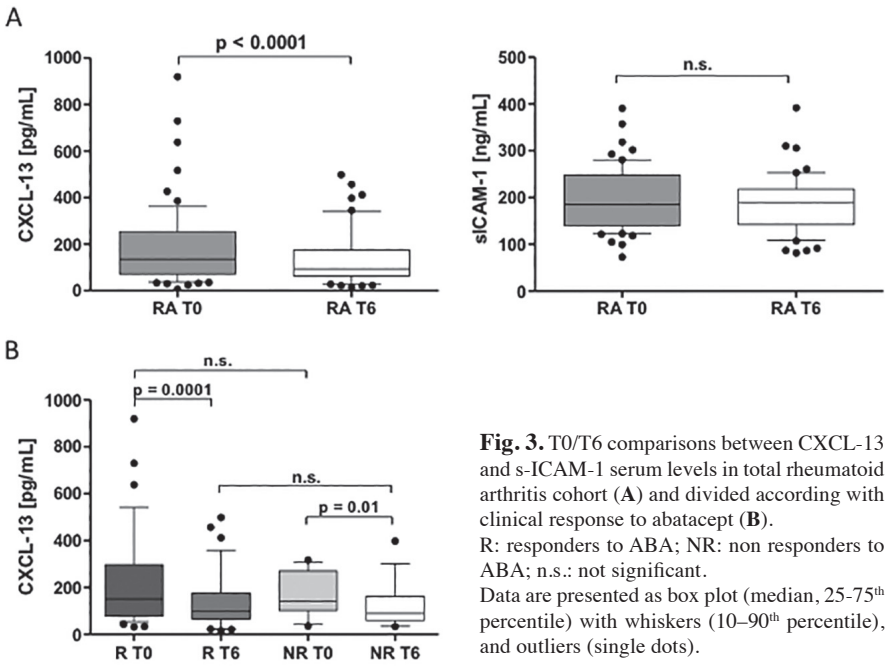


**Fig. 3.** T0/T6 comparisons between CXCL-13 and s-ICAM-1 serum levels in total rheumatoid arthritis cohort (**A**) and divided according with clinical response to abatacept (**B**).
R: responders to ABA; NR: non responders to ABA; n.s.: not significant.
Data are presented as box plot (median, 25-75$^{th}$ percentile) with whiskers (10–90$^{th}$ percentile), and outliers (single dots).

stimulation blockade in the synovium. In fact, CXCL-13 is highly expressed in the synovium from RA patients, in association with signs of both B- and T-cell ongoing activation (21). A major source of CXCL-13 production in the rheumatoid synovium was identified in an activated (PD-1high) helper T-cell population, which is markedly expanded in this tissue (22). The lack of significant correlations between serum levels of CXCL-13 with peripheral blood B-cells subpopulations or THF at baseline in our cohort of patients does not exclude this interpretation.

On the other hand, data from animal models and phenotypic analysis of circulating T-cells in RA suggest that ABA may act in the secondary lymphoid organ, and not directly on the synovium (23, 24). Thus, whether ABA exerts its effects causing reduced CXCL-13 production within lymphoid tissues in the periphery (synovium) or in central organs, or both, is at present unknown.

The effect of ABA on CXCL-13 serum levels were observed in the total population of RA patients who received this treatment. We could not therefore demonstrate that CXCL-13 levels predict the clinical response to ABA in this cohort of patients. This finding suggests that in patients who did not respond to ABA, despite partial deactivation of the CXCL-13-mediated axis, other pathophysiological mechanisms may operate in maintaining disease activity.

As far as sICAM-1, we failed to confirm previous reports of elevated levels in RA patients (4, 20); we confirmed a modest correlation with CRP, but not with the clinical disease activity. Correlations of sICAM-1 with clinical indices or acute phase reactants were generally reported to be modest and variable (17). We observed correlations between serum levels of sICAM-1 and signs of B-cell activation at time of enrollment, which might not be unexpected in the frame of inflammation (25), but these seemed to have not any clinical relevance in our cohort.

More importantly, sICAM-1 levels were not modified by treatment with ABA in RA patients, whereas others have shown a decrease of these levels in patients responding to TNF-blocking agents (20). These different observations can be explained by the fact that ICAM-1 expression is induced by TNF-α, and its soluble form is generated by cleavage mediated by matrix metalloproteases, which are also induced by TNF-α. Conversely, in accordance with our data, a study of synovial biopsies demonstrated that the number of synovial fibroblasts, macrophages and, particularly, ICAM-1+ cells, did not significantly change after treatment with ABA in RA patients, whereas this treatment induced a significant reduction of synovial infiltration by B-cells (26). Thus, these findings indicate that the mechanisms of action by which ABA can ameliorate RA do not involve modulation of ICAM-1 expression.

Our study had some limitations; since it was designed to be as close as possible to routine clinical practice, only peripheral blood samples, and not synovial fluid or synovial tissue biopsies, were obtained from patients. We acknowledge that CXCL-13 analysis on these biosamples will be needed to clarify the effect of T-cell costimulation blockade performed by ABA on the CXCL-13-mediated axis of lymphocyte recruitment and organisation within the rheumatoid synovium. Moreover, our main aim was to evaluate the possible use of serum levels of CXCL-13 as a biomarker of response to the treatment with ABA in routine clinical practice; the choice of this molecule was based on its specific role in the generation of follicle-like structures and in the interaction between TFH and B-cells, events which are likely to be targeted by ABA. Other chemokines involved in the recruitment of different lymphoid populations (*e.g.* CXCL-10 and CCL-20, which are mainly involved in the attraction of T-helper (Th) 1 and Th17, respectively) (26) were therefore not measured. Future studies are therefore needed to address their significance in the biologic effect performed by ABA in rheumatoid synovitis.

In conclusion, we could not demonstrate that CXCL-13 or sICAM-1 serum levels can predict the clinical response to ABA. On the other hand, we confirmed that levels of CXCL-13 are raised in RA patients as compared to HC, and that they are reduced by T-cell costimulation blockade by ABA. These data might support the hypothesis that CXCL-13 might distinguish RA from other forms of chronic arthritis sustained by different pathophysiological mechanisms in which adaptative immune system is less involved. Further studies might be warranted to evaluate the possible role of this biomarker in the differential diagnosis of chronic arthritis (*e.g.* in the setting of early arthritis clinics) (15).

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