Assessment of Damage in Korean Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the prevalence of systemic damage in Korean patients with systemic lupus erythematosus (SLE) and to elucidate associations between possible risk factors and the presence of damage.

Methods. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) was used to quantify systemic damage in 588 patients who were enrolled consecutively at the Hospital for Rheumatic Diseases, Seoul, South Korea. The frequencies and means of each variable were compared using the chi-square test or Student t test between the presence and absence of damage. Multivariate models were used to investigate the relationship between possible risk factors (age, disease duration, and use of intravenous cyclophosphamide) and the presence of damage.

Results. Among the 588 patients, 244 (41.5%) exhibited damage at a mean of 54 months after onset of disease. The musculoskeletal (14.3% of patients) and renal (13.3%) systems were involved most frequently, followed by neuropsychiatric (10.7%), ocular (4.6%), and pulmonary (4.1%) system involvement. The presence of damage was associated with higher age, longer disease duration, and a high frequency of intravenous cyclophosphamide use.

Conclusion. Systemic damage in at least one of the items of the SDI was present in 41.5% of our Korean patients with SLE, this damage being significantly more prevalent in patients who were older, had longer disease duration, and received more intravenous pulses of cyclophosphamide. (First Release Mar 15 2007; J Rheumatol 2007;34:987–91)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a multisystemic inflammatory disease, with a course characterized by periods of flare and remission[1]. Recently, there has been remarkable improvement in patients' survival due to earlier diagnosis, recognition of mild forms of the disease, and better approaches to therapy[1]. However, the increase in life expectancy means that patients with SLE are faced with considerable morbidity due to disease progression, treatment side effects, and concurrent illnesses. This morbidity may affect their longterm quality of life, because it is associated with problems related to the physical and psychological adaptation to chronic illness. Therefore, damage that occurs as a consequence of SLE or due to treatment of SLE has become a standard outcome measure in longitudinal studies of SLE[2].

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The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) was developed and validated to quantify systemic damage in patients with SLE[2]. The SDI score reflects damage caused directly by SLE as well as damage that is attributable to SLE-associated therapies and the effects of comorbid conditions. The SDI is used widely as a predictor of mortality in patients with SLE[3]. Several studies[4-11] have evaluated systemic damage in SLE patients from various ethnic backgrounds. The LUMINA (LUpus in MInorities: NAture vs nurture) study[4-6] and most other studies[7-10] were focused on Hispanic, African American, and Caucasian SLE patients, while Mok, *et al*[11] examined patients in southern China. These studies identified several potential predictors of damage, including autoantibodies, socioeconomic factors, and medication. However, systemic damage and associated risk factors have not been examined in Korean patients with SLE. We investigated the prevalence of systemic damage in Korean patients with SLE, and also whether the presence of damage was associated with clinical variables, autoantibody profiles, and a history of drug therapy.

MATERIALS AND METHODS

Patients. A total of 588 patients who fulfilled the ACR criteria for SLE[12] were enrolled consecutively at the Hospital for Rheumatic Diseases at Hanyang University in Seoul, South Korea, between January 1992 and June 2005. All patients were Korean and provided written informed consent prior to the study.

Clinical assessment. The presence of systemic damage was assessed by rheumatologists based on the SDI. The SDI comprises 41 items that include 12 systems, and the SDI score reflects damage that has occurred since the onset of SLE and has been present for at least the previous 6 months[2]. The SDI score ranges from 0 to 49. Prevalence of damage was the primary outcome for our study, defined as any organ damage in any of the 41 items of the SDI during the study period (from enrollment until the last assessment for each patient). We used the last data of each patient until March 2006. For patients who died during followup, we included the last data obtained prior to death in the cross-sectional analysis. Patients were dichotomized into the presence and absence of damage based on a cutoff of the SDI score of 1.

Demographic information was collected by interview at the time of enrollment and from medical records, and included sex, age, body mass index (BMI), level of education (dichotomized with a cutoff of 12 years of education), and marital status (married or single).

Clinical information included age at diagnosis of SLE, time to diagnosis (amount of time between onset of the first symptom in ACR criteria and the diagnosis of SLE), disease duration (amount of time between diagnosis of SLE and the last assessment for systemic damage), ACR criteria, current or past use of steroids, and use of intravenous cyclophosphamide.

Laboratory assessment. Antinuclear antibody expression (ANA test) was assessed using indirect immunofluorescence and IT-1 cells. Anti-double-stranded DNA (dsDNA) antibody expression was assessed using the *Crithidia luciliae* assay. Anti-Sm, Ro/SSA, La/SSB, and RNP (ribonuclear protein) antibody expression was assessed by double immunodiffusion. Expression of IgG and IgM anticardiolipin (aCL) antibody was assessed by ELISA. Detection of lupus anticoagulant in the laboratory was based on the dilute Russell viper-venom time test.

Statistical analyses. The frequencies and means of each variable were compared between the presence and absence of damage using chi-square test or Fisher's exact test for categorical variables and Student's t test for continuous variables.

Univariate logistic regression analyses were conducted to investigate the relationship between each possible risk factor (age, disease duration, use of intravenous cyclophosphamide) and the presence of damage. Multivariate logistic regression analyses were performed using all 3 possible risk factors. Disease duration was expressed in months for continuous variables and quartiles for the independent logistic regression models. Use of intravenous cyclophosphamide was expressed both as a binary variable (used or not used) and as a categorical variable based on the US National Institutes of Health pulse protocol for lupus nephritis and clinical experiences for other indications such as central nervous system (CNS) vasculitis, interstitial pneumonitis, thrombocytopenia, and so on. The categories of cyclophosphamide use were as follows: no use of cyclophosphamide, 1 to under 7 times, 7 to under 12 times, and at least 12 times.

All analyses were performed with SAS software version 8.1 (SAS Institute, Cary, NC, USA). Probability values of $p < 0.05$ were considered statistically significant.

RESULTS

Patient population and manifestations. A total of 588 patients fulfilled the criteria for inclusion. Table 1 lists demographic characteristics and ACR criteria of patients according to the presence of damage. Two hundred forty-four (41.5%, 8859.6 per 100,000 person-years) patients exhibited damage at a mean of 54 months after onset of disease, and they were older, had longer disease duration, and had used intravenous cyclophosphamide more frequently than the patients without damage. Among ACR criteria, neuropsychiatric or renal involvement and pleuritis/pericarditis were associated with the presence of damage, while nonerosive arthritis was more common in patients without damage. Gender, BMI, level of education, marital status, time to diagnosis, and age of diagnosis were not related to the presence of damage. The levels of antiphospholipid and anti-ENA antibody expression did not differ significantly between the 2 groups.

Prevalence of damage. Damage was present in at least one of the items in the SDI in 244 (41.5%, 8859.6/100,000 person-years) patients (SDI score ≥ 1). The median and mean SDI scores were 0 (range 0–9) and 0.71 (SD 1.1), respectively. The SDI scores were 1, 2, 3, 4, and ≥ 5 in 136, 67, 25, 12, and 4 patients, respectively. As indicated in Table 2, the musculoskeletal (14.3%) and renal (13.3%) systems were involved more frequently than other systems, followed by neuropsychiatric (10.7%), ocular (4.6%), and pulmonary (4.1%) systems. Six (1.0%) patients had developed diabetes, and 6 (1.0%) cases of malignancy were present. In our cohort, 14 patients died during the followup, and for these we used the last data obtained prior to death: 3 without damage prior to death and 11 with damage (median SDI score 1.00, range 0–3).

Risk factors for damage. Univariate analysis revealed that the risk ratio for the presence of damage was higher in the presence of higher age, longer disease duration, and more use of intravenous cyclophosphamide pulses. The multivariate risk ratios also were significantly higher for these variables: 1.03 for age (95% CI 1.01 to 1.04), 1.02 for disease duration (95% CI 1.01 to 1.02), and 2.97 for use of intravenous cyclophosphamide (95% CI 2.00 to 4.41).

Dose–response relationships between disease duration and the presence of damage are listed in Table 3. The risks of having damage were 2.53 and 4.03 times higher in the third and fourth quartiles of disease duration than in the lowest quartile, respectively, and 4.47 and 4.54 times higher in patients who had received intravenous cyclophosphamide pulses 7–11 times and ≥ 12 times than in patients who had not received cyclophosphamide (Table 3).

DISCUSSION

We evaluated the prevalence of systemic damage in Korean patients with SLE using the SDI, which is used as a standard outcome measure in SLE studies. Direct comparison between the results of our study and previous studies is not feasible due to differences in study design and patient selection at entry. Nevertheless, the mean SDI score and the frequency of cumulative damage in our SLE patients are comparable to values observed in SLE patients from southern China[11] as well as those in Caucasian SLE patients[13,14].

We found that irreversible damage involved the musculoskeletal, renal, and neuropsychiatric systems more frequently than other systems. The pattern of damage and the SDI scores of our patients were similar to those reported for Hispanic, African American, Caucasian, and southern Chinese SLE patients[10,11,13-16]. The only major difference was that renal damage was much more prevalent in Koreans than in other ethnic groups, with ocular or cardiac damage being less prevalent. In addition to ethnic differences, our patients were

Table 1. Demographic characteristics and clinical features of Korean patients with SLE. Damage was defined as any organ damage in any of the 41 items of the SDI during the study period (from enrollment until the last assessment for each patient).

Variable*	Damage			p†
	Patients with, N = 244	Pateints without, N = 344	All Patients, N = 588	
Demographic characteristics				
Age, yrs, mean ± SD	34.11 ± 11.57	31.03 ± 10.88	32.31 ± 11.26	0.0010
Sex				
Male	17 (6.97)	19 (5.52)	36 (6.12)	0.5857
Female	227 (93.03)	325 (94.48)	552 (93.88)	
Body mass index, kg/m^2, mean ± SD	21.54 ± 3.32	21.28 ± 2.83	21.38 ± 3.04	0.3395
Married	139 (58.90)	177 (53.47)	316 (55.73)	0.2317
More than 12 yrs education	99 (42.31)	148 (45.40)	247 (44.11)	0.5220
Clinical features				
Onset age, yrs, mean ± SD	28.23 ± 10.66	29.66 ± 11.51	28.82 ± 11.03	0.1212
Time to diagnosis, mo, median (range)	10.0 (0–413)	9.5 (0–291)	10.0 (0–413)	0.3784
Disease duration, mo, median (range)	69.0 (6–268)	37.0 (6–185)	49.0 (6–268)	< 0.0001
ACR criteria				
Malar rash	106 (43.44)	140 (40.70)	246 (41.84)	0.5619
Discoid rash	21 (8.61)	32 (9.30)	53 (9.01)	0.8854
Photosensitivity	73 (29.92)	104 (30.23)	177 (30.10)	1.0000
Oral ulcers	89 (36.48)	120 (34.88)	209 (35.54)	0.7567
Nonerosive arthritis	129 (52.87)	230 (66.86)	359 (61.05)	0.0008
Pleuritis or pericarditis	92 (37.70)	79 (22.97)	171 (29.08)	0.0002
Renal disorder	136 (55.74)	124 (36.05)	260 (44.22)	< 0.0001
Seizure or psychosis	32 (13.11)	14 (4.07)	46 (7.82)	< 0.0001
Hematological disorder	200 (81.97)	290 (84.30)	490 (83.33)	0.5246
Immunological disorder	216 (88.52)	297 (86.34)	513 (87.24)	0.5106
Positive ANA	244 (100.0)	344 (100.0)	588 (100.0)	—
Use of cyclophosphamide, n = 588	99 (40.57)	68 (19.77)	167 (28.40)	< 0.0001
Past or present steroid use, n = 567	220 (94.02)	302 (90.69)	522 (92.06)	0.1988
Laboratory assessment				
Autoantibody profile, n = 551				
Anti-Sm	26 (11.61)	43 (13.15)	69 (12.52)	0.6845
Anti-RNP	77 (34.38)	86 (26.30)	163 (29.58)	0.0518
Anti-Ro	87 (38.84)	117 (35.67)	204 (36.96)	0.5044
Anti-La	20 (8.93)	28 (8.56)	48 (8.71)	1.0000
Anti-dsDNA, n = 588	182 (74.59)	259 (75.29)	441 (75.00)	0.9230
Antiphospholipid antibody, n = 588				
ACA (IgM or IgG)	79 (32.51)	103 (30.03)	182 (31.06)	0.5831
Lupus anticoagulant	13 (5.49)	27 (7.99)	40 (6.96)	0.3199

* N (%) except where indicated. † p value comparing patients with damage to patients without damage.

relatively young and had relatively short disease durations at the time of assessment, which may have contributed to these interethnic differences in the pattern of systemic damage.

Several studies have attempted to identify predictors of systemic damage in SLE. Several potential risk factors for damage have been identified, including an older age at diagnosis[14,17], longer disease duration[14,17], a lower level of education[18], the presence of damage at diagnosis[5], greater overall disease activity[8], and cumulative use of high doses of prednisone[9]. In patients with juvenile-onset SLE, the presence of neuropsychiatric involvement at diagnosis, long duration of SLE, and a high number of intravenous cyclophosphamide pulses are the strongest predictors of cumulative damage[19]. The cross-sectional design of our study limited its ability to examine predictors of damage accrual, but we also performed a multivariate analysis to evaluate the association between possible risk factors and the presence of damage in Korean patients with SLE. Our findings concur with some of the above studies, in that we found that longer disease duration and the use of cyclophosphamide were associated with the

Table 2. SDI scores for the SLE patient cohort (n = 588).

Domain	Score
Ocular (n = 27, 4.59%)*	
Any cataract	19
Retinal changes of optic atrophy	10
Total†	29
Neuropsychiatric (n = 63, 10.71%)	
Cognitive impairment or major psychosis	40
Seizures requiring therapy for ≥ 6 mo	15
Cerebrovascular accident (score = 2 if > 1)	11 (12)
Cranial or peripheral neuropathy	8
Transverse myelitis	4
Total†	78 (79)
Renal (n = 78, 13.27%)	
Estimated or measured glomerular filtration rate < 50%	22
Proteinuria ≥ 3.5 g/24h	71
Endstage renal failure (regardless of dialysis or transplantation)	2 (6)
Total	95 (99)
Pulmonary (n = 24, 4.08%)	
Pulmonary hypertension	10
Pulmonary fibrosis	14
Shrinking lung	1
Pleural fibrosis	1
Pulmonary infarction or resection not for malignancy	2
Total	28
Cardiovascular (n = 12, 2.04%)	
Angina or coronary artery bypass	1
Myocardial infarct (score = 2 if > 1)	0
Cardiomyopathy (ventricular dysfunction)	0
Valvular change (murmur)	2
Pericarditis for ≥ 6 mo or pericardiectomy	9
Total	12
Peripheral vascular (n = 18, 3.06%)	
Claudication for ≥ 6 mo	7
Venous thromboses with swelling, ulceration, or venous stasis	7
Minor tissue loss (pulp space)	3
Significant tissue loss (score = 2 if > 1)	1
Total	18
Gastrointestinal (n = 5, 0.85%)	
Infarction or resection of bowel, spleen, liver, or gallbladder (score = 2 if > 1 site)	1 (2)
Mesenteric insufficiency	3
Chronic peritonitis	0
Stricture or upper gastrointestinal surgery (ever)	1
Pancreatic insufficiency (enzyme replacement or with pseudocyst)	0
Total	5 (6)
Musculoskeletal (n = 84, 14.29%)	
Muscle atrophy or weakness	8
Deforming or erosive arthritis	37
Osteoporosis with fracture or vertebral collapse	2
Avascular necrosis (score = 2 if > 1)	40 (66)
Osteomyelitis	0
Ruptured tendon	1
Total	88 (114)
Skin (n = 16, 2.72%)	
Alopecia	8
Extensive scarring or panniculum other than pulp space and scalp	6
Skin ulceration (excluding thrombosis) for ≥ 6 mo	6
Total	20
Premature gonadal failure (n = 2, 0.34%)	2
Diabetes (n = 6, 1.02%)	6
Malignancy (score = if > 1 site: n = 6, 1.02%)	6
Total SDI score	387 (419)
SDI score, median (range)	0 (0–9)
SDI score, mean ± SD	0.71 ± 1.1

* Number of patients who scored positive in each system category. † Total refers to the sum of the SDI scores for each system. Overlap is possible where a single patient had positive scores for several symptoms.

presence of systemic damage. A previous report indicated that age at diagnosis and level of education were associated with outcome in SLE[20], but we found only that the extent of damage was associated with age in our patients.

The association between the expression of autoantibody and the accumulation of damage is still controversial. For example, Ruiz-Irastorza, *et al*[21] showed that early organ damage can be predicted by the level of antiphospholipid antibody expression, and Mikdashi and Handwerger[22] reported that the risk of neuropsychiatric damage is increased by the presence of anti-Ro antibodies. Similarly, a cross-sectional study of Mexican patients with SLE identified an association between anti-dsDNA antibody expression and organ damage[10]. In contrast, Yee, *et al*[14] and Prasad, *et al*[23] reported that autoantibody expression did not predict the extent of organ damage. Our findings support the contention that there is no relationship between autoantibody expression and systemic damage in SLE.

Treatment with corticosteroids (particularly prednisone) may have a considerable effect on the amount of damage to the musculoskeletal, neuropsychiatric, and renal systems of SLE patients[9]. However, we found no association between corticosteroid use and the presence of damage. This finding might be due to the relatively short disease duration in our patients and the lack of information regarding the cumulative doses of steroids that were administered to them.

The use of cyclophosphamide and the number of intravenous cyclophosphamide pulses were both associated with the presence of systemic damage in our study. It is possible that the involvement of major organs, such as the kidney, would be a confounding factor for the presence of damage, because cyclophosphamide is generally administered to SLE patients with proliferative nephritis or CNS vasculitis. To limit confounding by indication, we performed a multivariate analysis controlling for renal involvement (since 84% of cyclophosphamide use was for renal involvement). After applying this control, the use of cyclophosphamide was still positively associated with the presence of damage (data not shown). However, elucidating the true contribution of cyclophosphamide use to damage requires further investigation of the relationship between the individual items in the SDI and cyclophosphamide use.

We found that systemic damage was present in 41.5% (8859.6/100,000 person-years) of Korean patients with SLE. The presence of damage was more likely to be observed in patients who were older, had longer disease duration, and received more intravenous pulses of cyclophosphamide. A prospective study of SLE patients would elucidate how different therapies or other factors contribute to damage accrual in Korean patients with SLE.

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Table 3. Relations between risk factors and the presence of damage.

Variable	Unadjusted Risk Ratio (95% CI)	Multivariate Risk Ratio* (95% CI)
Risk factors		
Age	1.025 (1.010–1.040)	1.027 (1.011–1.044)
Disease duration	1.016 (1.011–1.020)	1.015 (1.010–1.020)
Use of cyclophosphamide	2.771 (1.917–4.005)	2.966 (1.995–4.410)
Disease duration†, mo		
< 20, n = 149	1.000	1.000
≥ 20 and < 50, n = 146	1.476 (0.892–2.442)	1.358 (0.802–2.301)
≥ 50 and < 82, n = 146	2.547 (1.558–4.162)	2.527 (1.512–4.221)
≥ 82, n = 147	4.482 (2.732–7.354)	4.026 (2.394–6.769)
Frequency of cyclophosphamide pulses		
No use of cyclophosphamide, n = 421	1.000	1.000
Uses of cyclophosphamide		
≥ 1 and < 7, n = 68	1.595 (0.950–2.677)	1.714 (0.989–2.970)
≥ 7 and < 12, n = 34	3.980 (1.887–8.393)	4.372 (1.986–9.623)
≥ 12, n = 65	4.283 (2.437–7.526)	4.539 (2.505–8.226)

* Multivariate risk ratios were calculated using all 3 factors (age, disease duration, and use of intravenous cyclophosphamide) for the relationship between risk factors and the presence of damage. † Categorized according to quartiles of disease duration.

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