Accrual of Organ Damage Over Time in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the pattern of accumulation of damage in an inception cohort of patients with systemic lupus erythematosus (SLE) followed yearly for at least 15 years, and to identify damage items that might be related to corticosteroid therapy.

Methods. An inception cohort was identified from among patients with SLE followed prospectively in the University of Toronto Lupus Clinic. Only patients who had at least yearly evaluations and were followed for at least 15 years were included. Using the SLICC/ACR damage index (SDI) accumulated damage was calculated at yearly intervals. Each new organ system involved was designated as either definitely, possibly, or not at all related to corticosteroid therapy.

Results. Of the 73 patients, 85% were women and 87.7% were Caucasian. Their mean age at diagnosis was 34.9 years. The mean (range) SLEDAI at presentation was 11.9 (0–37). Prednisone was used by 87.7% of the patients (mean maximum dose 37.7 mg/day, mean cumulative dose 36.8 g) for a mean of 117.1 months. Antimalarial drugs were used by 70% of the patients and 50% were taking immunosuppressive agents. The mean SDI for the whole cohort increased over time from 0.33 (0.89) during the first year to 1.90 (1.99) at 15 years. A significant proportion of the damage both early and late could be attributed to corticosteroid therapy, and this damage accumulated over time such that it constituted most of the damage at 15 years.

Conclusion. While the overall accrual of damage is gradual, the specific systems demonstrate varying patterns of damage accrual. (J Rheumatol 2003;30:1955–9)

Key Indexing Terms:
ORGAN DAMAGE SYSTEMIC LUPUS

Mortality of patients with systemic lupus erythematosus (SLE) has decreased markedly over the last few decades[1]. As survival has become longer, organ damage tends to accumulate over time as a result of both the disease and its treatment. The assessment of accumulated damage related to SLE has been recognized as an important outcome[2]. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) for SLE is a reliable, validated instrument that indicates irreversible damage in the various systems after disease onset[3]. The SDI had been widely used in studies describing damage in lupus patients from various ethnic backgrounds[4-10]. However, most of the studies were cross-sectional and patients were not followed for long period of time. Therefore we undertook this study, first, to determine the pattern of organ damage accumulation in an inception cohort of lupus patients who had been followed for at least 15 years, and second, to assess the burden of damage that could be attributed to corticosteroid therapy.

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Submitted October 15, 2002; revision accepted February 18, 2003.

MATERIALS AND METHODS

Patient population. All SLE patients were followed at the University of Toronto Lupus Clinic, which was established in 1970 and since then has been enrolling patients with SLE as part of an ongoing prospective study. Patients were assessed every 3 to 6 months according to a standardized protocol including demographic, clinical, laboratory, and treatment variables. Steroid dose at visit and mean steroid dose between visits are documented in our protocol, allowing us to calculate cumulative steroid dose. Disease activity was calculated as a SLE Disease Activity Index (SLEDAI)[11]. Damage was scored yearly using the SDI[3] prospectively since 1995 as part of the standardized protocol. Prior to 1995, yearly SDI was scored retrospectively by reviewing the standardized protocol and written notes that accompanied each visit.

It would be difficult to describe the pattern of damage in the whole cohort as patients were followed for varying lengths of time; therefore, we identified an inception cohort of 73 patients who presented within 12 months of diagnosis of SLE and who were followed prospectively at least yearly for at least 15 years. The entire inception cohort accrued during the study period was 263 patients, of whom 57 died prior to 15 years of followup and 30 who had large gaps between clinic visits during their 15 years of followup.

SDI. SDI was defined as damage[9] in an organ or system that occurred since the onset of SLE, ascertained by clinical assessment, and was present for at least 6 months. It included 42 items encompassing 12 organ systems. Repeat episodes require at least 6 months between them to score 2. The same lesion cannot be scored twice[3]. By definition, the first SLICC could only be recorded at 6 months after the diagnosis of SLE.

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Corticosteroid-induced morbidity. New organ damage involvement according to the SDI was noted and categorized into the following groups: definitely related to corticosteroid therapy, possibly related to corticosteroid therapy, and independent of corticosteroid. SDI entries that were definitely corticosteroid related: ocular, musculoskeletal. SDI entries possibly corticosteroid related: cardiovascular, peripheral vascular disease, neuropsychiatric, diabetes. SDI entries independent of corticosteroid: renal, pulmonary, gastrointestinal, skin, premature gonadal failure, malignancy.

Data analysis. Data are expressed as mean ± SD (range) unless otherwise stated. Student's t and chi-square tests were used when appropriate to compare demographic features. The difference in the distribution of corticosteroid-induced morbidity over time was tested using chi-squared tests. Mean total SDI and 95% confidence intervals (CI) were evaluated and plotted as were the number of patients with each organ damage over time.

RESULTS

Of the 73 patients in the inception cohort followed for at least 15 years, 62 (85%) patients were women and 11 (15%) were men. Sixty-four (87.7%) were Caucasian and 5 (6.9%) were Black. Half the patients had education level of college or above. Seventy percent of patients were either employed or working as a homemaker at the last visit; 12.7% were retired and the rest were either disabled or on sick leave. The mean ages at diagnosis and presentation were 34.9 ± 13.1 (13.2–69.7) and 35.1 ± 13.1 (13.5–69.9) years, respectively. The mean SLEDAI at presentation was 11.9 ± 8.3 (0–37). Sixty-four (87.7%) patients were given prednisone, at a mean maximum dose of 37.7 mg/day, a mean cumulative dose of 36.8 g, for a mean cumulative duration of 117.1 months. Fifty percent of patients received immunosuppressants, 24 receiving azathioprine alone, 4 methotrexate alone, and the remainder received 2 or 3 drugs sequentially, and 70% of patients received antimalarial agents at some time during their disease course.

The mean SDI for the whole cohort increased over time more or less in a linear pattern (Table 1, Figure 1), from 0.33 ± 0.89 during the first year to 1.90 ± 1.99 at 15 years. Despite having long disease duration, the mean SDI was below 2, indicating that this group of patients in general had limited damage.

The number of patients who developed individual components of SDI increased over time. Three patterns of organ damage accrual in patients over time were observed clinically (Figure 2): (1) Progressive increase in patient numbers exhibiting a feature over 15 years, as in musculoskeletal and ocular systems. (2) Patient numbers reaching a first peak at 5 years and then a second peak at 15 years, as in cardiovascular (CVS) and neuropsychiatric systems. (3) Minimal increase in patient numbers exhibiting a feature over 15 years, as in other organs.

Few patients developed early damage within the first year of their disease. The most common organ damage occurred in the CVS. Three patients developed angina, whereas 2 patients already had myocardial infarction (MI) and 2 patients had valvular heart disease. The prevalence of both angina and MI remained stable for 10 years, subsequently increased, and reached a second peak at 15 years (12.3% had angina and 9.6% had MI).

The second most common early organ damage was observed in the neuropsychiatric system. Three patients had seizures that required prolonged anticonvulsants, one patient had cognitive impairment, and one had neuropathy. The damage accrual pattern observed in neuropsychiatric systems was similar to that seen in the CVS, with peaks at 5 and 15 years. The number of patients having neuropsychiatric damage remained static and then rose again after 10 years, mainly as a result of rising prevalence of cognitive impairment. Two patients developed cerebrovascular accidents at 5 and 15 years.

Early damage affecting the musculoskeletal system was unusual. However, the prevalence of damage was highest in this organ system from the fifth year onwards (Figure 2). By 15 years, more than half of the patients had already developed musculoskeletal damage. This was mostly due to

Table 1. Number of patients with individual organ system damage over time.

	Disease Duration, yrs			
	< 1	5	10	15
Mean (SD) total SDI	0.33 (0.89)	0.81 (1.30)	1.19 (1.59)	1.9 (1.99)
	n (%)*	n (%)	n (%)	n (%)
Musculoskeletal	2 (2.8)	16 (21.8)	23 (31.5)	40 (54.7)
Oscular	1 (1.4)	6 (8.2)	11 (15.1)	23 (31.5)
Cardiovascular	7 (9.5)	10 (13.7)	12 (16.4)	21 (28.7)
Neuropsychiatric	5 (6.9)	9 (12.3)	9 (12.3)	15 (20.5)
Skin	3 (4.1)	6 (8.2)	8 (11)	10 (13.7)
Gastrointestinal	4 (5.5)	5 (6.9)	6 (8.2)	9 (12.4)
Renal	0 (0)	2 (2.7)	3 (4.1)	4 (5.4)
Peripheral vascular	1 (1.4)	1 (1.4)	2 (2.4)	3 (4.1)
Pulmonary	0 (0)	0 (0)	0 (0)	2 (2.8)
Diabetes	0 (0)	1 (1.4)	2 (2.7)	2 (2.7)
Gonadal	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Malignancy	0 (0)	0 (0)	0 (0)	1 (1.4)

* Of 73 patients.

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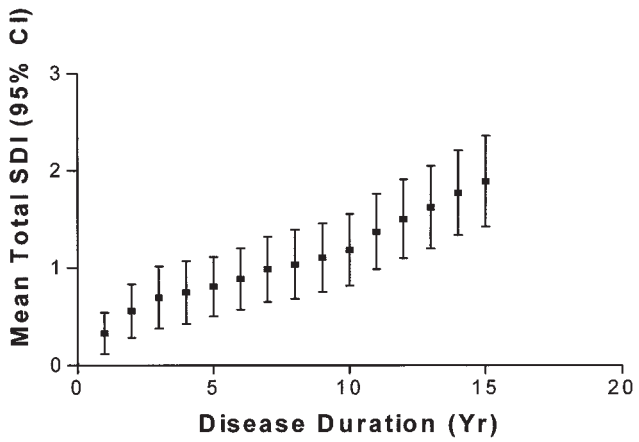

Figure 1. Accrual of damage over time.

progressive increase in number of patients with osteonecrosis and deforming arthritis. Patients also developed muscle atrophy, particularly after 10 years. Only one patient had osteoporosis associated with fractures or vertebral collapse at 15 years. Early ocular damage was even less common. Nonetheless, it became the second most common organ to have damage at 15 years, which was attributed to rapid increase in the prevalence of cataracts after 5 years.

Accrual of other organ damage remained gradual for other organs such as skin, gastrointestinal, and renal. Involvement of the remaining systems including peripheral vascular, pulmonary, diabetes mellitus, premature gonadal failure, and malignancies was exceedingly rare (< 5% after 15 years) in this cohort.

Table 2 describes the effect of corticosteroid therapy on damage accrual in our cohort over time. Within the first year of SLE, 42% of the morbidity described in the SDI could be attributed to disease-related factors, whereas 58% was possibly or definitely related to corticosteroids. This is compared to the late stages, where 20% was attributed to disease-related factors and 80% was possibly or definitely related to corticosteroids. Of the 9 patients who were not treated with corticosteroids, none had osteonecrosis and 2 developed cataracts, one at the age of 58, 8 years after diagnosis, and one at age 61, 15 years after diagnosis.

DISCUSSION

Our study described 3 patterns of organ damage accrual in a cohort of SLE patients who survived at least 15 years. This group was unusual in that although their mean SLEDAI at presentation and requirement for steroid and immunosuppressive agents were similar to our larger cohort[12], they were chosen for study because they were available for 15 years of consecutive followup. This group was deliberately chosen in order for us to understand the longterm consequences of living with SLE. As such these results may not be generalizable to other complete lupus cohorts, particularly those with a larger non-Caucasian representation.

Damage accrued in our patients gradually over time, with

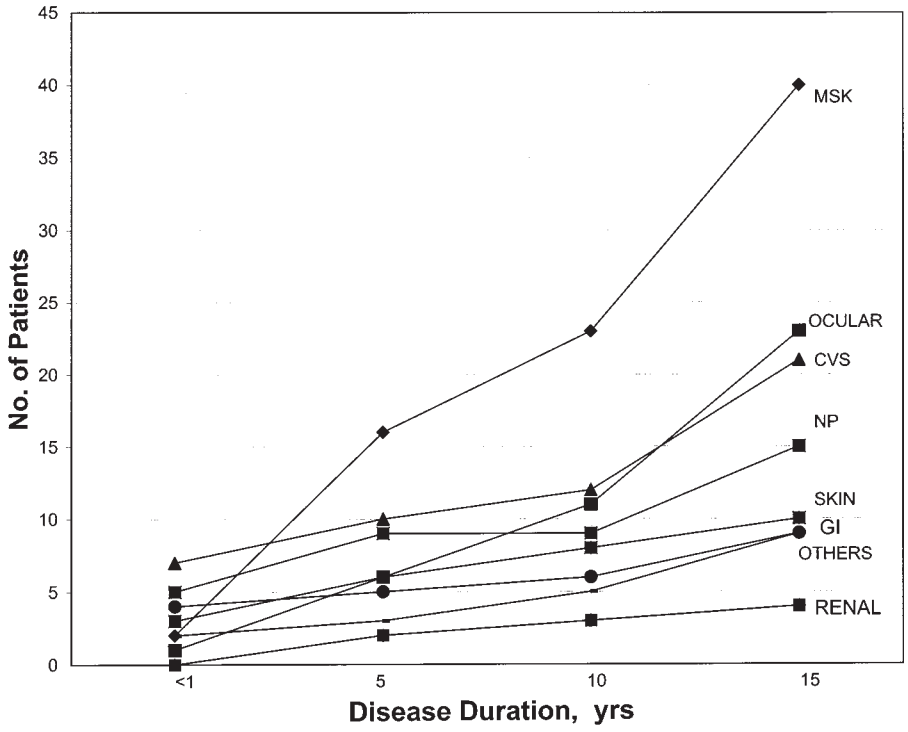

Figure 2. Pattern of accrual of organ system damage over time.

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Table 2. New SDI entries at various stages of SLE related to corticosteroid (CS) treatment.

	Disease Duration, yrs			
	< 1	< 5	< 10	< 15
Total new SDI entries	19	33	16	55
Definitely CS, total (%)	3 (16)	18 (54)	10 (62)	27 (49)
Ocular	1	4	4	11
Musculoskeletal	2	14	6	16
Possibly CS, total (%)	8 (42)	10 (30)	4 (25)	17 (31)
Cardiovascular	2	5	2	9
Peripheral vasc dis	1	0	1	2
Neuropsychiatric	5	4	0	6
Diabetes	0	1	1	0
Independent of CS, total (%)	8 (42)	5 (15)	2 (12)	11 (20)
Renal/pulmonary	0	1	0	3
Gastrointestinal	4	1	1	3
Skin	3	3	1	2
Gonadal/malignancy	1	0	0	3

Chi-square tests comparing the distribution of corticosteroid-induced morbidity: < 1 versus < 5, < 10, and < 15 years combined, p = 0.0063; < 5 versus < 10 versus < 15 years, p = 0.890.

SDI ranging from 0.3 to 0.8, 1.2, and 1.9 at < 1, 5, 10, and 15 years, respectively. The rate of damage accrual appeared less compared with most other studies, as patients from other ethnic origins as well as deceased patients were included in previous studies[5-7]. In a cross-sectional study, the mean SDI ranged from 2.0 to 2.4 for Mexican patients having a wide range of disease duration (< 5 to > 10 years)[8]. In an Afro-Caribbean group, the SDI increased from 0.6 to 2.4 after 6 years[7]. Patients who survived had a lower SDI compared to those who died (1.9 vs 3.4). The rate of damage accrual of the Caucasian subgroup from a British study was comparable to ours, with a mean SDI of 0.3, 0.6, and 1.2 at 1, 5, and 10 years, respectively, whereas the SDI almost doubled in the Afro-Caribbean and Asian subgroups[7].

Three patterns of organ damage accrual were observed in our cohort. The first pattern described mainly the progressive increase in the prevalence of osteonecrosis and cataracts, representing the most common complications of prolonged corticosteroid therapy. CVS and neuropsychiatric damage accrual tended to follow a second pattern, with peaks at 5 and 15 years. The initial peak in CVS SDI entries reflected early valvular damage features that could have resulted from disease activity persisting over at least 6 months, or coronary artery disease developing early in young SLE patients, possibly related to underlying vasculitis or accelerated atherosclerosis. The early neuropsychiatric SDI entries were seizures, cognitive impairment, and neuropathy, likely representing active disease persisting for at least 6 months. With both CVS and neuropsychiatric damage, the second peak that developed after 10 years may represent a consequence of prolonged corticosteroid therapy together with ongoing inflammation, leading to premature atherosclerosis and cognitive impairment.

The musculoskeletal system was the most commonly damaged organ system in patients from all ethnic backgrounds[5-8]. The Hopkins Lupus Cohort also noted that musculoskeletal damage accrued in a linear fashion[5], with osteonecrosis being the most common subtype, followed by deforming arthritis, similar to our cohort. In a recent European study examining lupus patients with mean disease duration of 16 years, osteoporosis was the most commonly observed subtype[10]. However, this was not a prospectively followed cohort and may be biased by patients with more active disease followed up more often. On the other hand, neuropsychiatric damage was noticed early in some of the studies[6,7], and remained a commonly involved system over time. The prevalence of other organ damage varied in different studies. Cardiovascular damage was frequently noticed in later disease in our cohort (16% at 10 years) and in others (10–15%)[6,8], but less frequently in the Mexican study (6%)[8]. In contrast, the peripheral vascular system was relatively spared from developing damage in our cohort (2.4% at 10 years), unlike other studies with a prevalence similar to the CVS (10–14%)[6,8]. Renal damage was uncommon in our cohort (5% at 15 years), in contrast to most other studies (14–32.4%)[6-8], which may be because the expression of renal disease is more aggressive in some ethnic groups[13] or because we treat differently or earlier. Our cohort had a remarkably small number of patients having gonadal damage (1%) compared to the Mexican group (11%)[8], and this may be explained by the use of azathioprine in our practice for treatment of nephritis compared with the use of cyclophosphamide in other centers.

SDI measures accumulative damage in SLE, whether the result of previously active disease, therapy, or comorbid conditions. As shown in Table 2, a significant proportion of

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the damage in both early and late SLE can be attributed to corticosteroid therapy directly. Corticosteroid-related damage tended to accumulate over a prolonged disease course. Thus the contribution of damage related to corticosteroid was lower in the early course of the disease, but constituted most of the damage at 15 years of disease. Zonana-Nacach, *et al*[14] reported that cumulative prednisone dose was significantly associated with osteoporotic fractures and symptomatic coronary artery disease and cataracts, and longer duration of exposure to high dose corticosteroid was associated with osteonecrosis and stroke. Our study was descriptive of damage in patients with SLE and did not address associated factors. The number of inception patients followed at least 15 years was small (73), precluding a case-control study of associated risk factors.

Patients with SLE are more effectively treated for their inflammatory disease in the modern era. However, the price paid for this more effective disease control is the accrual of manifestations of damage in these patients, due to the disease itself (primarily early) and from corticosteroid therapy (primarily late).

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