Serum Soluble Interleukin 2 Receptor Levels and Radiological Progression in Early Rheumatoid Arthritis

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ABSTRACT. ***Objective***. To investigate the association between serum soluble interleukin 2 receptor (sIL-2R) levels and radiological changes in patients with early rheumatoid arthritis (RA).

Methods. sIL-2R levels from 155 patients with active RA were measured by immunoassay over a 2 year period and the associations with radiological change and other measures of disease activity were analyzed.

Results. The area under the curve for sIL-2R is weakly associated with the change in the modified Larsen score over a 2 year period; this is weaker than the association of radiological change with serum C-reactive protein.

Conclusion. We found no significant association of sIL-2R levels with erosive change in early RA. (J Rheumatol 2001;28:2576–8)

Key Indexing Terms:
SERUM INTERLEUKIN 2 RECEPTORS C-REACTIVE PROTEIN
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In patients with rheumatoid arthritis (RA), synovial fluid levels of soluble interleukin 2 receptor (sIL-2R) are consistently higher than serum levels, suggesting that the inflamed synovial tissue is the source for the serum levels of sIL-2R[1,2].

A number of studies have investigated the relationship between serum sIL-2R levels and various variables of disease activity in RA. The results are conflicting, with some studies showing positive association of serum sIL-2R with variables such as joint tenderness, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)[3,4] and others showing no significant association[5,6].

There has been only one study of radiological change in RA in relation to sIL-2R serum levels[7]. No relationship between sIL-2R levels and severity of radiological change was found.

We investigated 155 patients with early RA to determine whether serum sIL-2R levels predict subsequent radiological change over a period of 2 years.

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MATERIALS AND METHODS

Study design. Our aims were to evaluate the association of serum sIL-2R levels with (1) radiological changes in patients with active RA and (2) measures of disease activity.

One hundred fifty-five patients were studied from a cohort recruited for a 5 year study of second line therapy[8]. The criteria for selection of patients were: disease duration of less than 3 years, taking corticosteroids, followed up for 2 years, and availability of stored serial serum samples. Patients were assessed at entry to the study and at 6 monthly intervals over 2 years, with a minimum of 5 assessments for each patient.

Data collected included Health Assessment Questionnaire (HAQ) scores, Ritchie index, hemoglobin, ESR, CRP, and rheumatoid factor. Radiographs of hands and feet were taken at entry and at yearly intervals and scored by the same radiologist using the Larsen method[9]. In the analysis grade 1 changes (soft tissue swelling and periarticular osteoporosis) were omitted, as they did not represent irreversible joint damage (modified Larsen score).

Serum IL-2 receptor assay. We used a commercial kit (Boehringer Mannheim, Germany) for a sandwich ELISA for the low affinity 55 kDa chain of the IL-2 receptor. Serum samples were stored at –70°C from the day drawn until analysis.

Statistics. Stepwise multiple linear regression analysis was used to evaluate the association between entry and exit variables and the relationship between the area under the curve for sIL-2R levels and the change in the modified Larsen score. Mann-Whitney U test was used to compare the variables in erosive and non-erosive patients at entry. The difference in sIL-2R levels at entry in those non-erosive patients who became erosive or remained non-erosive at 2 years was also evaluated by an independent sample t test. Bonferroni correction was applied for multiple comparisons in the secondary analysis. Chi-square test was used to compare serum sIL-2R levels in erosive and non-erosive patients at entry and sIL-2R levels at entry in patients whose erosions progressed compared to those who did not develop further radiological change.

RESULTS

Patient characteristics at baseline are outlined in Table 1. There was no significant difference in serum sIL-2R levels

Table1. Patient baseline characteristics. All variables, except for rheumatoid factor and sex ratio, are given as mean (standard deviation).

Variables	All Patients, N = 155	Erosive, N = 107	Non-erosive, N = 48
Age, yrs	51.1 (11)	50.5 (11)	53(11)
Disease duration, yrs	1.43 (0.85)	1.59 (0.85)	1.08 (0.77)**
Female:male	107:48	73:34	34:14
Rheumatoid factor positive	75%	76%	75%
SIL-2R, pmol/1	148 (50)	150 (46)	144 (49)
ESR, mm/h	48 (26)	50 (26)	43 (24)
CRP, mg/l	40 (35)	44 (35)	32 (34)
Hb, g/dl	12.3 (1.6)	12.1 (1.5)	12.7 (1.6)*
HAQ	1.7 (0.8)	1.6 (0.75)	1.8 (0.8)
Ritchie Index	24.3 (10)	23.7 (10)	25.4 (11)
Modified Larsen Score	12 (15)	19 (15)	0

Comparisons between erosive and non-erosive groups were determined by the independent samples T test for hemoglobin (Hb) and disease duration. Mann-Whitney U test was applied for the other variables.**p < 0.01; * p < 0.05 independent samples T test .

Table 2. Comparison of entry serum sIL-2R and CRP levels in patients with progressive erosive disease compared to those with no progression of erosions.

	Entry sIL-2R (SD)	Entry CRP
Non-erosive at entry		
Progression to erosions, N = 31	147.2 (66)	38.23 (40)
No progression of erosions, N = 17	136.8 (43)	20.53 (15)**
All patients		
Progression to erosions, N = 127	148.4 (52)	43.5 (37)
No progression of erosions, N = 28	145.7 (41)	23.7 (20)**

** p < 0.01 compared to erosive group.

at entry between the erosive and non-erosive patients. Both ESR and CRP were lower in the non-erosive patients but this difference was not significant. Hemoglobin levels were significantly lower in the erosive group ($p < 0.05$).

Comparison between patients with normal or raised sIL-2R levels at entry to the study. There was no significant difference in the proportion of erosive to non-erosive patients with raised sIL-2R levels compared to the proportion with sIL-2R levels within the normal range at entry to the study. Similarly, there was no difference in the proportion of erosive and non-erosive patients at 2 years between those groups who had raised or normal levels of sIL-2R at entry to the study (chi-square, $p > 0.05$).

Mean sIL-2R levels in the non-erosive group at entry who showed no progression to erosive disease were lower than in those who developed erosions (Table 2), but the difference was not significant. CRP was significantly higher at entry in the non-erosive patients who developed erosions compared to those who did not ($p < 0.01$).

The area under the curve for serum sIL-2R levels (Table 3) shows a weak association with the change in the modified Larsen score over 2 years ($p < 0.05$). There is a stronger association between the area under the curve for the CRP and the change in the modified Larsen score ($p < 0.01$).

Weak associations between serum sIL-2R levels and ESR, CRP, and hemoglobin were seen at entry to the study and at 2 years. A weak association of the sIL-2R level with the HAQ score was seen at 2 years. There was no association with Ritchie Index or with disease duration.

DISCUSSION

We investigated whether serum sIL-2R levels reflected or predicted the immunopathological process that resulted in progressive joint destruction in RA. We found that the area under the curve for the serum sIL-2R levels was very weakly associated with radiographic progression over 2 years. This association was weaker than the association found for the area under the curve for the CRP[10].

The association between serum sIL-2R and other variables of disease activity is weak at best and showed correlation coefficients for the acute phase markers such as ESR and CRP similar to those of studies that included substantial (> 50) numbers of patients followed serially[11,12]. Recent studies have shown that although synovial membrane from patients with RA is heavily infiltrated with CD3 positive T cells, significant cytokine expression is seen on only 3% of T cells[13]. In contrast, at least 60% of synovial T cells are activated and polyclonal. Synovial cytokines such as IL-15 stimulate antigen-independent contact mediated macrophage activation by T cells[14,15].

These mechanisms of cell activation and cytokine production within the rheumatoid synovium may explain the

Table 3. Correlation of serum sIL-2R and CRP with modified Larsen score

	Entry Larsen Score	2 Year Larsen Score	Change in Larsen Score
Entry serum sIL-2R	0	0.133	—
Area under the curve for serum sIL-2R	—	—	0.219 *
Area under the curve for CRP	—	—	0.463 **

* Correlation is significant at 0.05 level after adjustment for multiple comparisons by the Bonferroni method. ** p < 0.01.

lack of association of joint destruction with T cell related activation markers compared with markers that reflect macrophage activation.

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