Do elevated levels of serum soluble Fas contribute to the persistence of activated lymphocytes in Systemic Lupus Erythematosus?

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Summary

Systemic lupus erythematosus (SLE) is characterised by generalised immune activation. Part of this might be explained by a decreased rate of apoptosis, possibly related to elevated levels of soluble Fas (sFas) which can inhibit Fas mediated apoptosis of lymphocytes. In order to substantiate the relation between levels of sFas and lymphocyte activation in SLE we monitored sFas levels, lymphocyte activation and disease activity in twenty five SLE patients. SLEDAI-scores were registered and sera were assayed for sFas levels by an enzyme-linked immunosorbent assay. Flow cytometry was used to monitor the state of activation of lymphocyte subsets. Eighteen healthy, age-matched, volunteers served as controls. Soluble Fas levels were elevated in SLE patients (n=25) compared to healthy controls (n=18, p=0.002). Soluble Fas levels correlated with SLEDAI-scores (r=0.45, p=0.02). Levels of sFas correlated with the percentages of activated B cells defined as CD20<sup>+</sup>CD38<sup>+</sup> cells (r=0.47, p=0.009). Percentages of CD20<sup>+</sup>CD38<sup>+</sup> cells were increased in quiescent SLE compared to healthy controls (p=0.003). The expression of activation markers on CD4<sup>+</sup> T-lymphocytes (IL-2R, p=0.04; HLA-DR, p=0.01) and CD8<sup>+</sup> T-lymphocytes (HLA-DR, p=0.007) was increased as well in quiescent SLE compared to controls. Activation markers on all lymphocyte subsets tended to increase further during disease activity. No correlation was observed between percentages of activated T-lymphocyte subsets and levels of sFas. In conclusion, soluble Fas levels are increased in SLE patients and correlate with disease activity as measured by the SLEDAI-score. B and T cell subsets are activated even during quiescent SLE. Serum levels of sFas do correlate with percentages of activated B cells but not with that of activated T cells.

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterised by polyclonal activation of B lymphocytes and the production of a wide range of autoantibodies. B cell proliferation in SLE has been suggested to be T cell dependent and persistence of autoreactive B and T-lymphocytes is thought to be responsible for hypergammaglobulinaemia and autoantibody production in SLE [1]. One of the mechanisms by which elimination of autoreactive lymphocytes takes place is programmed cell death (apoptosis). A defect in apoptosis may thus contribute to the development of autoimmune disease [2]. One of the major routes which triggers apoptosis is the Fas pathway. Fas, also known as APO-1 or CD95, is a cell surface protein of 45-48 kD belonging to the tumor necrosis factor (TNF)/nerve growth factor (NGF) receptor family [3,4]. Fas is expressed on rapidly proliferating cells and is strongly up-regulated on lymphocytes upon activation [5]. Cross-linking of Fas by Fas ligand (FasL), a membrane glycoprotein of 40 kD [4], triggers apoptotic cell death with characteristic cytoplasmic and nuclear condensation and DNA fragmentation [6]. In the lpr and gld murine models
the development of SLE is directly linked to a defect in the Fas apoptotic pathway. It has been shown that in \textit{lpr} and \textit{gld} mice mutations in Fas and FasL, respectively, underlie the development of an autoimmune syndrome with loss of T cell tolerance, B cell defects, hypergammaglobulinaemia and autoantibody production [7-10]. In humans, recent findings illustrate the importance of Fas in the development of autoimmune and lymphoproliferative diseases [11,12]. Up till now, no common defects in the function or expression of the Fas antigen or FasL itself have been found in human SLE [13,14]. These findings do not imply, however, that apoptosis is normal in lupus patients. Lymphocytes from human SLE patients display an increased rate of spontaneous apoptosis \textit{in vitro} compared to lymphocytes of healthy donors and patients with rheumatoid arthritis [14,15]. The persistent occurrence of activated B and T cells even in quiescent disease \textit{in vivo} [16] points, however, to a decreased rate of apoptosis. These seemingly conflicting data can be explained by the occurrence of elevated levels of soluble Fas (sFas) in human SLE [17-21]. Soluble Fas results from alternative splicing and deletion of the transmembrane exon of the Fas molecule and is able to inhibit apoptosis [17,18]. Although the presence of elevated levels of sFas in SLE has been debated [22,23], we recently confirmed the data of Cheng and Jodo, showing increase in levels of sFas during active disease [24].

In this study we tested the hypothesis that elevated levels of sFas, even in quiescent SLE, contribute to the persistence of activated lymphocytes, by inducing a decreased rate of apoptosis. We monitored sFas and related sFas levels to disease activity and lymphocyte activation.

\section*{Materials and Methods}

\subsection*{Patients and controls}
Consecutive outclinic patients fulfilling at least four revised American College of Rheumatology (ACR) criteria for the diagnosis of SLE [25] could participate in this study. Patients who were pregnant or those who showed signs or symptoms suggestive of an infection at the moment of blood sampling were excluded. Eighteen healthy, age-matched, volunteers served as controls.

\subsection*{Study design}
Patients were seen at the outpatient department for clinical evaluation. Disease activity was scored and the SLE Disease Activity Index (SLEDAI) was calculated [26]. According to pre-defined criteria (table 1) it was decided whether or not the patient had a relapse of the disease [27]. Attention was paid to the occurrence of infections. Dosages of prednisolone and/or immunosuppressives were recorded. Blood samples were drawn in EDTA (Vacutainer; Becton Dickinson, Mountain View, CA) and heparin (Vacutainer, BD) between 8.30 and 10.00 a.m. to minimize circadian variations of circulating lymphocyte subsets. In case patients used corticosteroids medication was temporarily withdrawn for at
least 24 hours before blood sampling to exclude direct effects of corticosteroids. Samples were double-stained and analysed by flow cytometry (FACStar, BD). Plasma was stored at $-20^\circ$ C until needed for measurement of sFas. Blood samples from patients with a relapse were drawn before immunosuppressives were started.

**Table 1:**

*Criteria for major and minor disease exacerbations in SLE:*

Criteria for major exacerbation: fulfilling **one or more** of the following *:

1. **severe renal disease:**
   a. recent renal biopsy showing active proliferative lupus nephritis (>50% of glomeruli affected, and/or
   b. decrease of creatinin clearance of >25% within 4 months, accompanied by an active sediment (>5 ery's, h.p.f., and/or casts) and by proteinuria of >0.5 gram/day)
2. **severe central nervous system disease:** seizures, cerebral vascular accident, coma, transverse myelitis, psychosis, choreathetosis, central nerve palsy
3. **hematological disease:** hemolytic anemia (Hb<3.8 mmol/l) and/or thrombocytopenia (<50x$10^9$/l)
4. **severe serositis:** pericarditis with (impending) tamponade and/or massive pleural effusion
5. **uveitis and/or retinal vasculitis**
6. **myocarditis with arrhythmia and/or congestive heart failure**
7. **severe myositis with proximal muscle weakness**
8. **lung involvement with hemoptysis**
9. **major vasculitis:** with ulcerations and/or mononeuritis multiplex
10. **miscellaneous:** fever (>38°C rectally), serositis, hemolytic anemia (>3.8 mmol/l) or thrombocytopenia (>50x$10^9$/l), all without improvement after prednisolone in a maximum dosage of 30 mg/day during at least one week

Criteria for minor exacerbation: fulfilling **all** of the following items:

1. increase of activity index by $\geq$ 2 points within 6 months with a minimal activity score of 3 points accompanied by:
   2. the clinically judged necessity to start prednisolone at a dosage of at least 10 mg/day, or to increase the prednisolone dosage with $\geq$ 5 mg/day, or to start with anti-malarials, or immunosuppressive drugs, and:
   3. not fulfilling the criteria for a major exacerbation.

- Only features occurring within 2 weeks of the outclinic visit or admission under consideration are taken into account
Antibodies and staining procedure
Phycoerythrin (PE) or fluorescein isothiocyanate (FITC) conjugated monoclonal antibodies (MoAb) were used for staining blood samples (table 2). In brief, 10µl MoAb was added to 100 µl of whole blood as described [16]. After incubation for 15 minutes at room temperature in the dark, 2µl FACS-lysing solution (BD), diluted 1:10 in milipore water, was added. Samples were incubated for another 10 minutes and washed with phosphate buffered saline (PBS)/heparin. After the addition of 150 µl PBS/heparin, 10⁴ cells per sample were measured on a FACStar. Cells were gated for lymphocyte characteristics using both forward and right angle scatter, as well as a dual staining using CD14 and CD45 (Leukogate, BD) for 'back-gating'. In case of severe lymphopenia, a 'live-gate' was placed to obtain maximal results. Background red and green fluorescence was determined using combinations of CD20 (PE) with CD4 or CD8 (FITC) as a control for calculations in the CD4⁺ and CD8bright subsets respectively. As a control for calculations within the CD20⁺ subset, dual-staining for CD4 (PE) and CD20 (FITC) was used. Positive cells were determined by setting a region with reference to these controls. The list-mode data were analysed by the Lysis Stat software package (BD) for the calculation of percentages of populations. All analyses were performed consistently by the same person, without prior knowledge of the subjects' clinical status.

Measurement of anti-dsDNA antibodies and sFas
Anti-dsDNA antibodies were detected by Farr-assay using ¹²⁵I-labelled recombinant ds-DNA (Diagnostic Products Corporation, Los Angeles, USA) which is free of contamination with ssDNA. Farr assay was performed according to the manufacturer's instruction and positive samples were measured at different dilutions to obtain measurements within the range of the assay. Results of this assay were expressed in IU/ml using Wo/80 as the ultimate standard [28]. Normal value of this Farr-assay in our laboratory is < 10 IU/ml; intra- and interassay variations are both less than 10 %.

Soluble Fas was detected by sandwich ELISA as described [24]. The anti-human Fas specific monoclonal antibodies CLB-CD95/2 and CLB-CD95/6 that were used in this assay, had been generated by immunizing adult Balb/c mice with recombinant human Fas. In brief, microtitre plates (NUNC maxisorp, Nunc, Denmark) were coated with 100 µl/well CLB-CD95/2 (2 µg/ml) in 0.1 M NaHCO₃/Na₂CO₃ buffer (pH=9.6) overnight at room temperature. Coated plates were washed 5 times with 100 µl/well phosphate buffered saline (PBS) containing 0.02% Tween-20 (PBST). Samples and standards were diluted in high performance ELISA buffer (CLB, Amsterdam, The Netherlands) and 100 µl of each sample dilution was added to the plate. Next, 10 µl of a 10 µg/ml solution of biotin-labelled CLB-CD95/6 was added and the plate was incubated for 2 hours at room temperature. After washing (5 times with 100 µl/well PBST) 100 µl of streptavidine-polyHRP diluted 1:10.000 in PBS containing 2% whole milk was incubated for 30 minutes at room temperature. The plates were washed 5 times with 100 µl/well PBST and
developed with 100 µl substrate solution (0.1 mg/ml 3,5,3',5'-tetramethylbenzidine, Merck, Darmstadt, Germany), 0.003% H₂O₂ in 0.11 M NaAc (pH=5.5) for 10 minutes. The enzyme reaction was stopped by adding 100 µl 2 M H₂SO₄. Plates were read at 450 nm in a Titertek Multiscan reader (Labsystems Multiskan Multisoft, Helsinki, Finland). Background absorbance at 540 nm was subtracted. Intra- and interassay variations were 6.7% and 15.9%, respectively.

Table 2:

<table>
<thead>
<tr>
<th>mAb specificity</th>
<th>Label</th>
<th>Recognised subsets</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD45/CD14</td>
<td>FITC/PE</td>
<td>All leukocytes/monocytes ('leukogate')</td>
<td>BD</td>
</tr>
<tr>
<td>CD3</td>
<td>FITC</td>
<td>T cells</td>
<td>BD</td>
</tr>
<tr>
<td>CD4</td>
<td>FITC/PE</td>
<td>Helper/inducer T cells</td>
<td>MCA</td>
</tr>
<tr>
<td>CD8</td>
<td>FITC</td>
<td>Cytotoxic/suppressor T cells/NK cells</td>
<td>MCA</td>
</tr>
<tr>
<td>CD20</td>
<td>FITC/PE</td>
<td>B cells</td>
<td>MCA</td>
</tr>
<tr>
<td>CD25</td>
<td>PE</td>
<td>IL-2 receptor; activated T and B cells</td>
<td>BD</td>
</tr>
<tr>
<td>CD38</td>
<td>PE</td>
<td>Activated T and B cells</td>
<td>BD</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>PE</td>
<td>Activated T and B cells, and others</td>
<td>BD</td>
</tr>
</tbody>
</table>

BD, Becton Dickinson, Mountain View, CA; MCA, MCA Development BV, Groningen, The Netherlands. FITC, fluorescein isothiocyanate, PE, phycoerythrin.

Statistics

Differences between groups were calculated using the Student t-test (2-tailed). Correlations were determined by the Pearson correlation coefficient. P values less than 0.05 were considered significant.

Results

During the study period between January 1992 and June 1994, 25 patients (22 female, 3 male) and 18 controls (16 female, 2 male) were included. Their mean age was 34 (range 21-55) and 30 (19-45) years, respectively. SLE was diagnosed mean 9 years before entry of the study. Fourteen patients were analysed at the time of relapse. Five of the relapses were classified as major relapse and 9 as minor relapse. Further characteristics of the relapses are given in table 3. Eleven patients were analysed during quiescent disease. SLEDAI was increased in patients with active disease (p=0.002) and levels of anti-dsDNA tended to be higher (p=0.07). There were no differences in the use of prednisone or azathioprine between patients with quiescent or active disease (table 4). None of the patients was treated with cyclosporin or cyclophosphamide.
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Table 3:
Characteristics of 14 relapses in patients with systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of patients with symptom present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>major exacerbations (n=5)</td>
</tr>
<tr>
<td>renal disease</td>
<td>5</td>
</tr>
<tr>
<td>central nervous system disease</td>
<td>2</td>
</tr>
<tr>
<td>serositis</td>
<td>-</td>
</tr>
<tr>
<td>haematological disease</td>
<td>3</td>
</tr>
<tr>
<td>polyarthritis</td>
<td>1</td>
</tr>
<tr>
<td>skin involvement</td>
<td>1</td>
</tr>
<tr>
<td>fever</td>
<td>-</td>
</tr>
</tbody>
</table>

Soluble Fas
Levels of sFas in controls and patients are shown in figure 1. In controls (n=18) levels of soluble Fas were 628 ± 142 pg/ml (mean ± SD). Compared to controls, levels of sFas in patients with quiescent SLE were significantly higher (p=0.02, table 4). Soluble Fas levels were comparable between patients with quiescent disease and those with a minor relapse (866 ± 313 and 907 ± 443, respectively).

Table 4:
Levels of soluble Fas, leucocyte counts and percentages of lymphoid subsets in controls and clinically quiescent and active SLE patients

<table>
<thead>
<tr>
<th></th>
<th>controls (n=18)</th>
<th>quiescent disease (n=11)</th>
<th>active disease (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolon (mg/day)</td>
<td>3.9 ± 4.9</td>
<td>5.9 ± 6.4</td>
<td></td>
</tr>
<tr>
<td>Azathioprine (mg/day)</td>
<td>13.4 ± 37.7</td>
<td>15.4 ± 42.7</td>
<td></td>
</tr>
<tr>
<td>sFas (pg/ml)</td>
<td>628 ± 142</td>
<td>866 ± 313*</td>
<td>998 ± 375#</td>
</tr>
<tr>
<td>Leucocytes (x 10^6/ml)</td>
<td>6.8 ± 1.8</td>
<td>7.0 ± 5.6</td>
<td>5.1 ± 2.7</td>
</tr>
<tr>
<td>Lymphocytes (x 10^6/ml)</td>
<td>1.6 ± 0.45</td>
<td>1.4 ± 1.0</td>
<td>0.55 ± 0.36###</td>
</tr>
<tr>
<td>% CD4+HLA-DR+</td>
<td>5.2 ± 1.6</td>
<td>11.3 ± 6.6**</td>
<td>15.7 ± 11.5##</td>
</tr>
<tr>
<td>% CD4+IL-2R+</td>
<td>24.9 ± 7.9</td>
<td>34.1 ± 12.3*</td>
<td>39.4 ± 14.4##</td>
</tr>
<tr>
<td>% CD8+HLA-DR+</td>
<td>14.6 ± 8.7</td>
<td>23.1 ± 6.8**</td>
<td>29.2 ± 20.2#</td>
</tr>
<tr>
<td>% CD20+CD38+</td>
<td>58.0 ± 13.7</td>
<td>78.3 ± 15.7**</td>
<td>85.1 ± 11.5###</td>
</tr>
</tbody>
</table>

Mean ± SD values of different patient characteristics; corresponding p values were calculated by Student t-test. Percentages are expressed as percentages of total CD4+, CD8^{bright}, and CD20^{+} subpopulations. * p<0.05, ** p<0.01, comparison between controls and quiescent SLE. # p<0.05, ## p<0.01, ### p<0.001, comparison between controls and active SLE.
Levels of sFas in patients with a major relapse were higher (1160 ± 113), but this difference was not significant when compared to sFas levels in patients with a minor relapse or patients with quiescent disease (p=0.06). Between active (all minor and major relapses together) and clinically quiescent patients no differences in sFas levels could be observed. As sFas tended to increase with disease activity we looked for a correlation between sFas and the SLEDAI score (n=24). A correlation did exist (r=0.45, p=0.02), as shown in figure 2. This correlation was due to the relation between sFas levels and SLEDAI scores in patients with active disease (r=0.68, p=0.05).

**Figure 1:** Serum levels of soluble Fas in healthy controls (n=18), clinically quiescent SLE (n=11), and clinically active SLE represented as minor relapses (n=9) or major relapses (n=5).

**Analysis of lymphocyte subsets**

The number of leukocytes and lymphocytes did not differ between healthy controls (n=18) and SLE patients with quiescent disease (n=11), (table 4). The expression of activation markers on CD4\(^+\) T-lymphocytes (IL-2R, HLA-DR) and on CD8\(^+\) T-lymphocytes (HLA-DR) was increased. Also, percentages of activated CD20\(^+\) B-lymphocytes were higher in quiescent SLE compared to healthy controls. The number of lymphocytes in active disease was lower (p=0.003) compared to quiescent disease. No significant changes were detected in the percentages of activated B and T-lymphocytes between quiescent and active disease, although the expression of activation markers on all lymphocyte subsets further increased during active disease.

**Relation between sFas and lymphocyte activation**

As lymphocyte activation was increased in SLE and activated lymphocytes express Fas we sought for correlations between sFas levels and activation markers on lymphocyte
subsets. Levels of soluble Fas did not correlate with the number of leukocytes or lymphocytes. Neither did we find an association between the percentages of CD4+ IL-2R+ lymphocytes and levels of sFas nor between the percentages of CD4+HLA-DR+ lymphocytes and levels of sFas. Percentages of activated CD8+ lymphocytes did not correlate with levels of sFas. There was, however, a significant correlation between sFas levels and the percentages of CD20+CD38+ cells (r=0.47, p=0.009).

**Figure 2:** Correlation between levels of sFas and SLEDAI-scores in SLE patients (n=24), Pearson correlation coefficient = 0.45 (p = 0.01)

**Discussion**

We demonstrate that levels of sFas in patients with SLE are increased, even during quiescent disease. Levels of sFas correlated with disease activity scores and with the extent of activation of circulating B cells.

In several studies elevated levels of sFas in lupus patients have been reported [17-21]. Although other studies could not confirm these results [22,23], we recently also found increased levels of sFas in SLE [24]. In the present study, dealing with a group of SLE patients different from that studied previously [24], similar results were observed. Different affinities of antibodies generated with recombinant human Fas for catching native Fas may be responsible for the discrepancies in the published data concerning sFas levels in SLE patients. Furthermore, the existence of multiple forms of sFas cannot be excluded. Finally, patient selection and use of immunosuppressive drugs may have influenced results as corticosteroids lower levels of sFas [17]. In the present study this may have resulted in a masking of even more pronounced elevation of sFas, as patients with quiescent disease as well as those with active disease used immunosuppressives (table 4).

As Fas expression increases at the moment of lymphocyte activation [5,29] and sFas levels were found to be elevated in SLE patients we related sFas levels to disease activity and the percentages of activated peripheral blood lymphocytes. Indeed, a correlation
between sFas levels and SLEDAI-scores was observed, in agreement with the studies of Jodo et al and Tokano et al [19,20]. In our previous study we correlated SLEDAI-scores with sFas levels of individual patients, longitudinally monitored [24]. No association was found. This discrepancy can be explained by fluctuations of sFas levels in SLE patients in time independent of disease activity. Levels of sFas in controls were more stable in time (618 ± 98 pg/ml, mean ± SD) compared to patients with quiescent disease (809 ± 276 pg/ml). Indeed, when patients of the previous study were analysed during active disease separately, a correlation was found between sFas levels and SLEDAI-score (p=0.02, r=0.66, Pearson correlation coefficient). Other studies did not demonstrate an association between disease activity and sFas levels [21-23] and differences in genetic background were suggested to explain this discrepancy. As the genetic background of our patients (mainly Caucasian) was probably to that of the patients in the European studies mentioned before [21-23], other factors seem to be of influence. Particularly, differences in the assay used for the measurement of sFas may be relevant, which argues for standardisation of sFas assays.

Percentages of activated (CD38+) CD20+ B-lymphocytes in quiescent SLE were increased compared to normal controls. Also, the percentages of activated (IL-2R+, HLA-DR+) CD4+ T-lymphocytes were higher in quiescent SLE patients compared to controls. In patients with active disease percentages of CD4+HLA-DR+ T cells, CD8+HLA-DR+ T cells and CD20+CD38+ B cells were even higher although not statistically significant. This probably is due to the small number of patients studied, as in a previous study dealing with more data, significantly higher percentages of activated lymphocytes were observed in active disease compared to quiescent disease [16].

We found a correlation between sFas levels and activated B cells but not between sFas levels and percentages of activated T cells. The absence of a correlation between sFas levels and activation state of T cells might be explained by the fact that percentages of activated CD4+ and CD8+ T-lymphocytes were lower than that of B cells (table 4). Furthermore, a relation can be masked because most sFas is probably bound to membrane bound Fas ligand (or soluble Fas ligand) of which increased expression in activated T cells has been reported [30,31]. Finally, lymphocyte activation was assessed in the peripheral blood only, whereas the majority of activated lymphocytes that contribute to sFas production are localised in the extravascular compartment.

So far the significance of elevated sFas levels is unknown. Soluble Fas might play a pathophysiological role in the persistence of lymphocyte activation in SLE as it has been shown that sFas is functional and able to block Fas-mediated apoptosis [16,17].

Correlations between sFas levels and lymphocyte activation were sought because Fas expression and soluble Fas can be considered as markers of lymphocyte activation comparable with other cell-activation markers such as IL-2R as suggested by Ohsako et al [5]. Many of these markers are shed upon cell activation and can be detected in the circulation as soluble molecules [32-34]. For example soluble IL-2R levels are increased in SLE patients [32]. Increase of soluble Fas might also be the result from shedding of Fas which
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is upregulated on activated cells. Alternatively, sFas can arise by concomitant upregulation of the alternative splicing pathway on cell activation [17]. In this view Kovacs et al described one SLE patient out of 16 whose T cells secreted sFas lacking the transmembrane domain [18].

As B cells, particularly in SLE patients, are activated it might be assumed that the correlation between sFas levels and the percentage of activated B-lymphocytes found is a reflection of lymphocyte activation. A contributing role of sFas to persistence of B cell activation is suggested by our findings but needs further study.

In conclusion, this study shows that soluble Fas levels in SLE are increased and are correlated with disease activity as measured by SLEDAI. B and T cell subsets are activated even during quiescent SLE. Levels of sFas do correlate with percentages of activated B cells but not with that of activated T cell subsets. The exact role of soluble Fas is unknown and has to be elucidated. A prospective study in which, next to soluble Fas, also soluble FasL, lymphocyte activation, Fas and FasL expression and apoptosis are measured in relation to disease activity, will give further insight in the possibly disturbed balance of apoptosis in SLE.

References

Chapter III


Serum-soluble Fas in SLE


