ORIGINAL CONTRIBUTION

Follow Up Study on the Changes in the Clinical Features and Prognosis of Japanese Patients with Systemic Lupus Erythematosus During the Past 3 to 4 Decades

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Seven hundred and fifty four Japanese SLE patients were subdivided into the following 3 groups according to the year of diagnosis: Group A; 85 cases between 1955 and 1969, Group B; 322 cases between 1970 and 1979 and Group C; 347 cases between 1980 and 1990. The clinical features and prognosis were compared among the 3 groups. The number of SLE patients with persistent and/or profuse proteinuria, psychosis, unconsciousness, thrombocytopenia and other disorders in Group C was less than that of Groups A and/or B. The number of cases treated with steroids, immunosuppressants, non-steroidal antiinflammatory drugs, antihypertensive drugs in Group C was less than that of Groups A and/or B. However, the number of cases treated with pulse therapy and plasmapheresis in Group C was more than that of Groups A and/or B. The mortality rate of SLE, especially due to uremia, significantly decreased from Group A to Group C. Five-year and 10-year survival rates in Group C were 95.2% and 93.4%, respectively, revealing a significantly more favorable prognosis than that of the other groups. J Epidemiol, 1993; 3:19-27.

SLE, prognosis, treatment, diagnostic criteria, causes of death

During the past three decades, the prognosis of systemic lupus erythematosus (SLE) has been significantly improved. Changes in the clinical features and causes of death have also been observed¹⁻⁵, especially after the proposal by the American Rheumatism Association (ARA) in 1971 for diagnostic criteria. Recent improvement in the survival rate was most likely due to the changes in the diagnostic criteria, general medical care and specific therapies directed against SLE¹⁻⁵. Presumably, changes in the clinical features and prognosis of SLE have continued even after the establishment of ARA’s 1982 revised criteria. This study was conducted to investigate whether or not the clinical features and prognosis have indeed been changing in the past decade.

PATIENTS AND METHODS

The study group consisted of 754 SLE patients fulfilling four or more of the revised ARA criteria⁶ and who were diagnosed by our Internal Medicine Department during the period from 1955 to 1990. The diagnosis of SLE was established for each patient by at least 3 independent observers. In all cases, the diagnosis and treatment procedures were conducted during the period when the use of steroids and immunosuppressive agents prevailed. Patients were subdivided into 3 subgroups according to the year of diagnosis, those diagnosed as SLE between 1955 and 1969 were designated as Group A, those diagnosed between 1970 and 1979 were designated as Group B and those diagnosed between 1980 and 1990 were designated as Group C. Comparisons were made by computerized

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analysis of clinical manifestations, laboratory and immunological findings, treatments, complications, causes of death and prognosis between the 3 groups. The computer data bank held a total of 287 items, which included 176 items on clinical symptoms, manifestations and treatments, and 111 items on routine and immunological laboratory examinations and findings. For each case, items that described the patient’s findings prior to the initial visit and annually after the initial visit were stored into the computer. Since the possibility existed for the total number of clinical findings recorded for the patient to be dependent on the duration of the follow up, the clinical and laboratory examinations and findings and the treatments within 5 years of diagnosis and through the actual observation period were compared among the 3 groups.

Proteinuria was defined as a protein concentration more than 0.5 g/day, and profuse proteinuria as more than 3.5 g/day. Patients with SLE who underwent renal biopsy were also classified into 6 types according to their histological findings. These 6 types were (1) minimal change (MC), (2) focal proliferative glomerulonephritis (FGN), (3) diffuse proliferative GN (DPGN), (4) membranous GN (MGN), (5) membranoproliferative GN (MPGN), characterized by a widespread thickening of the glomerular capillary loops with hypercellularity of the mesangial and endothelial cells, and (6) advanced stage, characterized by involvement of all or nearly all glomeruli with a significant glomerular scar. Central nervous system involvement (CNS lupus) included grand mal seizures, cranial nerve signs, hemiparesis, unconsciousness, transverse myelopathy and psychiatric manifestations.

Antinuclear antibodies (ANA) were assayed by immunofluorescent technique using rat liver as the substrate (negative < x 10 dilution of sera) before 1987 and Hep 2 cells (negative < x 40) thereafter. Anti-DNA antibodies were examined using the DNA spot test after 1966 and the Farr assay was employed to measure anti-dsDNA antibody levels (normal < 10 U/ml) after 1974. The immunoglobulin classes and complement fixation of anti-dsDNA were detected by indirect immunofluorescence and complement fixation methods, respectively, using Crithidia luciliae kinetoplasts as the substrate. A double immunodiffusion method was used to detect precipitating antibodies to soluble nuclear antigens. Rabbit thymus extract was prepared as reported and used in the detection of antibodies to U1-RNP, Sm, SS-B, PCNA and Ki.

Table 1. Analysis of 754 patients with SLE.

|                        | A         | B         | C         | Total |
|------------------------|-----------|-----------|-----------|-------|
| The years of Diagnosis | 1955-1969 | 1970-1979 | 1980-1990 |       |
| Number of Patients     | 85        | 322       | 347       | 754   |
| Sex                    |           |           |           |       |
| Male                   | 5 (6)     | 22 (7)    | 31 (9)    | 58 (8) |
| Female                 | 80 (94)   | 300 (93)  | 316 (91)  | 696 (92) |
| Age at Diagnosis       |           |           |           |       |
| < 9                    | 3 (4)     | 1 (1)     | 2 (1)     | 6 (1)  |
| 10-19                  | 24 (28)   | 63 (20)   | 61 (26)   | 148 (20) |
| 20-29                  | 36 (42)   | 144 (45)  | 108 (31)  | 288 (38) |
| 30-39                  | 15 (18)   | 75 (23)   | 90 (26)   | 180 (24) |
| 40-49                  | 6 (7)     | 30 (9)    | 57 (16)   | 93 (12) |
| 50-59                  | 0         | 6 (2)     | 20 (6)    | 26 (3)  |
| 60-                    | 1 (1)     | 3 (1)     | 9 (3)     | 13 (2)  |
| Period of Observation (years) | 0.3-20.0 | 0.3-20.0 | 0.3-10.0 | 0.3-20.0 |
| Range                  | 0.3-20.0  | 0.3-20.0  | 0.3-10.0  | 0.3-20.0 |
| Mean                   | 11.9      | 9.4       | 5.4       | 8.0    |
| Duration from Initial Manifestations to Diagnosis of SLE (months) | 21.1±37.0 | 30.1±47.2 | 34.5±51.6 | 31.0±48.0 |

( ) %

1,2) and 3) There are significant differences (P<0.03), when compared with frames (A, B and C) having the same number.
Guinea pig liver extract was used as the source of antigen to detect antibodies to SS-A.

Concerning pulse therapy, 500-1,000 mg of methylprednisolone was administered intravenously for 3 days. Azathioprine and cyclophosphamide were administered for more than 3 months at 1-2 mg/kg/day. Concerning plasmapheresis, double filtration plasmapheresis was used. Two and a half liters of plasma were treated during each procedure. During a period of 2 to 4 weeks, this procedure was performed on each patient at least four times.

Significant differences were determined with the Fisher exact test and was set at corrected $P(P_c)<0.05$ after the P value was multiplied by three because of multiple comparison. Determination for the prognosis of SLE was obtained with the life table method. 

### RESULTS

#### Changes in Clinical Manifestations

Table 1 shows the analysis of 754 patients with SLE according to the year of diagnosis, difference in gender, age at diagnosis, period of observation and duration from initial manifestations to diagnosis. Group A consisted of 85 cases, Group B consisted of 322 cases and Group C consisted of 347 cases. Although gradual decrease in the ratio between male and female SLE patients were observed from Group A to Group C, there was no significant difference. Concerning age at diagnosis, there were significantly fewer patients in the 20's in Group C than in Group B, and significantly more in the 40's in Group C than those in Group B. The average period of observation was 11.9 years in Group A, 9.4 years in Group B and 5.4 years in Group C.

| Clinical manifestations                  | Within 5 years after diagnosis | Through the actual observation period |
|-----------------------------------------|--------------------------------|--------------------------------------|
|                                         | A 1955-1969 (n = 85) | B 1970-1979 (n = 322) | C 1980-1990 (n = 347) | A 1955-1969 (n = 85) | B 1970-1979 (n = 322) | C 1980-1990 (n = 347) |
| Fever (> 37.5°C)                         | 85%² | 83%² | 68%² | 88%¹ | 88%² | 70%² |
| Malar rash                               | 84¹ | 73² | 69² | 85 | 76 | 70 |
| Alopecia                                 | 4² | 63² | 44² | 48 | 66² | 46² |
| Purpura                                  | 9 | 16 | 8 | 9 | 20 | 9 |
| Erythema (exclude malar rash)            | 68 | 62 | 53 | 68 | 65² | 54² |
| Urticaria                                | 1¹ | 4² | 19² | 2¹ | 14² | 24² |
| Oral ulcer                               | 18² | 37² | 42² | 25² | 42² | 44² |
| Leg ulcer                                | 1 | 4 | 2 | 4 | 10² | 3² |
| Digital gangrene                         | 1 | 3 | 1 | 2 | 5² | 1² |
| Arthralgia                               | 74² | 91¹ | 85 | 84¹ | 94² | 82² |
| Aseptic bone necrosis                    | 1² | 10² | 7 | 5 | 14 | 8 |
| Myalgia                                  | 31 | 34² | 22² | 36² | 62² | 24² |
| Muscle weakness                          | 1² | 2² | 7² | 2 | 3² | 8² |
| Lymphadenopathy                          | 38 | 35² | 24² | 41¹ | 39² | 26² |
| Edema                                    | 48² | 45² | 32² | 60² | 55² | 36² |
| Heart murmur                             | 25² | 19² | 7² | 33² | 23² | 9² |
| Abnormal ECG                             | 39 (26/66) | 31 (38/279) | 33 (75/229) | 49 (39/79)¹ | 38 (113/294) | 32 (82/254)² |
| Pleuritis                                | 15 | 12 | 7 | 18 | 15² | 8² |
| Acute abdomen                            | 4 | 3 | 1 | 8² | 7² | 1² |
| Hepatomegaly                             | 3¹ | 13² | 7² | 36² | 15² | 7² |
| Psychosis                                | 19 | 23 | 16 | 26 | 29² | 17² |
| Unconsciousness                          | 4 | 3 | 1 | 12² | 7 | 3² |
| Abnormal ocular fundus                   | 38 (9/24) | 20 (12/59) | 22 (18/81) | 45 (17/37)¹ | 38 (23/85) | 17 (18/97)¹ |
| Hemolytic anemia                         | 3 (2/68)¹ | 8 (22/289) | 14 (39/271)¹ | 6 (5/78) | 11 (33/298) | 15 (42/286) |

¹,² There are significant differences ($P_c<0.03$), when compared with frames (A, B and C) having same number.

(·): (positive number/total number tested)
C, but there was no significant difference among the 3 groups.

The changes in clinical manifestations of SLE assessed through comparative analysis are shown in Table 2. There were significantly fewer cases of fever, malar rash, alopecia, purpura, myalgia, lymphadenopathy, edema, heart murmur and hepatomegaly in Group C both within 5 years of diagnosis, and through the actual observation period, compared with Groups A and/or B. On the other hand, the number of patients with urticaria, oral ulcer and muscle weakness was significantly higher in Group C than in Groups A and/or B both within 5 years of diagnosis and through the actual observation period. The number of cases with hemolytic anemia was significantly higher in Group C than in Group A within 5 years of diagnosis, but not through the actual observation period. On the contrary, the number of cases with abnormal ECG, pleuritis, acute abdomen, psychosis and unconsciousness was significantly lower in Group C than in the other 2 groups through the actual observation period, but not within the 5-year period after diagnosis.

Changes in laboratory and immunological findings

As shown in Table 3, the number of cases with lymphocytopenia and anti-DNA antibodies was significantly higher in Group C than in Groups A and/or B, both within 5 years of diagnosis and through the actual observation period. However, the number of cases with IgG class anti-dsDNA, complement fixing of anti-dsDNA and positive serological test for syphilis (STS) in Group C was significantly lower than in the other 2 groups, both within 5 years of diagnosis and through the actual observation period. A significant decrease in the number of cases with low hemoglobin levels, leukocytopenia, thrombocytopenia, hypergammaglobulinemia, positive CRP and anti Ki antibodies was observed in Group C through the actual observation period.

Changes in lupus nephritis are revealed in Table 4. The number of cases with intermittent proteinuria and urine casts was significantly higher and the number with persistent proteinuria was significantly lower in Group C than in the other groups, both within 5 years of diagnosis and through the actual observation period. A significantly lower number of cases with profuse proteinuria was observed in Group C than in Group A through the actual observation period. On the other hand, the number of cases with MC in the renal histological findings was significantly lower in Group C than in Groups A and/or B, both within 5 years of diagnosis and through the actual observation period.

| Laboratory and serological findings | Withing 5 years after diagnosis | Through the actual observation period |
|------------------------------------|----------------------------------|--------------------------------------|
| A 1955-1969 n=85                      | B 1970-1979 n=322                | C 1980-1990 n=347                     |
| Low Hb (<12.0 g/dl)                  | 52% (1)                          | 69% (1)                              | 61% (1)                              |
|                                   | 67% (2)                          | 79% (2)                              | 64% (2)                              |
| Leukopenia (<4000)                  | 53 (1)                           | 60 (1)                               | 56 (1)                               |
|                                   | 68 (2)                           | 75 (2)                               | 63 (2)                               |
| Lymphopenia (<1500)                 | 9 (1)                            | 15 (1)                               | 20 (1)                               |
|                                   | 32 (2)                           | 47 (2)                               | 80 (2)                               |
|                                    | 45 (1)                           | 62 (1)                               | 85 (1)                               |
| Thrombocytopenia (<100)             | 9 (1)                            | 15 (1)                               | 20 (1)                               |
|                                   | 33 (2)                           | 33 (2)                               | 18 (2)                               |
| Hyper γ-globulinemia (≥1.5 g/dl)    | 52 (1)                           | 60 (1)                               | 54 (1)                               |
|                                   | 64 (2)                           | 73 (2)                               | 60 (2)                               |
| CRP                                | 63 (1)                           | 62 (1)                               | 61 (1)                               |
|                                   | 74 (2)                           | 73 (2)                               | 63 (2)                               |
| Anti-DNA                           | 21 (1)                           | 44 (2)                               | 79 (2)                               |
|                                   | 36 (2)                           | 65 (2)                               | 81 (2)                               |
| IgG class anti-dsDNA               | 29 (1)                           | 53 (2)                               | 34 (2)                               |
|                                   | 50 (2)                           | 51 (2)                               | 35 (2)                               |
| CF of anti-dsDNA                   | 7 (1)                            | 23 (2)                               | 10 (2)                               |
|                                   | 8 (2)                            | 19 (2)                               | 10 (2)                               |
| Anti-Ki                            | 50 (1)                           | 24 (2)                               | 11 (2)                               |
|                                   | 50 (2)                           | 25 (2)                               | 12 (2)                               |
| STS                                | 14 (2)                           | 20 (2)                               | 9 (2)                                |
|                                   | 16 (2)                           | 20 (2)                               | 9 (2)                                |

CF: complement fixation, STS: serological test for syphilis.

1,2) There are significant differences (Pc<0.03), when compared with frames (A, B and C) having same number.

( ) : (positive number/total number tested)
Table 4. Changes in lupus nephritis.

| Urinalysis and histological findings | Within 5 years after diagnosis | Through the actual observation period |
|--------------------------------------|---------------------------------|--------------------------------------|
|                                      | A 1955-1969 | B 1970-1979 | C 1980-1990 | A 1955-1969 | B 1970-1979 | C 1980-1990 |
| proteinuria                          | n = 85     | n = 322    | n = 347    | n = 85     | n = 322    | n = 347    |
| negative                             | 9%        | 10%        | 14%        | 7%        | 8%        | 12%        |
| intermittent                         | 19         | 35(2)      | 47(2)      | 19         | 36(2)      | 47(2)      |
| persistent (< 3.5 g/day)             | 53(1)     | 40(2)      | 27(2)      | 51(1)     | 39(2)      | 28(2)      |
| profuse (≥ 3.5 g/day)                | 19        | 16         | 12         | 24(1)     | 16         | 12(1)      |
| urine casts                          | 57(1)     | 64(2)      | 76(2)      | 62(1)     | 76         | 80(2)      |

Renal biopsy

|                                      | n = 24 | n = 90   | n = 34    | n = 30 | n = 104  | n = 38   |
|--------------------------------------|--------|----------|----------|--------|----------|----------|
| minimal change                       | 58%(1) | 38%(1)   | 15%(1)   | 15%    | 35%(2)   | 5%(3)    |
| focal GN                             | 8      | 10       | 21       | 7      | 10       | 18       |
| diffuse proliferative GN             | 13     | 22       | 41       | 17     | 25       | 40       |
| membranous GN                       | 8      | 12       | 9        | 10     | 14       | 13       |
| membranoproliferative GN            | 4      | 16       | 15       | 10     | 15       | 16       |
| advanced                             | 8      | 2        | 0        | 7      | 2        | 0        |

GN: glomerulonephritis,

1,2) There are significant differences (P < 0.03), when compared with frames (A, B and C) having same number.

PSL: prednisolone, NSAIDS: non-steroidal antiinflammatory drugs,

Table 5. Changes in treatments in SLE.

| Treatments                  | Within 5 years after diagnosis | Through the actual observation period |
|-----------------------------|---------------------------------|--------------------------------------|
|                             | A 1955-1969 | B 1970-1979 | C 1980-1990 | A 1955-1969 | B 1970-1979 | C 1980-1990 |
| Steroids                    | n = 85      | n = 322     | n = 347     | n = 85      | n = 322     | n = 347     |
| no                          | 11%         | 6%          | 10%         | 5%          | 4%          | 10%         |
| PSL < 39 mg/day             | 75          | 64          | 62          | 72          | 65          | 62          |
| PSL 40-59 mg/day            | 8           | 15          | 11          | 12          | 16          | 12          |
| PSL ≥ 60 mg/day             | 6           | 14          | 16          | 12          | 15          | 16          |
| pulse therapy               | 1(1)        | 5(2)        | 12(2)       | 2(1)        | 7(2)        | 14(2)       |
| Immunosuppressants          | 18          | 23          | 18          | 32          | 31(2)       | 26(2)       |
| azathioprine                | 6           | 16          | 14          | 13          | 20          | 15          |
| 6-mercaptoprione            | 8(1)        | 2(1)        | 1(1)        | 13(1)       | 3(1)        | 13(1)       |
| cyclophosphamide            | 4           | 3           | 2           | 6           | 5           | 3           |
| others                      | 0           | 1           | 1           | 0           | 2           | 2           |
| Plasmapheresis              | 2           | 3(2)        | 10(2)       | 4           | 7           | 12          |
| Hemodialysis                | 1           | 1           | 1           | 4           | 3           | 1           |
| NSAIDS                      | 42(1)       | 74(2)       | 59(2)       | 53(1)       | 82(2)       | 62(2)       |
| Anti-hypertensive drugs     | 21          | 30          | 24          | 31          | 44(2)       | 28(2)       |

1,2) There are significant differences (P < 0.03), when compared with frames (A, B and C) having same number.
Changes in Treatment of SLE

Changes in the treatments are shown in Table 5. The number of cases treated with pulse therapy was significantly greater in Group C, while the number of cases treated with non-steroidal anti-inflammatory drugs (NSAIDS) was significantly lower in this group when compared to Groups A and/or B, both within 5 years of diagnosis and through the actual observation period. The number of cases treated with plasmapheresis in Group C was significantly higher than in Group B, within 5 years of diagnosis, but not through the actual observation period. The number of cases in which steroid therapy was not used was significantly higher in Group C, while the number of cases treated with immunosuppressants and antihypertensive drugs was also significantly lower in this group when compared to Group B through the actual observation period.

Changes in Mortality Rate and Causes of Death

Changes in mortality rate in accordance with the causes of death are shown in Table 6. The mortality rate of SLE significantly decreased from Group A to Group C, with the lowest mortality rate for uremia, infection, pneumonitis and malignancy in Group C. The survival curve of SLE patients for Groups A, B and C is shown in Figure 1. The five-year survival rate was 71.8% in Group A, 91.3% in Group B, and 96.0% in Group C. The 10-year survival rate was 63.8% in Group A, 84.0% in Group B, and 93.4% in Group C, revealing a more favorable prognosis for Group C.

**DISCUSSION**

Recently, the concept of SLE has changed from a usually rapid fatal disease to a chronic illness with a favorable prognosis. Many investigators have studied
the prognostic factors of SLE. A poor prognosis has been reported among blacks\textsuperscript{11-13}, men\textsuperscript{14}, children\textsuperscript{14}, older individuals\textsuperscript{13,15} and those of low socioeconomic status\textsuperscript{16}. However, the reason for recent improvement in the prognosis of SLE has not yet been clearly defined. We reported in 1982, that there were changing patterns in the clinical features and prognosis of SLE\textsuperscript{22}. At that time, the 1982 revised criteria for classification of SLE were proposed. These revised criteria were found to be 96% sensitive and 96% specific when tested with SLE and control patient data, showing an increase in sensitivity when compared with that of the 1971 preliminary criteria (88% sensitive)\textsuperscript{6}. Presumably, changes in the clinical features and prognosis of SLE would have continued in spite of the establishment of ARA’s 1982 revised criteria. The findings of the present study revealed considerable improvement in the prognosis of SLE with a 5-year survival rate of 96.0% and a 10-year survival rate of 93.4% in conjunction with the changing clinical features and causes of death. Although many factors were thought to have contributed to the above mentioned changes, one seemed to be the changes in the diagnostic criteria used by our hospital, which consisted of the Medical Research Council criteria\textsuperscript{17} utilized before 1971, preliminary criteria for classification of SLE\textsuperscript{19} utilized between 1971 and 1981, and the 1982 revised criteria\textsuperscript{6} utilized after 1982. Of course, all of the SLE patients in this study fulfilled 4 or more of the ARA’s 1982 revised criteria, but there may have been some bias in the selection process of the SLE patients.

In this study, it was observed that the number of SLE patients in the 40’s age group increased, while those in the 20’s age group decreased significantly during the past decade. Age of diagnosis might have influenced the prognosis of SLE. Since it is possible that the total number of clinical findings obtained in a patient depends on the duration of the follow up, the changing patterns were studied comparatively among the 3 groups, both within 5 years of diagnosis and through the actual observation period. In the past decade, SLE patients with representative clinical manifestations including fever, malar rash, alopecia, arthralgia, lymphadenopathy, STS, etc, have been decreasing, both within 5 years of diagnosis and through the actual observation period. On the contrary, SLE patients with urticaria, oral ulcers, lymphopenia and anti-DNA antibodies have been increasing. Concerning lupus nephritis, SLE patients with persistent and/or profuse proteinuria have been decreasing considerably, even though, patients with intermittent proteinuria and urine casts have been increasing suggesting an increase in cases with mild lupus nephritis. At the same time, patients with IgG class anti-dsDNA and complement fixation of anti-dsDNA, which were associated with active lupus nephritis\textsuperscript{19-21}, were less in Group C than in Groups A and/or B. The significant decrease in the positive rate of these antibodies might be related to the increase in patients with mild lupus nephritis. However, the number of cases with MC in the renal histological findings was significantly lower in Group C than in Group A or B, both within 5 years of diagnosis and through the actual observation period. Although the patients in which renal biopsies were performed in Group C were limited because of the low percentage of the biopsied cases in this group, there were no significant differences when the number of the cases with MC and FGN which was thought to give a better prognosis\textsuperscript{22}, was compared among the 3 groups.

Furthermore, in the past decade, the number of SLE patients with CNS lupus including psychosis, unconsciousness and abnormal ocular fundus, profuse proteinuria, abnormal ECG, pleuritis, acute abdomen, thrombocytopenia, anemia, hypergammaglobulinemia, and anti-Ki antibodies have been decreasing in Group C through the actual observation period, but not within the 5-year period after diagnosis. These items mentioned above may be related to the poor prognosis in Groups A and/or B. Reveille et al.\textsuperscript{13} noted that thrombocytopenia emerged as the only independent risk factor for worsening the prognosis of SLE. However, SLE patients with intractable diseases, including profuse proteinuria and CNS lupus, in the past decade did exist. In fact, CNS lupus has the highest mortality rate among the causes of death in Group C although this group had a low mortality rate for uremia. Ichikawa et al.\textsuperscript{3} who analyzed the causes of death for SLE from 1981 to 1983, reported that the cause of death due to CNS involvement has significantly decreased in comparison to previous years, but noted that the cause of death due to cerebral vascular accident (CVA) has been increasing. The length of time involved in the treatment is also implicated in the cause of death from SLE. For example, long-term treatment for SLE increases the risk of developing myocardial infarction and/or CVA due to arteriosclerosis. Death due to malignancy was observed in 5 patients of Groups A and B. It was not clear whether the use of immunosuppressants or aging was related to the development of malignancy. The incidence of malignancy may tend to increase in the future. A notable finding was that the cause of death due to uremia declined remarkably in Group C. Concerning lupus nephritis, nephrotic syndrome, DPGN, high chronicity indices, hypertension and childhood onset of nephritis were associated with a poorer outcome\textsuperscript{14,23}. In this study, the number of cases with
profuse proteinuria and treated with anti-hypertensive drugs was significantly lower in Group C. Furthermore, there were no cases at an advanced stage of lupus nephritis and only one case was treated with hemodialysis in this group. These results may reflect the fact that there were fewer severe lupus nephritis cases in Group C less than in the other 2 groups.

It was also observed that the mode of treatment has been changing. In the past decade, the number of SLE patients treated without steroids, immunosuppressants, NSAIDS and antihypertensive drugs has increased. On the other hand, patients treated with pulse therapy and/or plasmapheresis, which have been introduced as a new therapeutic strategies for intractable lupus patients, have also increased. These changes appear to be reflected directly in an increase in the number of milder SLE cases without arthralgia, myalgia, psychosis, unconsciousness, persistent and/or profuse proteinuria and are due to the selection of the most appropriate treatments with less adverse reactions for severe cases of SLE. One of the reasons why the mortality rate due to uremia declined remarkably over the past decade might have been the use of pulse therapy and/or plasmapheresis treatment for intractable lupus nephritis. However, there are some differences in the mode of treatment between Japan and other countries. For example, in Japan, antimalarials are prohibited and immunosuppressants are usually used sparingly. Plasmapheresis is covered with medical insurance issued by the Japanese government for patients with intractable lupus nephritis and CNS lupus. On the other hand, plasmapheresis is not usually used in foreign countries. Furthermore, it was also noted that there was a difference in the frequency of clinical manifestations between SLE patients in Japan and other countries (24-25). Studenski et al. (16) claimed significant independent effects in racial and socioeconomic status for the survival of SLE. The Japanese population consists largely of a homogeneous race. Furthermore, the expense of medical care for SLE patients has been supported and covered by the Japanese government since 1972. Consequently, it is possible that the factors contributing to the improvement of prognosis in SLE varies from country to country. Recently, SLE has become a well-known disease in Japan and development of diagnostic procedures, including the establishment of diagnostic criteria, social recognition and improvement in general medical care have also possibly contributed to the improvement of prognosis.

In conclusion, the prognosis of SLE patients who were diagnosed during the past decade has considerably improved in conjunction with an increase in the incidence of milder SLE cases. The use of pulse therapy and plasmapheresis might also be related to the favorable prognosis of SLE during the past decade.

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