Soluble CD30 in early rheumatoid arthritis as a predictor of good response to second-line therapy

R. Gerli, O. Bistoni, C. Lunardi1, R. Giacomelli2, C. Tomassini, P. Biagini and C. Pitzalis3

Department of Clinical and Experimental Medicine, Section of Internal Medicine and Oncological Sciences, Centre for the Study of Rheumatic Diseases, University of Perugia, 1Department of Clinical and Experimental Medicine, Section of Internal Medicine, University of Verona, 2Institute of Internal Medicine, University of L’Aquila, Italy and 3Department of Rheumatology, Division of Medicine, Guy’s, King’s and St Thomas’ School of Medicine (GKT), Guy’s Campus, London, UK

Abstract

Objective. To evaluate whether serum levels of the soluble form of CD30 (sCD30) correlate with disease activity in early rheumatoid arthritis (RA) and may have prognostic value in predicting the response to disease-modifying anti-rheumatic drugs (DMARDs).

Methods. The levels of sCD30 and C-reactive protein (CRP) were measured in the serum of 14 untreated subjects with early RA, before and during treatment with hydroxychloroquine, for a follow-up period of 8 months. At the end of the study, patients were also evaluated for their response to DMARDs.

Results. An inverse correlation between sCD30 and CRP serum values was demonstrated at baseline, but not during the follow-up. Patients who responded to DMARD therapy had higher sCD30 basal levels than non-responders.

Conclusions. The evaluation of sCD30 serum levels in early RA may reflect the attempt by CD30+ T cells to downmodulate inflammation and may be a useful marker to predict a good response to DMARDs.

Key words: CD30, sCD30, Rheumatoid arthritis, T lymphocytes, C-reactive protein, Disease-modifying anti-rheumatic drugs.

T-helper-1 (Th1)/T-helper-2 (Th2) cell balance could play a key role in modulating the development and persistence of chronic inflammation in the joint [1]. There is evidence that a Th1 polyclonal activation prevails in rheumatoid arthritis (RA) [2], although it is thought that Th2 cells may produce cytokines in an attempt to downmodulate inflammation [1]. The idea that the natural course of arthritis is modulated by cytokine balance is appealing, but whether disease-modifying anti-rheumatic drugs (DMARDs) may interfere with Th1/Th2 cell balance in RA synovitis is still a matter of debate [1, 3, 4]. In this setting, it is of interest that the recent finding by van der Graaff et al. [5] showed that a low Th1/Th2 ratio at the beginning of the disease is predictive of a good response to DMARDs. In this study, however, they did not find a correlation between the Th1/Th2 ratio and disease activity scores or C-reactive protein (CRP). Th1/Th2 balance is not easy to analyse due to the lack of reliable markers able to distinguish T-cell subsets with distinct cytokine secretion patterns at the site of inflammation. In van der Graaff’s study, for example, the analysis of the Th1/Th2 ratio was performed by intracellular staining for either interleukin-4 (IL-4) or interferon gamma (IFN-γ) in peripheral blood T cells, which do not strictly reflect the phenotype and function of T cells found in the joint. In addition, this methodology is unable to distinguish unpolarized Th0 cells, i.e. producing both IL-4 and IFN-γ.

Some of us have recently reported that sera of patients with active RA display high levels of the soluble form of the CD30 molecule (sCD30) [6], a member of the tumour necrosis/nerve growth factor receptor superfamily [7]. Similar findings have been described in other
rheumatic diseases, such as systemic lupus erythematosus and systemic sclerosis, and mirror recruitment/activation of CD30+ T cells at the site of inflammation [8–10]. Since CD30 is expressed and released by functionally primed Th0 and Th2 cells [11, 12], it is attractive to speculate that the increased release of sCD30 in the serum of patients with active disease may represent an attempt, not always successful, to control inflammation through the activation of a subset of T cells with down-regulatory activity.

Materials and methods

Serum sCD30 levels were evaluated by a commercially available ELISA kit (Ki-1 antigen ELISA, Dako A/S, Glostrup, Denmark) and were correlated with CRP levels, measured by laser nephelometry, in 14 Caucasian subjects (11 female, age range 23–62 yr), belonging to the same geographical area (centre regions of Italy), who fulfilled the 1987 American College of Rheumatology (ACR) diagnostic criteria for RA [13]. Twenty age- and sex-matched healthy volunteers from the same geographical area (16 female, age range 21–61 yr), acted as normal controls. All patients were rheumatoid factor positive and had active disease, as defined by the presence of six or more tender joints, morning stiffness lasting for >45 min or Westergren erythrocyte sedimentation rate (ESR) of ≥28 mm/1st h. Patients were studied at the time of diagnosis, early in the course of their disease (<6 months) and, in order to avoid possible pharmacological interference on the immunological data, immediately before starting a DMARD (hydroxychloroquine 400 mg/day). Serum sCD30 and CRP levels were then evaluated every 2 months after the beginning of the treatment. In addition, at baseline and at the end of the follow-up (8 months), ESR and disease activity were evaluated. Disease activity was assessed according to the number of tender and swollen joints, patient’s perception of pain measured using a 100 mm visual analogue scale, and patient’s and physician’s global assessment of disease activity measured with the same scale as above. The response to DMARD therapy, in individual patients, was determined according to the 1985 ACR definition of improvement in RA [14].

Wilcoxon’s two tailed test—normal approximation for paired data, Spearman’s rank correlation coefficient and simple linear regression were adopted for statistical analysis of the results. Values of \( P < 0.05 \) were chosen for rejection of the null hypothesis.

Results

Basal sCD30 values in patients were much higher than in controls (median 138 U/ml, range 76–415 vs 17 U/ml, 1–96; \( P < 0.001 \)). Interestingly, we found a strict inverse correlation between sCD30 and CRP serum levels (\( r = -0.62, P < 0.005 \)) at baseline, but not during the follow-up. As shown in Table 1, eight patients responded to therapy at the end of the follow-up. This patient subset had sCD30 values at baseline that were notably higher than those of the six patients who did not respond to therapy (Fig. 1). It is noteworthy that no demographic differences were present between responders and non-responders (data not shown).

Discussion

The results of this study demonstrated that sCD30 and CRP serum levels are inversely correlated in early RA.

Table 1. Outcome measures at baseline and at the end of the 8-month follow-up in the RA patients subdivided according to treatment response. Values are expressed as the median (range)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Responders (8)</th>
<th>Non-responders (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>8 months</td>
</tr>
<tr>
<td>Tender joint count (no.)</td>
<td>9.5 (3–20)</td>
<td>1 (0–5)*</td>
</tr>
<tr>
<td>Swollen joint count (no.)</td>
<td>18.5 (8–28)</td>
<td>5.5 (0–14)**</td>
</tr>
<tr>
<td>Pain (mm)</td>
<td>62.5 (30–84)</td>
<td>17.5 (0–54)*****</td>
</tr>
<tr>
<td>ESR (mm/1st h)</td>
<td>46.5 (29–66)</td>
<td>20 (7–32)****</td>
</tr>
<tr>
<td>Activity (patient) (mm)</td>
<td>63 (39–90)</td>
<td>23.5 (0–60)**</td>
</tr>
<tr>
<td>Activity (physician) (mm)</td>
<td>60 (38–85)</td>
<td>24 (0–60)*****</td>
</tr>
</tbody>
</table>

\*P < 0.01, \**P < 0.03, \***P < 0.02 vs baseline. The basal values of the responders were different from those of the non-responders (\( P = \text{NS} \)).

![Fig. 1. Serum levels of sCD30 at baseline in 14 early RA patients subdivided according to the response to hydroxychloroquine after 8 months of treatment.](image-url)
before starting DMARDs. In addition, they showed that RA patients with higher levels of sCD30 at diagnosis respond better to a DMARD than those with lower values.

These observations lend some support to the recent finding that a low Th1/Th2 ratio is predictive of a good response to the DMARDs [5]. As high levels of sCD30 may be indicative of a high turnover of Th0/Th2-like cells [11, 12, 15] and low levels of CRP expression may be indicative of low production of pro-inflammatory cytokines. Thus, the inverse correlation between sCD30 and one of the most reliable markers of inflammation may reflect a down-regulatory activity on inflammation, exerted by this T-cell subset during the early phases of RA synovitis, which may be crucial for a successful effect of second-line therapy. This agrees with the observation that a low serum level of CRP has favourable prognostic significance in early RA [16]. However, the fact that these two markers, which potentially look at opposite facets of the disease, did not correlate after starting therapy confirms the interference exerted by DMARD on pro- and anti-inflammatory cytokine balance.

In conclusion, our data suggest that evaluation of sCD30 serum levels may represent a simple method to assess the anti-inflammatory activity of Th0/Th2 cells in early RA. Investigations correlating sCD30 levels and the pattern of cytokine production by peripheral blood and synovial T-cell clones are in progress in our laboratory to verify this hypothesis. The present results also suggest that the evaluation of sCD30 may be helpful in predicting a good response to therapy. However, further studies using other DMARDs are necessary.

References