Serum Soluble Interleukin-2 Receptor Measurement in Patients With Sarcoidosis: A Clinical Evaluation

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Serum Soluble Interleukin-2 Receptor Measurement in Patients With Sarcoidosis*
A Clinical Evaluation

Jan C. Grutters, MD; Jean-Marc Fellrath, MD; Leontine Mulder, PhD; Rob Janssen, MD; Jules M. M. van den Bosch, MD, PhD, FCCP; and Heleen van Velzen-Blad, MSc

Objectives: To date, insufficient evidence is available to recommend serum soluble interleukin-2 receptor (sIL-2R) measurement as a routine test in the assessment of sarcoidosis. Therefore, we evaluated the clinical value of this test.

Design: Forty-seven patients with sarcoidosis, all presenting with active disease, were included in the study. Initial serum sIL-2R levels were determined by enzyme-linked immunosorbent assay, and clinical data at presentation and follow-up were collected retrospectively.

Results: The median follow-up period of all patients was 44 months (range, 6 to 100 months), and 38 patients had follow-up data present over at least 24 months. The median sIL-2R level was 1,068 U/mL (range, 248 to 4,410 U/mL; upper limit of normal, 710 U/mL). A positive correlation was found between serum sIL-2R levels and the number of CD4+ T lymphocytes in BAL (rs = 0.53, p < 0.001). In accordance with this result, both sIL-2R level and the number of CD4+ T lymphocytes were elevated in stage I compared to stage III disease (p < 0.05). Patients with extrapulmonary disease (ED) [excluding Löfgren’s syndrome] showed higher sIL-2R levels than those presenting with only pulmonary sarcoidosis (p = 0.001). No relation was found between sIL-2R level and response to treatment, and there was no association between sIL-2R levels and radiographic evolution and lung function outcome.

Conclusions: Our data suggest a role for serum sIL-2R as marker of pulmonary disease activity and ED in patients with sarcoidosis. (CHEST 2003; 124:186–195)

Key words: alveolitis; extrapulmonary disease; sarcoidosis; serum soluble interleukin-2 receptor

Abbreviations: BALF = BAL fluid; Dlco = diffusing capacity of the lung for carbon monoxide; ED = extrapulmonary disease; EN = erythema nodosum; IL = interleukin; IVC = inspiratory vital capacity; sACE = serum level of angiotensin-converting enzyme; sIL-2R = soluble interleukin-2 receptor

Sarcoidosis is a multisystem granulomatous disease of unknown etiology presenting with a wide spectrum of clinical manifestations, having a highly variable natural course and a difficult to predict outcome.1 One of the most characteristic immunologic features of the disease is the accumulation of activated CD4+ T-helper type 1 cells at sites of disease, notably in the alveolar and interstitial spaces.2 Among the secreted T-helper type 1 cytokines, interleukin (IL)-2 plays a key role, as it induces T-cell proliferation.3,4 IL-2 acts via binding to its receptor, which is mainly expressed on activated T cells and in part released into the microenvironment.5 Increased levels of the soluble IL-2 receptor (sIL-2R) have been found in serum and BAL of patients with sarcoidosis.6,7

Although the specific role of sIL-2R in the immune response has not yet been fully described,
elevated serum sIL-2R levels have been found to correlate with the activity of T-cell-mediated diseases and for this reason are considered a marker of T-cell activation. The value of sIL-2R as a marker of disease activity and as a marker of progression over 6 months in patients with sarcoidosis has been assessed in previous studies, however, to our knowledge, no study has yet assessed the usefulness of sIL-2R in identifying sarcoidosis patients with severe disease at presentation and those at risk for chronic pulmonary disease in the long term.

With this background, the aims of the present study were as follows: (1) to compare sIL-2R as a marker of sarcoidosis activity with that of other well-recognized markers of activity; (2) to determine the value of serum sIL-2R as an index of severity of sarcoidosis at presentation; (3) to determine the value of serum sIL-2R as a predictive marker for chronic disease, which is a marker predicting functional and radiologic outcome, focusing notably on the subgroup of untreated patients with no resolution of their abnormalities within 2 years after diagnosis; and (4) to assess the clinical value of a second serum measurement of sIL-2R.

**Patients and Methods**

**Study Population**

This retrospective study included a random series of 47 patients with sarcoidosis investigated in the Department of Pulmonology of the Sint Antonius Hospital (a secondary referral center) between 1984 and 1996. The diagnosis of sarcoidosis was established on the basis of clinical findings and histologic evidence of noncaseating epithelioid-cell granulomas after the exclusion of known causes of granulomatous diseases. All patients had active disease at presentation, and none of them received corticosteroids, nor had they within the previous 3 months. The criteria used to affirm that the sarcoidosis was active were as follows: (1) recently developed or increasing cough or dyspnea; and/or (2) presence of compatible systemic symptoms such as cutaneous lesions, eye manifestations, fever, and arthralgia; and/or (3) recently developed abnormalities on chest radiograph; and/or (4) increased T lymphocytosis in BAL; and/or (5) elevated level of serum angiotensin-converting enzyme (sACE). The characteristics of the study population are summarized in Table 1.

Assessment of sarcoidosis at time of diagnosis included clinical features, chest radiography, lung function tests, BAL examination, and routine blood studies, including notably sACE and WBC counts. Ga scanning was not included in this study, as this test is not routinely performed in our hospital. Serum samples were obtained at this time and stored at ~80°C until analysis. All chest radiographs were available for review and assessed blindly by a radiologist, and classified according to the standard chest radiographic stages: stage 0, normal chest radiograph; stage I, bilateral hilar lymphadenopathy without parenchymal infiltration; stage II, bilateral hilar lymphadenopathy with parenchymal infiltration; stage III, parenchymal infiltration without lymphadenopathy; stage IV, advanced fibrosis with evidence of honeycombing, hilar retraction, bullae, cysts, and emphysema. Lung function test results were regarded as normal or impaired. Impairment was defined as FEV1 and inspiratory vital capacity (IVC) < 80% of predicted value (restriction), FEV1/IVC ratio < 55% in men and < 89% in women (obstruction), or diffusing capacity of the lung for carbon monoxide (DLCO) < 80% of predicted value (gas exchange abnormality), in agreement with the European Respiratory Society recommendations. These results provided a baseline value for the functional assessment at follow-up.

The usefulness of sIL-2R as a marker of sarcoidosis activity was assessed by comparing the sIL-2R levels in serum with those of sACE, BAL lymphocytosis, BAL CD4+/CD8+ ratio, and blood lymphocyte count, notably CD4+ T cells. The severity of sarcoidosis at presentation was assessed on the basis of clinical, functional, and radiologic data related to the following: (1) presence vs absence of extrapulmonary manifestations (erythema nodosum [EN] was analyzed as a separate extrapulmonary condition because of its association with mild disease and absence of local granuloma formation); (2) acute vs insidious onset of disease, referring to patients presenting with Löfgren syndrome or those with stage I disease and EN as acute-onset type sarcoidosis (Löfgren syndrome was defined as the presence of stage I disease on chest radiograph, EN, and arthralgia); (3) presence vs absence of lung function impairment; and (4) chest radiographic stage. The project was approved by the Ethics Committee of the Sint Antonius Hospital.

**Follow-up Study**

Forty-five of 47 patients with sarcoidosis included in this study underwent repeat chest radiography at least every 6 months during the first 2 years from diagnosis, and every 6 to 12 months thereafter. At the same time, intervals data for functional assessment (FEV1, IVC, DLCO) were available for 41 patients. This provided the opportunity to assess the predictive value of sIL-2R concerning functional and radiologic outcome. Due to the retro-
spective nature of the study, it was not possible to assess the evolution of clinical symptoms with sufficient accuracy; therefore, we decided to leave out this variable for the follow-up study.

For analytic considerations, the patients were allocated to two groups: patients with (group A) and without (group B) indication for corticosteroid therapy. The decision to treat was based on the following criteria: (1) progressive deterioration of pulmonary function, (2) progressive change on chest radiographs or extensive pulmonary involvement, (3) impairment of organs other than the lung, and (4) persistent symptoms in combination with parameters of disease activity. In group A, only the radiologic outcome could be assessed, as too many of the lung function data in this group were missing. Group A was divided in two subgroups according to radiologic progression (group A1) or nonprogression (group A2; including normalization, improvement, or stabilization) of chest radiographic stage, which allowed the assessment of sIL-2R as index of response to treatment. Similarly, group B was divided in two subgroups according to complete radiographic resolution of disease (group B1) or not (group B2) within 2 years from diagnosis, which allowed the assessment of sIL-2R as index of progression to a chronic disease.12

For FEV1 and IVC, a change of 15% from the baseline value, and for DLCO, a change of 10% from the baseline value was regarded as significant in both groups. For radiologic follow-up assessment, one or more chest radiographic stage changes were regarded as significant. Final radiologic outcome was categorized as follows: (1) normalized or improved chest radiographic findings, defined as stage 0 or improvement; (2) stabilized chest radiographic findings, defined as stage 0 or improvement ≥1 stage at the end of the follow-up period, respectively; (2) stabilized chest radiographic findings, defined as unchanged chest radiographic findings at the end of the follow-up period; and (3) deteriorated chest radiographic findings, defined as ≥1 stage worsening of chest radiographic findings at the end of the follow-up period.

At a median follow-up of 20 months (range, 11 to 33 months), a second serum sample for sIL-2R measurement was available for a random series of 14 of 47 patients. These data were used to assess the clinical value of a second sIL-2R measurement during the follow-up of patients with sarcoidosis.

**BAL**

BAL was performed during fiberoptic bronchoscopy at the time of the diagnosis. BAL was performed in the right middle lobe with four 50-mL aliquots of sterile isotonic saline solution. Lavage fluid samples, kept on ice in a siliconized specimen trap, were centrifuged (10 min at 3500 g) and separated into cells and supernatant. The cell pellet was washed twice, counted, and suspended in minimal essential medium (Gibco; Grand Island, NY), supplemented with 1% bovine serum albumin (Organon; Teknika; Boxtel, the Netherlands). Preparations of cell suspensions were made in a cytocentrifuge (Shandon; Runcorn, UK). Cytospin slides of BAL fluid (BALF) cells were stained with May-Grunwald-Giemsa (Merck; Darmstadt, Germany) for cell differentiation. At least 1,000 cells were counted.

**Immunophenotyping of BAL Lymphocytes**

Before 1993, T-cell (sub)populations in BALF were identified by staining with monoclonal antibodies CD2 (OKT11), CD3 (OKT3), CD4 (OKT4), and CD8 (OKT8) [Ortho-Pharmaceuticals, Diagnostic Systems; Beere, Belgium]. Stained T cells were subsequently detected by conventional indirect immunofluorescence technique using fluorescein isothiocyanate-labeled goat-antimouse-Ig (GAM; Nordic Immunological Laboratories; Filburg, the Netherlands; and the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, the Netherlands). From 1993, a flow cytometric method was used for determining T-cell (sub)populations, which were stained by monoclonal antibodies anti-CD14-PE, anti-CD45-FTTC, anti-CD3-FTTC, anti-CD4-PE and anti-CD8-PE from Becton Dickinson (Woerden; the Netherlands). Flow cytometric analysis was performed on a FACScan flow cytometer (Becton Dickinson).

**Assay for sIL-2R in Serum**

Serum sIL-2R was quantitatively determined using enzyme-linked immunosorbent assay (DPC; Breda, the Netherlands). As no serum of controls was available for this study, we used the normal range in healthy individuals given by the manufacturer: 223 to 710 U/mL (derived from a series of Dutch subjects). To avoid interassay variation, all samples were analyzed simultaneously.

**Statistical Analysis**

Data were expressed as median values (range). Comparisons between the groups were made with the Mann-Whitney U test. Correlations between different variables were determined with the Spearman rank coefficient (rs). Sensitivity of sIL-2R measurement was calculated using the upper normal limit (710 U/mL). All statistical analyses were performed using the Statistical Package for Social Science for Windows (SPSS; Chicago, IL). Values of p < 0.05 were considered as statistically significant.

**RESULTS**

**Serum sIL-2-R Level in Relation to Demographic Data**

The median serum sIL-2R level in this cohort of active, untreated patients with sarcoidosis (n = 47) was 1,065 U/mL (range, 248 to 4,410 U/mL), and sensitivity of the test was 79%. No difference was observed in smoking (n = 9) vs nonsmoking (n = 38) patients. Seven patients were African American, and 40 were white. The median sIL-2R level at presentation was significantly higher in African Americans (1,656 U/mL; range, 905 to 3,322 U/mL) compared to whites (1,001 U/mL; range, 248 to 4,410 U/mL; p = 0.03).

**Correlations Between Serum sIL-2-R Level and Common Markers of Activity in Blood and BAL**

The median sACE level at disease presentation was 83 U/L (range, 5 to 157 U/L; upper normal limit in our hospital, 55 U/L). No correlation between serum sIL-2R and sACE level was found (rs = 0.20, p = 0.21).

There was a positive correlation between percentage and absolute number of BAL lymphocytes and sIL-2R level (rs = 0.48 and rs = 0.47, respectively; p = 0.001). Further lymphocyte subset analysis showed a correlation between sIL-2R level and the number of CD4+ T lymphocytes in BAL (rs = 0.53, p < 0.001).
p < 0.001; Fig 1), whereas no such correlation was found for CD8+ T lymphocytes. Serum sIL-2R levels also correlated with CD4+/CD8+ T lymphocyte ratios in BAL (rs = 0.45, p = 0.002).

Analysis of comparable relations in blood yielded results in the opposite direction: both the absolute number of lymphocytes and CD4+ T lymphocytes showed a negative correlation with sIL-2R level (rs = 0.38, p = 0.008, and rs = 0.36, p = 0.02, respectively; Fig 2). No correlations with CD8+ blood T lymphocytes were found.

**Serum sIL-2R Level in Relation to Severity of Disease**

Forty-six patients presented with pulmonary sarcoidosis, and 21 of them also had extrapulmonary organ involvement. Only one patient presented solely with extrapulmonary sarcoidosis. The extrapulmonary organs involved consisted of skin (EN and other skin diseases; n = 12), liver (n = 4), peripheral lymph glands (n = 3), eye (n = 4), salivary glands (n = 3), heart (n = 1), kidney (n = 1), CNS (n = 1), joints (n = 1), and nose (n = 1). EN was regarded as a separate manifestation of extrapulmonary disease (ED), because it is not associated with local granuloma formation but thought to be an immune complex-associated skin reaction, which can also be observed in other diseases. Ten patients had EN, 6 of whom showed classical Löfgren syndrome; 2 patients had also other forms of ED (peripheral lymph glands, liver); and 2 patients had EN only.

Patients with lone pulmonary sarcoidosis showed a median sIL-2R level of 928 U/mL (range, 248 to 1,670 U/mL), those with pulmonary sarcoidosis and EN had a median of 1,280 U/mL (range, 821 to 4,410 U/mL), and those with pulmonary sarcoidosis and ED other than EN had a median of 1,691 U/mL (range, 484 to 3,340 U/mL). These differences were statistically significant (p = 0.03 and p = 0.001, respectively; Fig 3). Further, the median sIL-2R concentration in patients presenting with acute onset sarcoidosis, i.e., Löfgren syndrome and stage I disease with EN, did not significantly differ from those presenting with insidious-onset sarcoidosis (1,365 U/mL [range, 821 to 4,410 U/mL] vs 975 U/mL [range, 248 to 3,340 U/mL]; not significant).

Lung function impairment at presentation (i.e., FEV1 < 80% of predicted, IVC < 80% of predicted, and DLco < 80% of predicted value) was found in 22 patients, 7 patients, and 24 patients, respectively. FEV1/IVC ratio < 88% was found in 7 of the male patients, and 19 of the female patients presented with an FEV1/IVC ratio < 89%. Furthermore, combined obstructive/restrictive impairment was found in four patients, who also showed impaired DLco. The median sIL-2R level was higher in patients with
an impaired IVC vs those with a normal lung function, but this difference did not reach statistical significance (1,431 U/mL [range, 905 to 3,322 U/mL] vs 1,014 U/mL [range, 248 to 4,410 U/mL]; p = 0.07; Table 2). By comparison, analysis of the various lymphocytic markers in BAL and blood yielded a significantly decreased number of blood CD4+ T cells in the patients with an impaired IVC (median, 0.20 x 10^6/mL [range, 0.08 to 0.66 x 10^6/mL] vs 0.63 x 10^6/mL [range, 0.21 to 1.25 x 10^6/mL] in patients with a normal IVC; p = 0.001; Table 2). Further, no relation was found between sACE levels and impairment of lung function (Table 2).

Distribution of chest radiographic stages at presentation showed that 1 patient presented with stage 0, 27 patients presented with stage I, 7 patients presented with stage II, and 12 patients presented with stage III disease. No patient presented with stage IV disease. There was a gradually decline in median sIL-2R level between stage I and stage III disease. Patients presenting with stage I disease showed the highest sIL-2R levels, whereas the lowest sIL-2R levels were found in patients presenting with stage III disease (p = 0.02; Table 2). Analyzing patients with hilar adenopathy with and without parenchymal infiltration (stage I and stage II) against parenchymal infiltration only (stage III) showed the same significance (p = 0.02). By comparison, the number of BAL lymphocytes did not differ significantly between the chest radiographic stages, but the number of CD4+ T lymphocytes and the CD4+/CD8+ ratio were higher in patients presenting with stage I compared to stage III disease (p = 0.01 and p = 0.002, respectively; Table 2).

**Serum sIL-2R Level as a Predictive Marker of Radiologic Outcome in Treated Patients (Group A)**

Fifteen patients were treated with oral corticosteroids during a median period of 30 months (range, 8 to 66 months). The median follow-up period was 59 months (range, 14 to 94 months). The median sIL-2R level at presentation was 950 U/mL (range, 248 to 3,322 U/mL). Analysis of the radiologic outcome revealed the following: 4 patients showed progression (group A1) and 11 patients did not show progression (group A2). The median sIL-2R level in these subgroups was not significantly different (1,391 U/mL [range, 484 to 2,347 U/mL] vs 855 U/mL [range, 248 to 3,322 U/mL], respectively; p = 0.5).

**Serum sIL-2R Level as a Predictive Marker of Functional and Radiologic Outcome in Untreated Patients (Group B)**

The predictive value of serum sIL-2R level for radiologic and functional outcome of pulmonary sarcoidosis was evaluated in the 32 untreated patients. The correlation between serum sIL-2R level and the absolute number of CD4+ T lymphocytes in peripheral blood of 47 untreated patients presenting with active sarcoidosis is illustrated in Figure 2.

![Figure 2](https://example.com/figure2.png)
patients. The median follow-up period in these patients was 38 months (range, 6 to 100 months). The median sIL-2R level at presentation in this group was 1,228 U/mL (range, 345 to 4,410 months).

Fifteen patients showed a spontaneous normalization of their chest radiograph within 2 years (group B1), 11 patients did not show normalization within 2 years (regarded as "chronic disease"; group B2), 4 patients had a follow-up < 2 years, and in 2 patients no chest radiograph was available for this evaluation. No difference in sIL-2R level was found between group B1 (1,371 U/mL; range, 400 to 4,410 U/mL) and group B2 (1,253 U/mL; range, 814 to 3,340 U/mL). Subsequently, we analyzed the radiographic stage at the end of the follow-up period in both groups. Patients showing a final normalization of their chest radiograph tended to have higher initial sIL-2R levels compared to patients with persistent abnormalities, but this difference did not reach statistical significance (1,375 U/mL [range, 400 to 4,410 U/mL] vs 969 U/mL [range, 814 to 3,340 U/mL]; p = 0.2). Further, analysis of lung function at the end of the follow-up period showed that 63.6%, 7.7%, and 47.4% of the patients had an obstruction, a restriction, and gas exchange abnormalities, respectively. No significant difference in sIL-2R levels between patients with and without lung function impairment was found in any of the three categories (p = 0.5, p = 0.9, and p = 0.9, respectively). Finally, classifying patients as those having lone pulmonary sarcoidosis and those with extrapulmonary manifestations, the above-mentioned analysis did not reveal additional differences.

Clinical Utility of a Second Measurement

From 14 patients, a second serum sample for sIL-2R concentration measurement was available during the follow-up period. Changes in sIL-2R level and chest radiographic stage in these patients are presented in Table 3. The initial sIL-2R levels correlated inversely proportional to the extent of change in follow-up sIL-2R level (rs = −0.72, p = 0.003). In accordance with the results in the previous paragraph, the initial sIL-2R level in this group of patients was higher in the five patients showing normalization of their chest radiograph during follow-up, and this difference seemed to
reach statistical significance (2,354 U/mL [range, 1,202 to 4,410 U/mL] vs 961 U/mL [range, 484 to 3,340 U/mL]) in the nonnormalized group; p = 0.02). However, after correction for treatment, the difference was no longer significant (p = 0.1). Finally, when analyzing change in sIL-2R level in relation to change in chest radiographic stage, a positive correlation was observed, which remained significant after correction for treatment (rs = 0.69, p = 0.007, and rs = 0.67, p = 0.048, respectively; Table 3).

Table 3—Serial Serum sIL-2R Levels in Relation to Chest Radiographic Stage Outcome in 14 Patients With Sarcoidosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Serum sIL-2R, U/mL</th>
<th>Chest Radiographic Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Level*</td>
<td>Follow-up Level†</td>
<td>Change, %</td>
</tr>
<tr>
<td>1</td>
<td>4,410</td>
<td>3,429</td>
</tr>
<tr>
<td>2</td>
<td>3,340</td>
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</tr>
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<td>14</td>
<td>484</td>
<td>518</td>
</tr>
</tbody>
</table>

*The initial serum sIL-2R level was the value at presentation of sarcoidosis.
†Serum sIL-2R levels during follow-up were available at median 20 mo (range, 11 to 33 mo).
‡Change in sIL-2R level was defined as follow-up sIL-2R level minus initial sIL-2R level divided by initial sIL-2R level, times 100%.
§Change in chest radiographic stage was defined as stage number at follow-up minus stage number at presentation.
¶Positive correlation between change in sIL-2R level and change in chest radiographic stage (rs = 0.69, p = 0.007; corrected for treatment rs = 0.67, p = 0.048).
gans involved, pulmonary disease activity, and duration of disease. Furthermore, genotype differences in the genes encoding these markers, which are related to ethnicity, such as Japanese and white, might also influence the finding of associations. Another interesting result was the inverse correlation between serum sIL-2R level and the number of CD4+ T lymphocytes in the peripheral blood. This finding might be related to the lymphocytic depletion seen in the blood of patients with sarcoidosis. An explanation for this phenomenon is the chemotactic activity at sites of disease, causing T-lymphocyte attraction from the blood to these sites and resulting in peripheral blood T lymphopenia. Further, the negative association between sIL-2R level and blood lymphocytes, and the positive association between sIL-2R level and BAL lymphocytes, suggests that serum sIL-2R is not manufactured in the blood, but more likely at sites of disease activity (e.g., the alveolar and interstitial spaces), and then released into the blood. Consequently, the sIL-2R level will not only be influenced by the intensity of inflammation in the lung but also by the presence of ED, since sIL-2R release from these organs might also contribute to its actual level in the blood.

Evaluation of the initial serum sIL-2R level as an index of severity in sarcoidosis showed that there was indeed a clear association between sIL-2R level and the presence of ED manifestations. Similar results have been reported by Tsutsumi and colleagues. These results, therefore, support the concept that circulating sIL-2R is the reflection of local inflammatory activity within all organs involved. Interestingly, after leaving out the patients presenting with EN, this association became even stronger, suggesting that the sIL-2R test might clinically be useful in the evaluation of patients with sarcoidosis with respect to the existence of extrapulmonary granuloma.

Since there are only very few studies on the predictive value of the serum sIL-2R measurement, we investigated this issue thoroughly. Although one study reported an association between increased initial serum sIL-2R levels and disease progression after 6 months, in the present study no predictive value was found: the initial sIL-2R level could not predict chronic disease on chest radiograph at 2 years and was also not associated with significant change in lung function during follow-up. The reason for this inconsistency might be the longer period of follow-up in our study, as it is known that spontaneous regression of sarcoidosis can occur up to 2 years after disease presentation. Therefore, the situation at 6 months might not necessarily be representative for that at 2 years, even in cases where there is evidence of progression in the first months. This study rather suggests the opposite as we found...
a weak association between higher initial sIL-2R levels and normalization of chest radiograph at long-term follow-up. In our opinion, this finding, although not significant, is consistent with the afore-mentioned correlation (ie, between sIL-2R level and the number of CD4+ T lymphocytes in BAL), as spontaneous remission of sarcoidosis is more likely to occur in patients presenting with a high degree of alveolitis and low chest radiographic stage.13,22

Apparently, from the above, elevated serum sIL-2R levels should be carefully interpreted in the presence of clinical, radiographic, and BAL findings. There is a good correlation between elevated serum sIL-2R level and CD4+ BAL lymphocytosis, suggesting active, stage I-associated disease. Secondly, elevated serum sIL-2R level points toward presence of extrapulmonary or disseminated disease. Taken together, this indicates that especially when increased sIL-2R levels are found in the absence of CD4+ BAL lymphocytosis, this should put the clinician on the alert for serious ED activity. Therefore, whether elevated sIL-2R levels mean bad or good news largely depends on the clinical context. We hypothesize that this divergent effect in sarcoidosis is caused by the fact that the circulating sIL-2R level is an integral of the total release of sIL-2R from all sites of disease activity, ie, the interstitial compartment of the lung and/or the extrapulmonary organs involved.

Finally, we investigated the value of a second serum sIL-2R measurement during follow-up. This study was performed in 14 patients and showed a positive correlation between change in sIL-2R level and change in chest radiographic stage, suggesting a predictive value of the second sIL-2R measurement in relation to the initial level; however, the initial sIL-2R level itself already showed a correlation with chest radiographic improvement, making the usefulness of a second sIL-2R measurement as indicator for radiologic evolution questionable. In addition, if the serum sIL-2R level indeed reflects intensity of inflammation in the lung and involvement of extrapulmonary organs, a follow-up measurement might have additional value in decisions on starting treatment and dose tapering. For example, if a patient shows improvement of chest radiographic abnormalities during treatment but follow-up serum sIL-2R measurement still gives a high level, this might indicate caution in tapering the dose too quickly and, in addition, it might especially prompt the assessment of ED involvement. Further studies are needed to elucidate this value in the management of sarcoidosis.

In conclusion, although this study has weaknesses related to its retrospective character, which necessitate prospective studies to validate the results, it demonstrates an association between serum sIL-2R level and the extent of T-lymphocyte alveolitis in sarcoidosis, supporting its value as a marker of disease activity. Additionally, it suggests that patients presenting with extrapulmonary manifestations have higher serum sIL-2R levels than those presenting with lone pulmonary sarcoidosis, indicating that sIL-2R might be useful as marker of severity, especially in patients without evidence of a high-intensity alveolitis. Therefore, in our opinion, interpretation of sIL-2R levels in patients with sarcoidosis needs to be done in the context of the clinical, radiographic, and BAL findings.

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