Anti-Tumor Necrosis Factor-α Response in Rheumatoid Arthritis Is Associated with an Increase in Serum Soluble CD30

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ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) display high serum concentrations of soluble CD30 (sCD30), which correlate with counter-regulatory activity of CD30+ T cells in the inflamed joint. To verify the contribution of this T cell subset to disease remission, sCD30 levels were analyzed longitudinally in patients with active RA following infliximab therapy.

Methods. Infliximab plus methotrexate were started in 39 patients with active RA, while 20 patients with inactive disease, controlled by stable doses of methotrexate, acted as controls. Serial evaluations of sCD30 concentrations and disease activity indexes were performed throughout 38 weeks.

Results. sCD30 levels were higher in patients than in healthy controls. Rapid infliximab-induced decrease in disease activity was associated with an overall increase of sCD30 levels. In contrast, levels remained stable in controls. An inverse correlation between sCD30 levels and Disease Activity Score 28 was observed from the 22nd week of infliximab treatment. Analysis of sCD30 levels according to American College of Rheumatology response showed, after an initial general enhancement of sCD30 concentrations, a persistent increase of sCD30 in responders, but not in nonresponders.

Conclusion. sCD30 serum levels are enhanced by tumor necrosis factor-α (TNF-α) blockade in patients with active RA and inversely correlated with disease activity, but only after some weeks of treatment. Of interest, a sustained increase of sCD30 is present only in subjects with evidence of persistent clinical response to anti-TNF-α. As sCD30 serum levels mirror antiinflammatory activity of joint T cells, the present data may suggest a role of synovial counter-regulatory CD30+ T cells in the induction of infliximab-mediated remission in RA. (First Release Dec 1 2007; J Rheumatol 2008;35:14–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS — ANTI-TUMOR NECROSIS FACTOR-α
CD30 — INFLIXIMAB — T CELLS

The CD30 molecule is a type I transmembrane protein, member of the tumor necrosis factor (TNF) receptor superfamily, which is expressed on activated T and B lymphocytes and on some neoplastic cells[1]. Its extracellular domain can be cleaved by metalloproteases, producing a soluble form of the molecule (sCD30)[1,2]. Increased serum levels of sCD30 are found during infections, B lymphoproliferative disorders, and autoimmune diseases, including rheumatoid arthritis (RA)[1-3]. Serum concentration of sCD30 in RA is related to the presence of CD30-expressing T cells in the synovium[4]. Several studies have highlighted the link between CD30 expression on T cells and a prevalent Th2-type immune response associated with a specific pattern of cytokine production in normal and pathological conditions[5,6]. Although RA is considered primarily a Th1-driven condition, Th2-type cytokine-producing T cells are detectable in both membrane and synovial fluid of patients with RA[7,8]. In this setting, it is notable that RA synovial CD30+ T cells are able to produce interferon-γ (IFN-γ), but also significant amounts of interleukin 4 (IL-4) and IL-10 that likely represent a physiopathological mechanism attempting to achieve a homeostatic balance through counter-regulatory activity[3,8-10]. On the basis of these and other observations, it has been proposed that chronic inflammation in RA may be sustained by an imbalance between pro-Th1 and anti-Th2 inflammatory cytokines and, while Th1 cytokines normally

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Accepted for publication August 22, 2007.

prevail, sCD30 serum levels reflect the attempted antiinflammatory T lymphocyte response within the joint[3,7,8].

The introduction of TNF-α antagonists in the treatment of RA has been based on the evidence that TNF-α is one of the key mediators of RA synovitis[11,12]. However, the mechanisms underlying the successful therapeutic effect of anti-TNF-α agents are not yet entirely understood[12,13]. Given its pleiotropic biological activities, TNF-α appears to affect many of the cell types of the immune/inflammatory cascade involved in RA synovitis. These include endothelial cells, stromal cells, and macrophages, as well as B and T cells[11,12]. Thus, TNF-α blockade, in addition to its considerable therapeutic benefit for patients, offers a unique opportunity to determine the role of this molecule in the complex immunological network operating *in vivo* in RA. For example, there is evidence that anti-TNF-α therapy is able to influence cell trafficking, cytokine production, programmed cell death, and regulatory as well as effector functions of immune cells[12-19]. There is also evidence that TNF-α blockade can shift the Th1/Th2 balance towards a Th2-driven response as documented by the detection of autoantibodies in treated patients[12]. In light of this observation, therefore, the powerful effect of TNF-α blockade in suppressing disease activity may also be partially related to the redirection of this Th1/Th2 balance within the joint[16]. However, documentation of this phenomenon is difficult, as the evaluation of cytokine production changes is problematic to perform at joint level (absence of material following remission), while the findings in the peripheral blood may not necessarily reflect the synovial environment. A possible way forward could be represented by the evaluation of circulating sCD30 levels, since they may be used as a surrogate marker for antiinflammatory cytokine-producing T cells in the rheumatoid synovium[3,7,8]. We carried out a longitudinal study in RA patients treated with an anti-TNF-α agent, infliximab, in order to analyze possible correlations between sCD30 levels in the blood and biochemical and clinical response to therapy.

MATERIALS AND METHODS

Patient characteristics and treatment groups. The study group included 59 Caucasian subjects (51 women and 8 men, with a mean age at baseline of 55.9 yrs, range 31–70, and a mean disease duration of 8.4 yrs, range 1–30) fulfilling the American College of Rheumatology (ACR) classification criteria for RA[20]. Thirty-two were followed up at the Rheumatology Unit of the University of Perugia and 27 at the Rheumatology Unit of the University of Pavia. Rheumatoid factor (RF) was positive in 49 of them (83%). Thirty-nine patients had active disease, according to a Disease Activity Score in 28 joints (DAS28) higher than 5.1[21], despite traditional treatment with at least 2 different disease modifying antirheumatic drugs (DMARD), including methotrexate. Consequently, they were enrolled into a standard protocol of treatment with infliximab (3 mg/kg at 0, 2, 6 wks and every 8th wk thereafter) in association with methotrexate (10 mg/wk). Twenty patients with mildly active or inactive disease controlled with methotrexate alone (7.5–15 mg/wk) were used as control patients and were followed up with stable drug dosage. Nonsteroidal antiinflammatory drugs (NSAID) and/or prednisone (2.5–7.5 mg/day) were allowed in both patient groups. A second control group, represented by 44 age- and sex-matched healthy blood donors, acted as normal controls in order to obtain a normal range of sCD30 values (Table 1). Written informed consent was obtained from each subject, according to the local ethical committee recommendations.

Clinical and biochemical assessment. A careful clinical evaluation was performed in each patient at baseline and before each infliximab infusion. At the same time, a venous blood sample was also collected for the determination of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP; evaluated by nephelometry), RF (nephelometry), and sCD30 (Ki-1 antigen ELISA, Dako, Glostrup, Denmark). The same clinical and serological evaluations were carried out in the control RA patients.

Disease activity was evaluated in each patient with RA according to the DAS28 before each infusion[21]. In addition, an evaluation of 20%, 50%, and 70% improvement (ACR20, 50, 70), according to the ACR clinical criteria[22], was also performed. Patients were classified as responders when an improvement of at least 50% was obtained (ACR50/70), and as nonresponders when the response was mild or absent (≤ ACR20).

Statistics. Student's t-test was used to compare baseline variables between anti-TNF-α-treated and untreated patients, as well as between responders and nonresponders to therapy. Correlations between baseline variables were calculated using the Spearman's rho. Analysis of variance for repeated measurements was used to assess differences among various times of observation and stepwise multiple linear regression tested the relationship of several baseline variables to treatment response. Significant differences were assumed to be at $p < 0.05$ for 2-tailed tests.

RESULTS

Longitudinal evaluation of sCD30 serum levels and correlation with clinical and biochemical parameters. As shown in Table 1, patients with active disease were comparable to control RA subjects for age, sex, disease duration, and RF levels, but, as expected, they had higher values of ESR and CRP. Control RA patients had the highest values of sCD30 serum levels, although a statistically significant difference was reached only in comparison to normal controls, but not to patients with active RA. Infliximab infusion led to a dramatic and rapid decrease in disease activity, reflected by a drop in the mean ESR, CRP, swollen and tender joint count (Figure 1). The levels of sCD30 and RF were correlated at baseline in the entire group of patients with RA ($r = 0.41$, $p < 0.001$; active patients: $r = 0.39$, $p < 0.03$; inactive patients: $r = 0.54$, $p < 0.001$), but the correlation was lost in patients treated with infliximab already at the first evaluation (Week 2), due to progressive decrease of RF values and increase of sCD30 levels (data not shown). The increase of sCD30 serum concentrations reached a peak at Week 6, with a subsequent decline and lack of significant difference from baseline at Week 22 from the first infusion (Figure 1). By contrast, the sCD30 and RF levels did not change significantly over time in control patients with stable mild or inactive disease (Figure 1).

Analysis of the correlation between sCD30 serum levels and Disease Activity Score. As Figure 2 shows, although sCD30 serum levels did not correlate with DAS28 at the first 3 evaluations following infliximab treatment, a stable inverse correlation between sCD30 levels and DAS28 was observed from the 22nd week of treatment until the end of the followup (Week 38).

Evaluation of sCD30 serum levels according to infliximab

Table 1. Comparison of epidemiological and serological data between patients with active rheumatoid arthritis (RA), control RA patients, and normal control population.

Measure	Normal Controls, n = 44	Control RA Patients, n = 20	Active RA Patients, n = 39	p (control vs active RA patients)
Age, yrs	55.9 ± 10*	55.7 ± 10	56.0 ± 10	NS
Sex (men/women)	6/44	3/17	5/34	NS
Disease duration, yrs	—	7.9 ± 6	7.2 ± 5	NS
ESR, mm/h	11 ± 4	31.0 ± 20†	49.3 ± 2.5†	0.007
CRP, mg/l	0.4 ± 0.3	1.59 ± 0.8†	4.2 ± 3.3†	0.001
RF+ patients, %	0	85.0†	87.2†	NS
RF levels, U/ml	< 20	115 ± 119†	132 ± 122†	NS
sCD30, U/ml	13.2 ± 8	59 ± 67†	34 ± 26†	NS

* Mean ± SD. † $p < 0.001$ vs controls. NS: not significant; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; sCD30: soluble CD30.

response. In order to better evaluate these data, infliximab-treated patients were also analyzed according to the ACR improvement criteria. Ten and 13 patients had mild or absent response to treatment (≤ ACR20) after 6 and 14 weeks, respectively. At Weeks 22, 30, and 38, the nonresponder patients were 16. On the basis of this observation, sCD30 serum levels were analyzed separately in the group of the subjects classified as responders (n = 23) and nonresponders (n = 16) according to the treatment response after 22 weeks. Infliximab responders showed a fast and persistent increase in sCD30 serum concentration that lasted until the 38th week, whereas nonresponders, after a transient enhancement at Week 6, showed no changes in sCD30 levels compared to baseline (Figure 3).

DISCUSSION

Our study confirms that patients with RA have higher circulating sCD30 levels than healthy matched controls, as reported in previous studies[4,9,23]. The rapid and significant decrease in disease activity induced by infliximab in patients with active RA was paralleled by fast increase in sCD30 levels. This finding is in keeping with the notion that circulating sCD30 is a marker of antiinflammatory activity exerted by a subset of synovial T cells in RA[3,7]. Further, the increased levels of sCD30 triggered by infliximab supports the idea that CD30+ T cells are involved in the biological mechanisms implicated in the downmodulation of inflammation induced by TNF-α blockade. This hypothesis fits with the observation that infliximab treatment is able to induce a shift from a proinflammatory Th1-type cytokine profile to a predominant antiinflammatory Th2-type cytokine production in patients with RA[16].

However, it is also possible that the rise of sCD30 induced by TNF-antagonists may be the result of additional and more complex mechanisms. Serum levels of sCD30 are believed to reflect the cleavage of the molecule from CD30+ T cells present in the inflamed joints, as indicated by the highest levels of sCD30 found in the synovial fluid[4,9]. Hence, it is conceivable that sCD30 would exert its main biological role at a local synovial level. This concept is also supported by preliminary data showing that the ligand for the CD30 molecule (CD153/CD30L) is expressed by RA synovial mononuclear and endothelial cells (Lunardi C, *et al*, manuscript in preparation). Although the role of CD30/CD30L interaction is still not completely understood, there is evidence that the CD30L binding to CD30+ cells induces signals leading to cell proliferation or death[24-27]. It has been shown that sCD30 is able to bind CD30L with high affinity and block transmembrane signalling via CD30[28]. Thus, the prevention of CD30/CD30L interaction, favored by the high concentration of sCD30 in RA joints, may inhibit the apoptotic death of CD30+ cells with antiinflammatory properties. Alternatively, sCD30 may mimic the activity of CD30+ cells activating CD30L-expressing cells. Upon binding to CD30, indeed, CD30L is also able to trigger a reverse signal that directly leads to proliferation and impairment of Th1-response development[25]. As shown in experimental animal models and in mixed lymphocyte reactions, soluble CD30 is able to block the generation of interferon-γ-producing cells and may represent a potent inhibitor of Th1-, but not Th2-, mediated inflammation *in vivo*[29].

Altogether, these data indicate that part of the modulatory activity of TNF-α blockade may be exerted via direct or indirect action on T cell-mediated antiinflammatory activity, as suggested by previous studies[14,18,19]. Further, CD30/CD30L interaction may also be implicated in modulating humoral immunity. Activated B cells express CD30 and CD30L and have been found to be a potent mediator of mouse B cell growth and differentiation *in vitro*[1,2,24,27]. Although it is unclear if this mechanism is also operating in humans, CD30/CD30L cell interaction in RA synovium may account for the correlation between sCD30 and RF found in the patients before starting infliximab. The loss of correlation with the beginning of the treatment was due to the increase of serum sCD30 levels and to the decreased production of RF[30,31] that correlates with the reduction of disease activity[30,32].

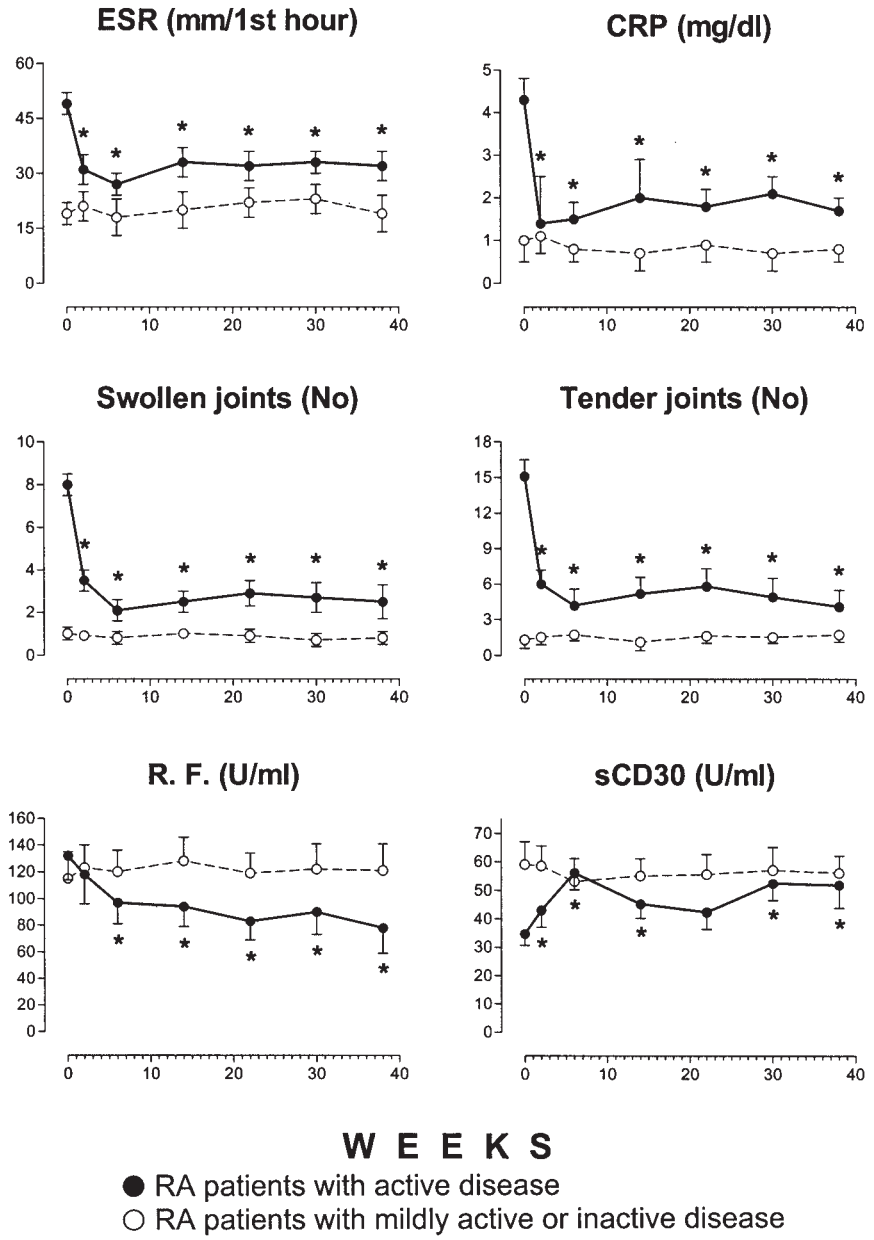

Figure 1. Values of ESR, CRP, swollen and tender joint count, rheumatoid factor (RF) and serum soluble CD30 (sCD30) at different examinations (from Week 0 to Week 38) in 39 RA patients with active disease treated with infliximab and 20 RA patients with mildly active or inactive disease. Data are expressed as mean ± SEM. *$p < 0.05$ vs basal values.

Interestingly, the sCD30 increase induced by infliximab was detected in almost all the patients in the first 6 weeks of treatment. However, an inverse correlation between sCD30 serum concentrations and disease activity, evaluated by the DAS28 score, was evident only later in the treatment. This observation was justified by a different behavior of sCD30 levels in the responder and nonresponder patients after the first 6 weeks of therapy. Indeed, subjects with persistently good remission according to the ACR criteria showed a sustained elevation of sCD30, confirming the association between high sCD30 levels and antiinflammatory activity. In contrast, the nonresponder patient group presented only a transient elevation of sCD30 concentrations at the sixth week of therapy.

The reason for the lack of sCD30 increase in nonresponders is not entirely clear, but it may be due to 2 different and non-mutually exclusive explanations. The first possibility is that in the balance between Th-1 proinflammatory cytokine-producing cells and counter-regulatory T cells, in the nonresponders the former prevail, leading to the persistence of local

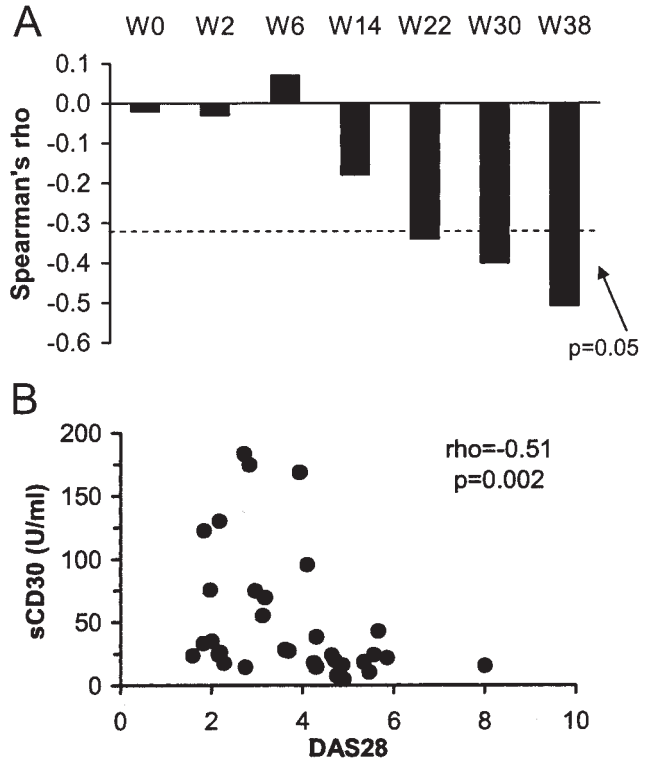

Figure 2. A. Pearson's correlation coefficients between log-transformed sCD30 levels and DAS28 score at different examinations (from Week 0 to Week 38). Broken line denotes statistical significance of the correlation (p = 0.05). B. Inverse correlation between log-transformed sCD30 levels and DAS28 score at Week 38.

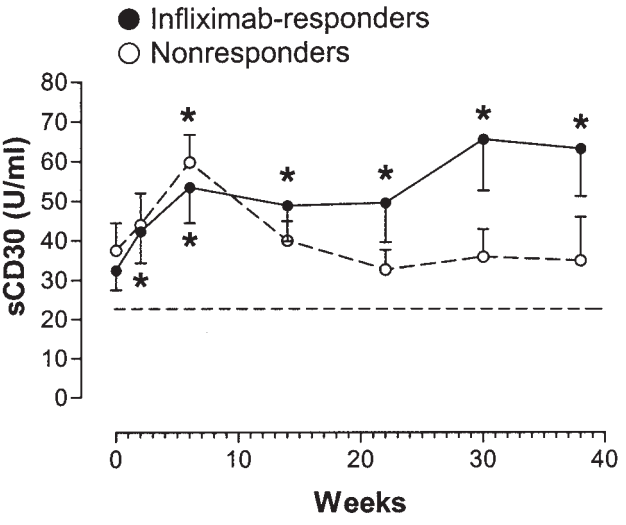

Figure 3. Levels of sCD30 in the 23 infliximab-responders and in the 16 non-responder patients with RA according to the ACR response criteria. Broken line denotes the normal value cutoff. Data are expressed as mean ± SEM. *p < 0.05 vs basal values.

inflammation. This in turn may induce increased CD30L expression on mononuclear and endothelial cells, thereby favoring apoptosis of CD30+ cells[2,27]. Another possibility is that the binding of infliximab to cell membrane TNF-α[11-13] may alter the activity of TNF-α-converting enzyme (TACE)[33], a metalloprotease responsible for the cleavage of TNF-α and CD30 molecules expressed on the cell surface[34]. TACE plays a key role in cholesterol-dependent CD30 shedding[35], and anti-TNF treatment seems to negatively influence HDL cholesterol concentration[36]. These mechanisms may partially explain the decrease of sCD30 levels over time, with consequent decreased activity on immune modulation.

Our study demonstrates that TNF-α blockade with infliximab in RA is able to enhance sCD30 serum levels that remain high over time only in patients with a persistent clinical and serological response to the treatment. This may suggest a regulatory function of CD30-expressing synovial T cells, which contribute to the maintenance of disease remission in RA, as demonstrated also in subjects with juvenile idiopathic arthritis[37]. Although we have previously shown that serum concentration of sCD30 is a predictor of good response to conventional DMARD therapy in early RA[38], the results of our study indicate that the initial determination of sCD30 serum concentration is not helpful to predict the response to TNF-α antagonists. This may be due to the transient enhancement of sCD30, which occurs also in the nonresponders in the early phases of anti-TNF treatment. Nonetheless, our data suggest that the sCD30 increase is expression of a mechanism involved in modulating disease activity and may represent an additional and helpful way to monitor treatment response. Further studies are required to better understand the biological mechanisms implicated in TNF-α resistance and the antiinflammatory activity of CD30+ cells.

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