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Glucocorticoid Therapy in Systemic Lupus Erythematosus – Clinical Analysis of 1,125 Patients with SLE

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1. Introduction

Systemic lupus erythematosus (SLE), which is an inflammatory disease of unknown cause, is a representative autoimmune disease. Although SLE has multisystem organ involvement with a predilection for females, the disease varies from mild to severe and/or from active to inactive. The severity and activity of the disease affect SLE prognosis [1]. Glucocorticosteroids (steroids) have anti-inflammatory and immunosuppressive effects, although the biological effects of steroids are multiple. The anti-inflammatory effect of steroids is powerful and acts rapidly, and the immunosuppressive effect after administration of large doses of steroids is also strong. Therefore, steroids play a major and essential role in the treatment and management of SLE patients, especially those having severe and active SLE. However, the effectiveness and usefulness of steroids are limited because of their severe side effects, unresponsiveness and resistance to steroids. In these situations, additional therapies such as immunosuppressive agents or plasmapheresis, etc. are usually used in conjunction with steroids.

This paper will present clinical data related to steroid therapy from 1,125 patients with SLE who were examined and treated in Juntendo University Hospital between 1955 and 2002. It will show the benefits and risks of treatment with steroids and/or combined therapy with steroids and immunosuppressants.

2. Clinical presentation of 1,125 patients with SLE

2.1. Clinical findings

One thousand one hundred and twenty-five SLE patients fulfilling four or more of the revised ACR (American College of Rheumatology) criteria [2] were examined and treated at

the Department of Internal Medicine and Rheumatology in Juntendo University School of Medicine between 1955 and 2002. In all patients, the diagnosis and treatment procedures were conducted during a period when the use of steroids and immunosuppressive agents was common. Computerized analysis of clinical manifestations, laboratory and immunological findings, treatments, complications, causes of death and prognosis was conducted.

The distribution of age at diagnosis and the difference in gender, showing that mean age at diagnosis was 27.1 years old and the male to female ratio was 1:9. In children and adults over the age of 50, the incidence of SLE demonstrated only a slight female predominance, however, for those in their twenties, thirties and forties, close to 90% of patients were women. The frequencies of major clinical manifestations and laboratory findings from observations together with the data from other investigators [3-6] are shown in Table 1.

Manifestations	Harvey, et al. [4] 105 cases 1954	Dubois, et al. [5] 520 cases 1964	Pistiner, et al. [6] 464 cases 1991	Hashimoto, et al. 1125 cases 2002
I. Systemic				
fever	86	84	41	79
weight loss	71	51	-	-
adenopathy	34	59	10	28
II. Musculoskeletal				
arthritis/arthralgia	90	92	91	89
myalgias	-	48	79	31
aseptic bone necrosis	-	5	5	10
III. Cutaneous-vascular				
butterfly area lesions	39	57	34	70
alopecia	3	21	31	48
photosensitivity	11	33	37	40
discoid lesion	-	29	23	17
urticaria	7	7	4	25
oral/nasal ulcer	14	9	19	42
subcutaneous nodules	10	5	-	5
Raynaud's phenomenon	10	18	25	48
IV. Renal				
proteinuria/abnormal sediment	65	46	31	95
nephrotic syndrome	-	23	14	17
V. Cardiopulmonary				
cardiomegaly	15	16	-	-
pericarditis	45	31	2	7
myocarditis	40	8	12	2
heart murmur	44	20	12	14
Libman-Sacks valvitis	32	-	1	(10/45) 22
hypertension	14	25	25	38
pleurisy	56	45	31	11
lupus pneumonitis	22	1	6	4
pulmonary hypertension	-	-	-	(11/487) 2
VI. Nervous system				
psychosis	19	12	5	21
seizures	17	14	6	8
peripheral neuritis	-	12	5	7
cytoid bodies	24	10	4	(8/63) 13

Manifestations	Harvey, et al. [4] 105 cases 1954	Dubois, et al. [5] 520 cases 1964	Pistiner, et al. [6] 464 cases 1991	Hashimoto, et al. 1125 cases 2002
VII. Gastrointestinal				
abdominal pain	10	19	1	5
ascitis	-	11	-	2
peritonitis	-	-	-	1
hepatomegaly	-	-	-	11
splenomegaly	-	-	-	4
VIII. Laboratory findings				
anemia	78	57	30	63
hemolytic anemia	-	-	8	11
leukopenia	-	43	51	62
thrombocytopenia	26	7	16	34
elevated IgG	-	-	-	(634/1011) 63
elevated IgM	-	-	-	(438/1010) 43
elevated IgA	-	-	-	(154/1010) 15
low CH50	-	-	-	(660/1025) 64
low C3	-	-	39	(712/ 940) 76
low C4	-	-	-	(659/ 939) 70
false positive STS	15	11	-	(78/ 510) 15
anti-cardiolipin antibody	-	-	38	(177/ 349) 51
lupus anticoagulant	-	-	-	(151/349) 43
LE cell	82	82	42	(448/957) 47
antinuclear antibody	-	-	96	97
anti-DNA antibody	-	-	40	(645/935) 69
anti-U1RNP antibody	-	-	14	(314/876) 36
anti-Sm antibody	-	-	6	(645/935) 20
anti-SSA antibody	-	-	19	(371/814) 46
RAHA test	-	-	-	(308/739) 42
RAPA test	-	-	-	(195/557) 35
RA test	-	-	-	(352/908) 39

Table 1. Cumulative percentage incidence of clinical and laboratory manifestations in SLE

2.2. Treatment according to disease severity

Clinical subsets of SLE were divided into three groups according to disease severity that related to prognosis [7]. They were severe, moderate and mild diseases. Severe disease included organ-threatening conditions: lupus nephritis; rapidly progressive glomerulonephritis (RPGN), diffuse proliferative glomerulonephritis (DPGN), nephrotic syndrome, neuropsychiatric lupus (NPLe); acute confusional state or organ brain syndrome,

while pulmonary manifestations included acute lupus pneumonitis, alveolar hemorrhage, etc. Moderate disease: lupus nephritis without renal failure, pleuritis, pericarditis, meningitis, hemolytic anemia, thrombocytopenic purpura, etc. Mild disease: arthralgia/arthritis, myopathy, skin rash, etc.

Nonsteroidal anti-inflammatory drugs	800/1125 (71%)
Steroids (initial dose of steroids) (n=1125)	
no	99 (9%)
PSL \leq 39mg/day	769 (68%)
PSL 40-59mg/day	133 (12%)
PSL \geq 60mg/day	124 (11%)
Pulse therapy	171 (15%)
Immunosuppressants	300/1125 (27%)
azathioprine	160 (53%)
6-mercaptoprine	26 (9%)
cyclophosphamide	70 (23%)
mizoribin	32 (11%)
others	12 (4%)
Plasmapheresis	105/953 (11%)
Hemodialysis	25/1125 (2%)

PSL:prednisolone

PSL \leq 39mg/day was used for patients with mild or moderate diseases.

PSL 40-59mg/day was used for patients with moderate or severe diseases.

PSL \geq 60mg/day was used for patients with severe diseases. Pulse therapy was used for patients with severe diseases followed by large doses of steroids.

Table 2. Treatments of 1125 SLE patients

Treatments including steroids and immunosuppressive agents are shown in Table 2. Steroids were a mainstay of treatment for SLE. Although there are several kinds of steroids, prednisolone (PSL) is commonly used to treat SLE. The initial dose of steroids was usually determined according to the severity and activity of the disease. The above severe diseases required large doses of steroids usually of 1 mg/kg/day of PSL or more. Sometimes steroid pulse therapy (methylprednisolone 0.5-1g/day, intravenously administration, for 3days) was used followed by large doses of steroids. The above moderate to mild diseases usually required 0.5-1mg/kg/day and less than 0.5mg/kg/day of PSL, respectively. When a satisfactory response was achieved, the daily dose was reduced by 5 to 10% over 2 or 3 weeks until reaching a maintenance dose of 0.2 to 0.3mg/kg/day.

Steroids have sometimes little or no effect because of impaired bioavailability due to reduced steroid absorption, increased steroid metabolism, induction of activating protein 1(AP-1) which is mutually antagonistic with steroid receptors for trans-activation effects [8], and insensitive steroid-mediated apoptosis of T cells [9], etc. Furthermore, steroids characteristically have a high risk of serious side effects such as infection, gastric ulcer, diabetes mellitus, osteoporosis, etc. Therefore, the effectiveness and usefulness of steroids were limited because of severe side effects, unresponsiveness and resistance to steroids. In

these situations, immunosuppressive agents such as cyclophosphamide, azathioprine, mizoribine, tacrolimus and/or plasmapheresis or other innovative therapies were usually used in conjunction with steroids. Recently, belimumab (anti-BLyS antibody), the first targeted biological drug, was approved for treatment of SLE by the FDA [10]. Targeted biological and small-molecule therapies in SLE are going to begin to take the place of steroids that have been used as the major drug in SLE for more than 50 years.

2.3. Prognosis and causes of death

In this paper, the survival rate was 93% at 5years, 89% at 10years and 69% at 20years after diagnosis. One hundred and fifty-one out of 1,125 patients (13%) died. The causes of death were renal failure (30%), cerebrovascular diseases (23%), infection (19%), and others. Infections which led to causes of death included sepsis or bacteremia due to *E. coli*, methicillin resistant *Staphylococcus aureus* (MRSA), candidiasis, asprgilosis, *Klebsiella*, *Pseudomonas*, etc., and tuberculosis, pneumocystis carini pneumonia, *Cryptococcus meningitis*, listeria meningitis, cytomegalovirus infection, etc. In the last 2 or 3 decades it has been noted that the prognosis of SLE has improved [11-13]. Changes in the mortality rate in accordance with the cause of death in SLE patients were also observed, showing a significant reduction in death due to renal failure.

3. Steroid therapy in principal organ involvement in SLE

3.1. Lupus nephritis (LN)

3.1.1. Clinical analysis of LN

LN is one of the diseases influencing the prognosis of SLE. The diseases of LN vary from mild to severe and from active to inactive. The clinical pictures of LN and the types of the World Health Organization (WHO) classification according to histopathological findings [14] in this study are shown in Table 3.

Persistent proteinuria of more than 0.2g/day and less than 3.5g/day was observed in approximately 37% of cases and profuse proteinuria of more than 3.5g per day was observed in approximately 17% of cases. Patients without proteinuria accounted for 16%. Abnormal urinary sediments including erythrocytes, leukocytes and casts were observed frequently. An increasing serum creatinine level was observed in 41% of cases. The WHO classification according to histopathological findings of LN by renal biopsy was used in this study, although the classification of LN by the International Nephrology/Renal Pathology Society (ISN/RPS) was proposed in 2003[15]. Diffuse proliferative glomerulonephritis (DPGN) of Type IV, which has a poor prognosis, could be seen in 55 of 216 cases (25%), which underwent renal biopsy. Membranous glomerulonephritis (MGN) of Type V characteristic of nephrotic syndrome, was observed in 18% of cases. Types I and II, which are thought to have better prognosis, were observed in 23% and 16% of cases, respectively. Advanced Type VI, which indicates end stage GN, could be seen in 12% of cases.

A. Urinalysis, Renal function	n=1125 (%)
No proteinuria	176 (16)
Proteinuria	949 (84)
Intermittent	431 (45)
Persistent	354 (37)
Profuse (>3.5g/day)	164 (17)
Microhematuria	1066 (95)
Urine casts	838 (74)
Elevated BUN	659/1063 (62)
Elevated S-creatinine	429/1047 (41)
B. Histopathological findings (WHO classification)	n=216 (%)
I. Minimal change (MC) or Normal	49 (23)
II. Mesangial alteration	34 (16)
III. Focal segmental glomerulonephritis (FGN)	35 (16)
IV. Diffuse proliferative glomerulonephritis (DPGN)	55 (25)
V. Membranous glomerulonephritis (MGN)	39 (18)
VI. Advanced	4 (12)

Table 3. Lupus nephritis in 1125 cases

3.1.2. Treatment of LN

The available therapeutic procedures include steroids, immunosuppressive agents, plasmapheresis, anticoagulants and hemodialysis, etc. Steroids were the first choice for treatment of LN. However, doses of steroids were determined according to urinary findings, renal function and renal histopathological findings evaluating the activity and severity of LN. The patients with active and /or severe LN, including persistent or profuse proteinuria, renal dysfunction, DPGN of type IV, rapidly progressive glomerulonephritis (RPGN) or MGN of Type V in conjunction with low serum complement levels and high titers of anti-dsDNA antibodies, were initially treated with large doses of steroids (PSL 1-1.5mg/kg/day) as induction therapy for remission. Steroid pulse therapy was often administered at first. It led to more rapid recovery which might be result of a rapid nongenomic physicochemical effect. The patients with intermittent proteinuria, abnormal urine sediments, and Type II or III, were initially treated with PSL less than 0.5-1mg/kg/day. After PSL administration for 3-6 weeks, the dosage of PSL was then reduced by nearly 10% every 2–3 weeks according to the improvement in proteinuria, urinary sediments, abnormal renal function, low serum complement levels and high titers of anti-dsDNA antibodies. If PSL had no or incomplete response, the dosage was increased by 20% or steroid pulse therapy was conducted again. In the patients with DPGN or RPGN, intravenous pulse therapy of cyclophosphamide (IVCY) (500-750mg, monthly for 3 to 6 months), as immunosuppressive agent, was used. Alternative induction therapies included combined therapies with steroids and immunosuppressive agents such as daily oral cyclophosphamide, azathioprine, tacrolimus, mizoribine, and cyclosporine, etc. If an incomplete response after 2 months treatment with

PSL alone was also observed, immunosuppressant agents were administered in addition to PSL. If the patients had high titers of anti-dsDNA antibodies and/or immune complexes, plasmapheresis was conducted in conjunction with the above steroid and immunosuppressant agent treatment. In patients who achieved remission showing less than 0.5g/day of proteinuria, inactive urine sediment, normal complement levels and /or quiescent extrarenal lupus activity, they continued maintenance treatment with a maintenance dosage of steroids of PSL 5–15mg/day. Thereafter, the PSL dosage was tapered to discontinuance in an extremely gradual manner.

3.1.3. Outcome and prognosis of LN

During the past half century, the prognosis of SLE has significantly improved. One of the major factors in this improvement is the significant reduction in renal death. This is assumed to be partially due to early diagnosis and early treatment with the development of diagnostic procedures, as well as the development of treatments including the implementation of hemodialysis [1,11-13]. However, the remission rate of lupus nephritis was not so high.

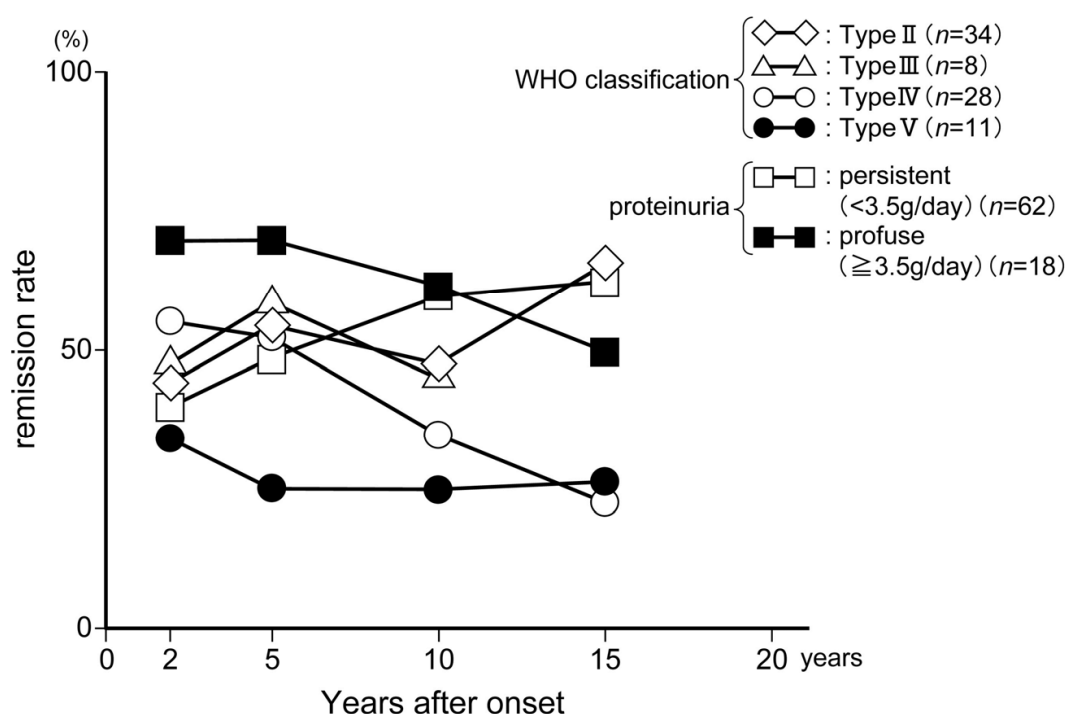


Figure 1. Remission rate of lupus nephritis according the WHO classification type and degree of proteinuria

Figure 1 shows the remission rate after onset according to the WHO classification type and degree of proteinuria. The remission rates of patients with Type IV (DPGN) and profuse proteinuria or nephrotic syndrome tended to decrease during the course of the disease, while the remission rates of patients with Type II and persistent proteinuria tended to increase. Patients with Type V (MGN) had a low remission rate through out the course of

the disease, but no decrease in the remission rate was observed until later on. Furthermore, in the outcome of 32 patients who were treated over the long-term for over 20 years, the complete remission rate was 27%, the incomplete remission rate was 37.8%, and the worsening rate was 21.6 %. As for the treatments used, those that contributed to remission could not be specified. This fact suggests that the underlying disease types had a greater influence on the remission rate than the treatment method.

3.2. Neuropsychiatric manifestations of SLE (NPLE)

3.2.1. Clinical analysis of NPLE

The frequencies of various neuropsychiatric manifestations of SLE (NPLE) have been reported to vary from 28 to 59%. In our study, NPLE could be observed in 47.6% of 1,125 cases as shown in Table 4.

Total SLE patients	1125
The number of patients with NPLE	535 (48%)
1. Neurological manifestations	
1) seizure, unconsciousness	146 (13%)
2) cerebrovascular disease	158 (14%)
3) neuropathy, cranial	45 (4%)
4) myelopathy	45 (4%)
5) aseptic meningitis	45 (4%)
6) peripheral neuropathy	79 (7%)
7) headache	101 (9%)
2. Neuropsychological syndromes	236 (21%)

Table 4. Frequencies of neuropsychiatric manifestations (NPLE) in 1125 lupus patients

The American College of Rheumatology (ACR) proposed new criteria for the classification of neuropsychiatric syndrome of systemic lupus erythematosus (NPSLE) in 1999 [16]. NPLE is divided into psychiatric and neurological manifestations. The frequency of psychiatric manifestations was higher than that of neurological manifestations. The former included acute confusional state or organ brain syndrome, cognitive dysfunction, anxiety disorders and psychosis, etc., while the latter included seizure, cerebrovascular disease, myelopathy, aseptic meningitis, headache, and peripheral neuropathy, etc.

Although no single pathogenetic process could explain all these manifestations, it was assumed that other potential causes of these manifestations, such as side effects from treatment, complications including infections, etc., had been excluded except for causes due to lupus itself. Many NPLE cases were considered to be caused by lupus itself, excluding obvious causes such as antiphospholipid antibody syndrome (APS), necrotizing angitis, and complications.

NPLE is one of the diseases that influence the prognosis of SLE as well as LN. Especially, patients with acute confusional state or organ brain syndrome (OBS), cognitive dysfunction, recurrent seizure, and cerebrovascular disease, etc., had poor prognosis. Acute OBS exhibits characteristic malfunctions such as consciousness disorders (i.e. delirium), disorientation, memory disorders, and cognitive dysfunction. Acute OBS showed an 85% correlation with SLE activity and exacerbation, which was greater than that of the psychiatric illness group (57%) and the psychosyndrome group (23%) [17].

Although acute OBS was correlated with active SLE lesions, correlations with high titers of anti-dsDNA antibodies and low complement levels, which were seen in active LN, were not necessarily observed. Serologically, acute OBS correlated with the serum anti-liposomal P antibody, interferon α and IL-6 in cerebrospinal fluid (CSF) [18-19].

On the other hand, acute neurologic syndrome has been reported to correlate with the anti-asialo GM1 antibody, anti-liposomal P antibody, anti-lymphocyte antibody, and anti-neurocyte antibody, as well as the anti-PCNA antibody and anti-Sm antibody [7,20].

Psychiatric symptoms often required differentiation from steroidal psychiatric symptoms. Differentiation from secondary psychiatric symptoms due to uremia and/or infection was also important. Although quite a number of cases were difficult to determine, the following information might have been helpful:

- a. The actual incidence of steroid-induced psychosis is small, probably about 5%, which is less than that of lupus-induced psychosis [21].
- b. The psychiatric side effects of steroids include, most commonly, mild to moderate mood changes such euphoria, sleeplessness, or depression rather than unconsciousness disorders, although there are also perceptual changes, hallucinations, anxiety, insomnia and confusion.
- c. Steroid-induced psychosis appears half a month to one month after administration of steroids. It has been reported that the incidence of steroid-induced psychosis increases when over 40mg/day of PSL is administered [22].
- d. Although lupus psychosis may not always be improved by increasing of the dosage of PSL, deterioration of lupus psychosis after increasing the dosage of PSL is rare.
- e. High levels of IgG index and IL-6 in CSF can be seen in lupus psychosis [23].

The evaluation of NPLE should always include an assessment of whether SLE is active or not. In addition, patients with both focal and diffuse syndromes should have various examinations including CSF, electroencephalogram (EEG), and an imaging studies (such as computed tomography (CT) and magnetic resonance imaging (MRI)), cerebral blood flow by angiography or single photon emission computerized tomography (SPECT), etc. The more serious the NPLE, the more aggressive immunosuppressive therapy, including steroids, is needed.

3.2.2. Treatment of NPLE

If NPLE was active and there was severe major organ involvement, steroid therapy was indicated. In particular, patients with an acute confusional state or organic brain syndrome,

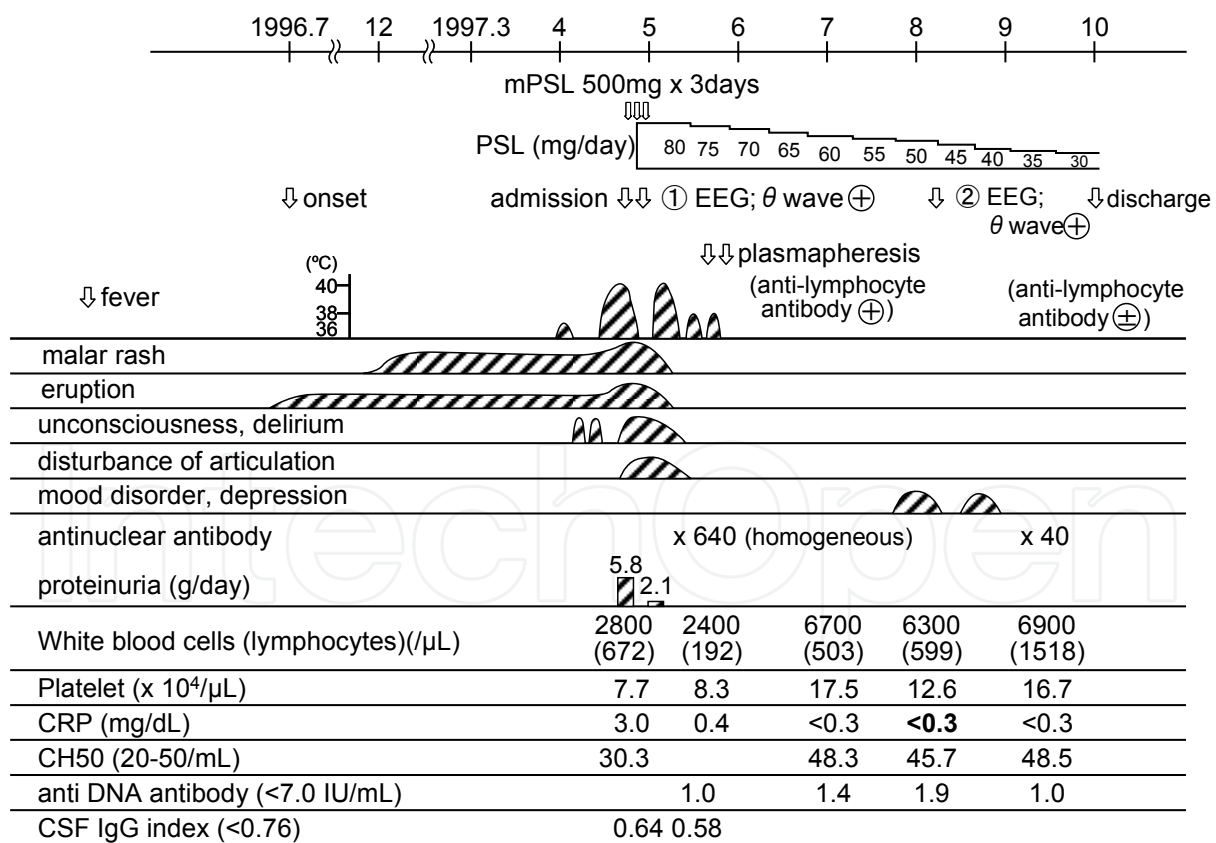
and recurrent convulsive seizures were treated with high steroid doses (PSL 1–2 mg/kg/day) in conjunction with steroid pulse therapy. However, when improvement could not be seen within 48 hours after treatment, 250 to 500mg of hydrocortone was administered every 12 hours. If improvement could not be seen after treatment of steroids alone, IVCP pulse therapy or oral administration of CP in conjunction with steroids and/or plasmapheresis was given.

When signs of clinical manifestations were stable for more than 6 weeks and acute phase reactants or tests of organ function were improved or stable for 6 weeks, the dose of PSL was reduced by approximately 10 to 20% every two weeks. When the dose of PSL reached about 15mg/day, it was slowly tapered and reduced by 1mg every week.

When the patients showed panic or marked agitation and their hallucinations and delusions were threatening, several antipsychotic drugs in conjunction with steroids were also used.

3.2.3. Outcome and prognosis of NPLe

Almost all patients with NPLe improved after immunosuppressive therapies including steroids, immunosuppressive drugs and /or plasmapheresis.



PSL: prednisolone, mPSL: methylprednisolone, EEG: electroencephalogram, CSF: cerebrospinal fluid.

Figure 2. The clinical course of SLE patient (46 years old, female) with organic brain syndrome (OBS)

Figure 2 shows the clinical course of an SLE patient with OBS who was a 46-year old female. She was diagnosed as SLE with malar rash, eruption, leucopenia, thrombocytopenia, proteinuria and positive anti-nuclear antibodies, etc. in March 1997. In April 1997, she had recurrent unconsciousness with delirium, disturbance of articulation with high fever and a worsening malar rash. Although anti-DNA antibodies and low complementemia could not be seen, she was diagnosed as OBS or acute confusional state and treatment with steroid pulse therapy followed by a PSL dose of 80mg/day. Plasmapheresis was also conducted to remove anti-lymphocyte antibodies. Although mood disorder and depression were observed in August, 1997, her disease improved without increasing doses of steroids or additional treatment with immunosuppressive agents.

As for prognosis of lupus patients with NPLE according to the different treatment, patients treated with combined therapy of steroid pulse therapy and other therapies was significantly more favorable than those treated with steroids alone (PSL>40mg/day) and those treated with combined therapy of immunosuppressive agents and steroids.

3.3. Pulmonary manifestations

3.3.1. *Pleuritis*

Pleuritis is by far the most common pulmonary manifestation, occurring at some time in the course in 40 to 50% of lupus patients. However, the frequency of pleuritis in Japanese SLE patients was lower than that in European countries and the United States. The frequency of pleuritis was 11% in this study. . Clinically, fever, chest pain, cough, dyspnea etc. could be seen in patients with pleuritis. On chest X-rays, slight to moderate pleural effusion caused by pleural inflammation could be observed bilaterally in approximately half of cases.

Pleuritis mostly improved after administration of PSL (20-40mg/day). However, in cases with a large amount of pleural effusion , thoracic drainage was needed.

3.3.2. *Interstitial pneumonitis*

Lupus pneumonitis is classified as acute lupus pneumonitis and chronic interstitial pneumonitis/pulmonary fibrosis. Acute lupus pneumonitis was relatively rare with an occurrence of 0.5–11.7% [24-25]. It was observed in 6 of 1,125 patients (0.5%) in this study. As clinical symptoms, fever, chest pain, dry cough, severe dyspnea, and occasional hemoptysis were noted. Bibasilar Velcro rales were noted in all instances. The majority of patients were hypoxic, requiring supplemental oxygen or intubation for assisted ventilation. Acute lupus pneumonitis was diagnosed by several examinations including X-ray, CT scan, KL-6 and/or SP-D as biomarkers, and various kinds of infectious examination to exclude infectious diseases.

All 6 patients with acute lupus pneumonitis were treated with steroid pulse therapy following 1-2mg/kg/day of PSL. Half of the patients drastically improved, but the remaining

3 patients died of pulmonary hemorrhage despite combined therapy with steroid and immunosuppressant agents and /or plasmapheresis.

Chronic interstitial pneumonitis in SLE is also rare, showing a low frequency of 3-5%. Six patients with chronic interstitial pneumonitis were observed in this study and they were treated with maintenance therapies including low doses of steroids and/or immunosuppressant agents. In one patient, chronic interstitial pneumonitis deteriorated to acute interstitial pneumonitis during the course of the disease and a large dose of steroids was needed.

3.3.3. Alveolar hemorrhage

Alveolar hemorrhage in SLE is relatively rare, and it has been reported to occur in 1.4–1.7% of SLE patients in Europe and the United States [26].

It is a serious complication and results in poor prognosis. It was observed in 8 out of 1,125 patients (0.7%) in this study.

SLE patients with alveolar hemorrhage had hemoptysis and hypoxemia and rapid progression of anemia in conjunction with active LN and/or NSLE disease.

All patients with alveolar hemorrhage were treated with steroid pulse therapy following large doses of PSL, but it was also necessary to concomitantly use other immunosuppressive therapies such as cyclophosphamide including IVCY, and plasmapheresis. Unfortunately, all of the patients with alveolar hemorrhage died, confirming that the prognosis was very poor.

3.4. Cardiac manifestations

3.4.1. Pericarditis

The most common cardiac abnormality was pericarditis, which occurred in 8-25% [27], but it was relatively rare in Japan, with a frequency of 7% (47 out of 1,125 cases) in this study. Pericarditis is often one of the first manifestations. Most of the cases with pericarditis improved with administration of PSL 0.5–1 mg/day, but cases with cardiac tamponade, which was rare in this study, needed large doses of PSL over 1mg/day and/or steroid pulse therapy.

3.4.2. Myocarditis

Myocarditis was rarely observed in 2% in this study. In cases with myocarditis, positive CRP, elevated CK, IgG class anti-dsDNA antibodies, hematuria, etc., in conjunction with tachycardia, cardiac enlargement, congestive heart failure could often be observed. A myocardial biopsy was performed in order to confirm the diagnosis in one patient. The patients with myocarditis associated with congestive heart failure were treated with large-dose administration of steroids (PSL 1–1.5 mg/kg/day, divided into 3~4 dosages). All of the patients with myocarditis improved after steroid therapy.

3.4.3. Myocardial infarction and coronary artery disease

Coronary artery disease due to arteriosclerotic changes is more common in SLE patients. Death from myocardial infarction late in the course of the disease is one of the most frequent causes of death after 10 to 30 years of SLE [28]. Eleven lupus patients with myocardial infarction could be seen in this study. The average age at diagnosis of SLE was 37 years old (26–63 years old), and the average age at development of myocardial infarction was 51 years old (41–66 years old) in these patients. There were two death cases, including one case of death from cardiac rupture.

Several risk factors that cause myocardial infarction due to atherosclerosis in SLE are considered. They are renal involvement, hypertension, hyperlipidemia, long-term administration of steroids, diabetes mellitus, anti-phospholipid syndrome, smoking, etc. In this study, 4 patients had hypertension, hyperlipemia and diabetes mellitus as risk factors. Furthermore, positive antiphospholipid antibodies were observed in 5 cases. Death from myocardial infarction due to inflammation of the coronary arteries has been reported in SLE patients dying early in the course of their disease, but this is a rare event [28].

Regarding the treatment in this study, conservative medical management without large doses of steroids was used in most cases. PTCA and AC bypass procedures were also occasionally conducted.

3.5. Intestinal vasculitis

Acute abdomen caused by intestinal vasculitis is often observed. Occasionally, surgery is needed. According to a report by Zizic, et al. [29], acute abdomen was observed in 15 of 140 cases, and caused death in 53% of cases. Vasculitis was observed in 9 of 11 cases with abdominal surgery, and intestinal perforation was observed in 6 cases. In this study, 4 patients had intestinal vasculitis and 3 died of intestinal perforation. Intestinal bleeding and peritoneal bleeding due to vasculitis were often observed. In cases with mesenteric arteritis, acute abdomen with severe abdominal pain in conjunction with nausea/vomiting, diarrhea, ascites, gastrointestinal bleeding, and fever, etc., were observed. Those symptoms may be masked by steroids or immunosuppressive drugs used for treatment, thus resulting in a delayed diagnosis.

Patients with intestinal vasculitis and/or mesenteric arteritis were treated with large dose steroids including steroid pulse therapy.

When a rapid improvement was not obtained, intermittent IVCY therapy was simultaneously used. In cases associated with bowel infarction or perforation, treatment for infection was also needed.

3.6. Hematologic manifestations

Hematologic manifestations in SLE include normochromic-normocytic anemia caused by chronic inflammation, autoimmune hemolytic anemia (AIHA), iron-deficiency anemia,

leukocytopenia, lymphocytopenia, thrombocytopenia, thrombocytopenic purpura (TP), thrombotic thrombocytopenic purpura (TTP), and antiphospholipid syndrome (APS), etc. The diseases, which needed high doses of steroids were AIHA, TP, and TTP.

3.6.1. AIHA

AIHA was observed in 11% of patients in this study. AIHA is rare in Japanese SLE patients in comparison to those in Europe and the United States. Steroids were the mainstay of the treatment for AIHA and a response was achieved in about 75% of patients. PSL was given initially at a dose of 1.0 to 1.5 mg/kg and continued at that level for at least 4 to 6 weeks. Following a satisfactory response, the dose was reduced gradually by 10% every week. The reticulocyte count was a reliable indicator of both responsiveness to treatment and relapse. In cases of severe fulminant hemolysis, steroid pulse therapy was conducted. Patients with AIHA who failed to respond to steroids were treated with immunosuppressant agents and/or splenectomy. Plasmapheresis, high-dose intravenous gammaglobulin therapy (IVIg), and danazole were also used for some refractory cases.

3.6.2. TP

Thrombocytopenia lower than 150,000 was observed in 34% of cases in this study. However, thrombocytopenia lower than 50,000 was relatively rare, and it occurred in approximately 10% of cases. Thrombocytopenia in SLE is usually due to antiplatelet autoantibodies (platelet associated-IgG; PA-IgG, platelet binding-IgG; PB-IgG). In some cases, thrombocytopenia was associated with antiphospholipid antibodies. In rare case, so-called Evans syndrome, in which AIHA and TP coexist, was observed. Some cases did not tend to bleed until platelet counts were less than 20,000/ul. Patients with thrombocytopenia less than 20,000 were treated with large doses of steroids. The initial dose of PSL was usually 1-2 mg/kg/day. After an increase in platelet count occurred in response to steroids, the dose was gradually reduced after 4 weeks. If thrombocytopenia did not respond to steroids with bleeding from the major organs such as gastrointestinal tract, kidney, bladder, other mucosal surface, steroid pulse therapy was used. IVIg was useful to achieve a temporary improvement in thrombocytopenia in surgical operations such as splenectomy, which was often conducted in steroid resistant cases. In steroid resistant cases, immunosuppressive drugs such as azathioprine, cyclophosphamide, and cyclosporine, danazol, and vincristine, etc., were also used.

3.6.3. TTP

TTP usually consists of a pentad of TP, microangiopathic hemolytic anemia, fever, renal failure, and neurologic manifestations. TTP has been reported in association with various other diseases, including SLE, most of which are characterized by some degree of vasculitis of the small vessels and circulating immune complexes [30]. The main cause of acquired TTP including SLE is assumed to be an autoantibody that is an inhibitor (IgG inhibitor) of von Willebrand factor cleaving protease [31]. It has been clarified that congenital TTP is caused

by a mutation in the *ADAMTS-13* gene of cleaving protease. TTP must be differentiated from DIC or catastrophic antiphospholipid syndrome, but coexistence of both are often observed.

Regarding treatment, plasmapheresis using fresh frozen plasma, and transfusion therapy of normal plasma are used. In addition, large-doses of steroids including steroid pulse therapy, immunosuppressive drugs, IVIg therapy, and anti-platelet drugs, etc. are simultaneously used.

3.7. Pregnancy and birth

When an SLE patient wished to conceive and give birth, a medical determination as to whether pregnancy would be possible was considered. Basically, there were presumed to be almost no problems in pregnancy when the patient was in remission with a maintenance dosage of steroids, and when serious organ failure was not observed. Moreover, even if the patient had active disease, pregnancy was allowed after the disease improved with treatment.

3.7.1. Treatment and management during pregnancy

It was important for the physician and the gynecologist to be in close communication for the treatment and management during pregnancy. Usually, it was unnecessary to change the maintenance dose of the steroid during pregnancy. When mild deterioration was observed in the early stage of pregnancy, an increased steroid dosage was attempted according to the clinical manifestations. If the clinical manifestations required administration of a large-dose of steroids, considering the risks to the mother and the effect of the steroids on the fetus, an artificial abortion was performed at an early stage. Although the level of serum cortisol in the fetus decreases during the steroid administration, cortisol secretion and response to ACTH are believed to remain normal [32]. If a mother is treated with prednisolone or hydrocortisone, these steroids are assumed to have a minimal effect on the fetus because they are inactivated by 11- β -dehydrogenase in the placenta. However, the use of dexamethasone and betamethasone is avoided because these steroids are difficult for the enzyme to inactivate and were assumed to have an adverse effect on the fetus.

3.7.2. Treatment and management during and after delivery

3.7.2.1. Prevention of exacerbation

The mother was hospitalized prior to the expected delivery date for management of the mother and fetus. If pregnancy remained steady, and SLE activity was not observed, the dose of steroids was increased immediately after delivery to prevent any exacerbation of SLE. The dose of steroids was usually increased to two or three times the pre-delivery dose. The dose was reduced by 10% every 4 to 7 days while confirming no exacerbation, and continually observed until eventually reducing it to the dosage at the time of delivery. If an exacerbation of SLE such as active LN or serositis was observed in the late stage of

pregnancy, the delivery of the fetus was attempted as early as possible in order to start treatment of the mother's clinical manifestations.

3.7.2.2. Breast-feeding

Because the amount of steroids was increased upon delivery, breast-feeding was prohibited until the dose was reduced to less than 20 mg of PSL, considering the rate of transfer of steroids (0.1–0.3%/day) to the mother's milk [33].

3.8. Adverse effects and complications due to steroid treatment

Side effects of prolonged treatment with oral steroids are well known. Changes in the physical appearance could usually be seen. They were acne, hirsutism, moon face, buffalo hump, obesity, and abdominal striae, etc. Although reversible with a discontinuation or reduction in dose, hypertension, peptic ulcer, diabetes mellitus, pancreatitis, osteoporosis, psychosis, etc. were also induced. Thinning of the skin, cataracts, glaucoma, osteoporosis, and osteonecrosis could be observed as irreversible side effects.

Infections were major complications in SLE and one of the major causes of death. Susceptibility to infection, particularly bacterial infection, was increased with steroid use. Staples et al. found that the infection rate in hospitalized patients increased from 0.43 to 1.63 per 100 hospital days with an increase in steroid dose from zero to more than 50mg/day [34]. Although infection rarely occurs with a small dose of PSL (2–10 mg/day), the SLE patients treated with PSL of more than 20mg/day have a higher risk of infection due to the higher dose of PSL, especially after 14 days of administration. PSL was also noted to be a major risk factor for the development of opportunistic infection, with the most common organisms including *Salmonella*, *Candida*, *Strongyloides*, and *Aspergillus.sp* according to a case controlled study of 797 SLE patients [35].

It has been noted that systemic administration of steroids could be linked to the higher occurrence of vascular diseases such as coronary artery disease, stroke, peripheral vascular disease than the expected occurrence in SLE. However, it is unclear whether this reflects pro-atherogenic effects of the underlying disease process or adverse metabolic effects associated with steroid use [36]. Recently, the number of patients with complications such as myocardial infarction/angina pectoris, cerebral infarction, diabetes mellitus, hypertension, and aseptic bone necrosis, has tended to increase over a long-term observation period due to a favorable SLE prognosis.

Table 5 shows the frequencies of these complications at the time of occurrence in 97 SLE patients who had been observed for over 20 years. The number of patients with myocardial infarction/angina pectoris, diabetes, cerebral infarction increased from the ninth year of the observation period. Hypertension and aseptic osteonecrosis were seen from the onset of SLE. Most of the above complications were thought to be due to treatment including steroids, as well as aging. It was also noted that GC-associated damage accumulated over time to constitute most of the damage at 15 years, although disease –activity related damage occurred early [37].

Years after diagnosis (yrs)	1-2	3-4	5-8	9-12	13-16	17-20	>21
Myocardial infarction				1			3
Angina pectoris			1		1		2
Diabetes mellitus				3	1	3	5
Cerebral infarction				1	3	3	4
Hypertension	10	9	5	8	4	5	10
Aseptic osteonecrosis	1	3	5	1	4	3	3

yrs: years, number: cases

Table 5. Frequencies of complications related to vascular diseases according to the year (s) of the occurrence in 97 SLE patients who had been observed for over 20 years

Steroid use contributes significantly to risk of osteoporosis in women with SLE. Ramsey-Goldman et al. surveyed the frequency of fractures and associated risk factors in 702 women with SLE who had been followed for 5951 person-years and found that fractures occurred in 12.3% of patients, an almost fivefold increase compared with a background population [38]. Older age at diagnosis and longer duration of steroid use were important variables. Sinigaglia, et al. reported that osteoporosis in 22.6% of 84 premenopausal patients with SLE according to bone mineral density (BMD) was observed, and both disease duration and glucocorticoids were associated risks [39]. Steroid-induced osteoporosis leading to fracture, particularly vertebral collapse, was a major problem.

Aseptic osteonecrosis (AON) was observed in approximately 10% of SLE, with the femoral head being a common site. It also appeared in the femoral condyle, caput humeri, proximal end and distal end of the tibia, etc.. It has been suggested that increased doses of steroids (especially in the first year of treatment) and the duration of steroid therapy are correlated with a greater risk of AON in SLE patients [40]. In a prospective survey of SLE patients with administration of high-dose steroids (more than 30 mg/day of PSL for more than one month), AON occurred in 15% (9/62 patients) and the average period from the administration of a large dose of steroids to onset of AON was 640 days [41].

4. Conclusion

In this paper, steroid therapy for SLE based on the clinical analysis of 1,125 cases, especially for principal organ involvement that required large doses of steroids, was evaluated. Although there is no doubt that steroids contribute to a significant improvement in the prognosis in SLE, the effectiveness and usefulness of steroids are limited because of severe side effects, unresponsiveness and resistance to steroids.

Now, new biological agents that target B cells, T-B cell interaction, co-stimulatory pathways, intracellular molecules, etc. are being developed and are going to begin to revolutionize nonspecific therapy to a more specific pathophysiological therapy in SLE.

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