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ORIGINAL ARTICLE

Chronic high-dose glucocorticoid therapy triggers the development of chronic organ damage and worsens disease outcome in systemic lupus erythematosus

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Abstract Long-term survival of patients with systemic lupus erythematosus (SLE) improved worldwide; thus, prevention of cumulative organ damage became a major goal in disease management. The aim of our study was to investigate the chronic organ damages and their influence on disease outcome in SLE. We evaluated clinical conditions, laboratory findings and medications of 357 consecutive SLE patients and assessed their impact on Systemic Lupus Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) and disease outcome. We detected one or more SDI scores in 77.87% of patients. Patients with disease duration of more than 10 years and subjects diagnosed at age above 40 had significantly higher SDI values. The most frequent damages were valvulopathies, cognitive dysfunction, angina pectoris and venous thrombosis. Higher cumulative glucocorticoid dose increased SDI, while chloroquin treatment was favourable for patients. Male gender, elevated SDI scores and higher cumulative doses of glucocorticoids increased mortality risk. Our data confirmed that disease duration, age at diagnosis and chronic high-dose glucocorticoid therapy have significant effects on the development of chronic organ damage. Higher SDI score is characterized with worse survival ratios. The most common chronic organ damages affected the cardiovascular or neuropsychiatric system. As long-term survival in SLE improves, it becomes increasingly important to identify the determinants of chronic organ damage. Most of the chronic organ damage occurs in the cardiovascular and the neuropsychiatric systems; thus, regular follow-up, screening and adequate therapy are essential for the best clinical outcome.

Keywords Chronic organ damage · Disease outcome · SLICC/ACR Damage Index · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect almost any organs and tissues of the body, leading to a wide spectrum of clinical manifestations. For a long time, lupus was considered to be a disease with a poor prognosis, but in recent years, the long-term survival in SLE has improved significantly. While during the 1960s, the 5-year survival rate was 60%, by the 2000s, it has increased up to 90% in most countries and centres [1, 2], although ethnic and geographic variations remained significant [3, 4]. However, the increased longevity of patients with SLE leads to the accumulation of chronic organ damage over time in patients, which became one of the most important factors that contribute to mortality in SLE [5]. Disease activity and certain comorbidities are the main factors; however, several other factors are known to influence the development of chronic organ damage. Importantly, immunomodulatory treatments can be also associated with adverse events, organ damages and mortality. La Gonzales et al. identified menopause as well as gender, age and ethnicity as further significant influencing factors; moreover, they reported that certain psychosocial factors can also promote chronic damage [6]. Therefore, it is important to examine and understand the factors and mechanisms that influence disease prognosis and patients' quality of life.

The Systemic Lupus Collaborating Clinics (SLICC) and the American College of Rheumatology (ACR) proposed the internationally validated damage scoring system, namely, SLICC/

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ACR Damage Index (SDI) for the evaluation of chronic organ damage. SDI can be used to measure the degree of damage and to check its change over time [7]. Previous studies revealed significant associations between damage; disease activity; and certain demographic, clinical and laboratory features [8, 9].

Due to lack of data from East-Central Europe, the aims of our work were to survey SDI values in a large cohort of Hungarian SLE patients, to compare our results with international data and to identify additional influencing factors.

Material and methods

Patients

In our present cross-sectional study, we evaluated 357 Hungarian patients with SLE who were diagnosed between 1 January 1971 and 31 December 2012 and also treated at the Division of Clinical Immunology in the Medical Center of University of Debrecen. All patients were followed up on a routine basis, and their records contained detailed information on symptoms, clinical conditions, laboratory and other findings of each visit. The diagnosis of SLE was established based on the ARA preliminary classification criteria or ACR classification criteria revised in 1982 or in 1997, according to the date of first visit [10–12]. Patients diagnosed with SLE before 1997 were revised according to the revised 1997 ACR criteria for SLE classification. Sapporo and Sydney criteria were used to establish the diagnosis of anti-phospholipid syndrome [13, 14]. All experiments carried out in the study were in compliance with the Declaration of Helsinki.

Clinical evaluations

All patients were followed up on a routine basis, and their records contained detailed information on symptoms, clinical conditions and laboratory and other findings of each visit. The following demographic and clinical data were analyzed: gender, age, age at diagnosis, duration of disease, clinical symptoms and organ manifestations of SLE, comorbidities, laboratory parameters, immunoserological abnormalities and therapy used during the disease course. Disease activity was measured using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [15, 16]; flare was defined as an increase in SLEDAI score with at least 3 points. The assessment of chronic organ damage was performed using SDI [7].

Laboratory measurements

Immunoserological tests were performed at the Regional Immunology Laboratory of the Division of Clinical Immunology and included the measurement of antinuclear antibody (ANA), rheumatoid factor (RF), antibodies against extractable nuclear antigen (ENA), anti-dsDNA, anti-Sm, anti-RNP, anti-SS-A, anti-SS-B, antiphospholipid antibodies, serum immunoglobulins, haemolysis test and complement levels. Hep-2 cell-based indirect immunofluorescence assay was performed as a screening test for anti-ENA antibodies, and further identification was carried out by enzyme-linked immunosorbent assay (ELISA) with AUTOSTAT II kits (Hycor Biomedical, Indianapolis, IN, USA), according to the manufacturer's instructions. Immunoglobulin levels and complement activity were determined with turbidimetry and nephelometry techniques and haemolysis test in sheep red blood cell suspension, respectively. General laboratory parameters (blood count, kidney and liver function, haemostasis parameters, lupus anti-coagulant, urinalysis) were assessed at the Clinical Biochemistry and Molecular Pathology Institute of University of Debrecen.

Therapy

We registered the use of medications, including glucocorticoids, immunosuppressive agents, chloroquine and biologics. Additionally, we also calculated the cumulative dosage of glucocorticoids and analyzed the relationship between SDI and the different treatment modalities.

Statistical analyses

The IBM SPSS ver. 22.0 (SPSS Inc., Chicago, IL, UDA) was used for statistical analysis. In cases of continuous variable, we determined mean and standard deviation (SD) values and used independent samples t test or Mann-Whitney test for statistical evaluation. When the strength of the linear relationship between two variables was evaluated, Pearson's correlation coefficient was used, while in cases of non-normal distribution, Spearman's correlation coefficient was applied. Chi-square test and Fisher's exact test were used to discriminate between patient groups. Data on disease outcome are given in mean values with 95% confidence intervals (CIs). We used the Cox regression model to predict chronic organ development in the disease. Survival time and rate were assessed using the Kaplan-Meier estimator. Chi-square test and Fisher's exact test were used to discriminate between patient groups, and we used the Cox regression model to predict poor outcome of the disease. Differences were considered statistically significant at $p < 0.05$.

Results

Table 1 summarizes the demographic data, clinical and laboratory features of the 357 SLE patients. The mean follow-up

Table 1 The main demographic, clinical and serological features of SLE patients (n = 357)

Demographic features	
Male/female	33/324
Age (years) mean ± SD (range)	51.57 ± 13.48 (21–86)
Age at disease onset (years) mean ± SD (range)	32.11 ± 11.49 (7–67)
Disease duration (years) mean ± SD (range)	19.14 ± 9.15 (1–44)
Clinical damages, N (%)	
Cardiovascular damage	108 (30.25)
Neuropsychiatric damage	91 (25.49)
Musculoskeletal damage	65 (18.21)
Peripheral vascular damage	57 (15.97)
Ocular damage	56 (15.68)
Renal damage	56 (15.68)
Skin damage	50 (14.01)
Pulmonary damage	35 (9.8)
Gastrointestinal damage	3 (0.84)
Serological abnormalities, N (%) last time of the follow-up	
ANA	355 (99.44)
Anti-dsDNA	195 (54.62)
Anti-Sm	86 (24.09)
Anti-SSA	99 (27.73)
Anti-SSB	59 (16.53)
Anti-cardiolipin IgG/IgM	86 (24.09)
Anti-beta2 GPI IgG/IgM	75 (21.01)
Lupus anti-coagulant	24 (6.72)
Low C3/C4	153 (42.86)
Medications, N (%)	
Glucocorticoids	310 (86.83)
Cumulative dosage of glucocorticoids (g) mean ± SD	32.878 ± 25.506
Chloroquine	158 (44.26)
Azathioprine	171 (47.9)
Cyclophosphamide	103 (28.85)
Methotrexate	40 (11.2)
Biologics	36 (10.08)
Cyclosporine A	21 (5.88)
Leflunomide	16 (4.48)
Mycophenolate mofetil	12 (3.36)

period was 19.14 ± 9.15 years with a range 1 to 44 years. The mean age of patients at the time of their last follow-up visits was 51.57 ± 13.48 years with a range 21 to 86 years, while their mean age at disease onset was 32.11 ± 11.49 years (range 7–67 years). There were 33 male (9.24%) and 324 female (90.76%) patients; male to female ratio was 9.8:1.

Chronic organ damage

Based on our observations, men had higher mean SDI value (SDI: 2.03 ± 1.55) compared to women (SDI 1.88 ± 1.73), but the difference was not significant.

Out of 357 patients, 278 patients (77.87%) were found to have developed at least one chronic organ damage. Damage scores 1 and 2 were the most frequent [N = 104 (29.13%) and N = 62 (17.37%), respectively], followed by scores 3 and 4 [N = 56 (15.69%) and N = 25 (7%), respectively] and scores 5 and 6–8 [N = 15 (4.2%) and N = 16 (4.48%), respectively]. The cardiovascular organ system was the mostly affected in patients during the disease course (N = 108, 30.25%). Ninety-one patients (25.49%) were found to have developed neuropsychiatric, 65 patients (18.21%) musculoskeletal and 57 patients (15.97%) peripheral vascular, and both ocular and renal damage affected 56 patients (15.68%). Fifty patients (14.01%) were found to have dermatological, 35 patients (9.8%) pulmonary and 3 patients (0.84%) gastrointestinal organ system damage (Table 1). The ten most frequent types of chronic organ damage are listed in Fig. 1.

Based on our results, the number of chronic damages was significantly higher in patients with disease duration of more than 10 years (mean SDI value of patients with disease duration of 6–10 years, 1.15 ± 1.68 vs. mean SDI value determined in patients with disease duration of 11–15 years, 2.02 ± 1.81, respectively, p = 0.014). Patients with a disease duration of more than 25 years had even higher SDI values (mean SDI value of patients with disease duration of 21–25 years, 2.21 ± 1.84 vs. mean SDI value determined in patients with disease duration of more than 25 years, 2.83 ± 2.14, respectively, p = 0.018) (Fig. 2).

We examined the relationship between the SDI value and disease activity, as well. Of patients without chronic damage, 25.32% developed a disease flare during the last 10 years of the study. Of patients with a score of 1–3, 28.63% showed

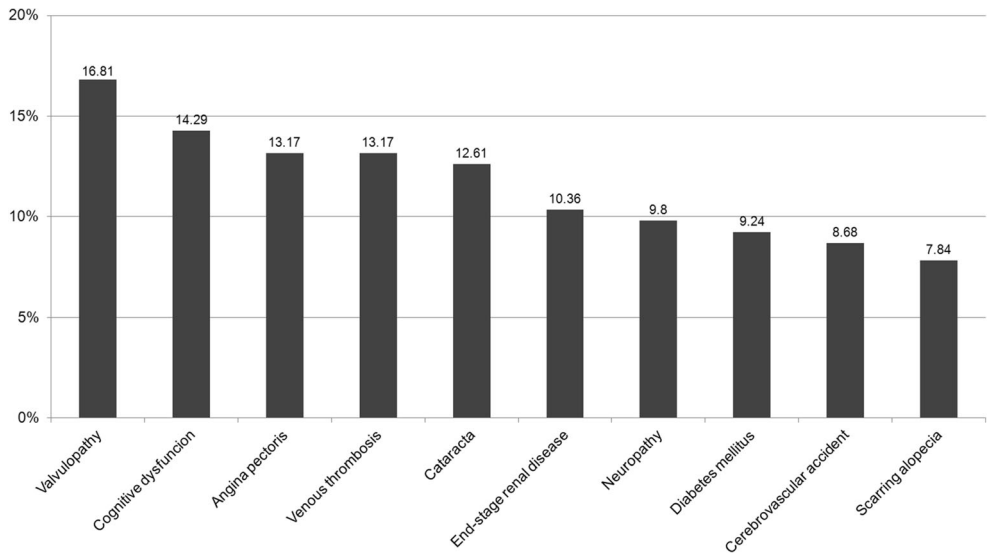

Fig. 1 Percentages of the ten most frequent specific chronic organ damages in SLE patients (n = 357)

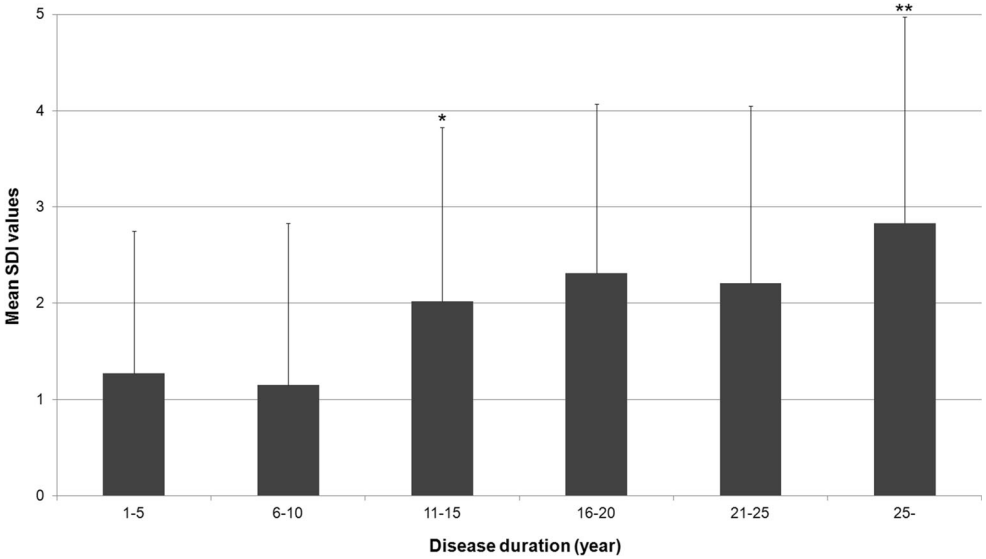

Fig. 2 Association between the disease duration and SDI. Patients with disease duration of more than 10 years had higher SDI values (*$p = 0.014$). Patients with disease duration of more than 25 years had even higher SDI values (**$p = 0.018$)

active disease. Of patients with an SDI value of at least 4, 32.29% demonstrated disease flare. The increase in SDI values was mirrored by an increase in the number of patients with disease flare, but the difference was not significant.

The patients' mean age at diagnosis had an influence on the SDI value. The SDI value of SLE patients who were diagnosed above the age of 40 years ($N = 102$) was significantly higher than the mean SDI value of patients diagnosed under 40 years ($N = 255$) (2.28 ± 1.92 vs. 1.74 ± 1.6, respectively, $p = 0.007$).

We also investigated the relationship between SDI and the different treatment modalities. Regarding long-term glucocorticoid therapy, patients with a higher SDI score (6–8) had a significantly higher ($p < 0.001$) cumulative glucocorticoid dose than patients with lower SDI scores (1–2). Patients who received higher-dose glucocorticoid therapy had higher mean SDI scores (Fig. 3). Furthermore, significantly higher average cumulative glucocorticoid dose was administered to SLE patients with cataracts ($p < 0.001$) or osteoporosis ($p = 0.041$). Cumulative doses were also higher in patients with cerebrovascular events, lower extremity claudication, myopathy and avascular necrosis of the femoral head, but the difference was not statistically significant. We also revealed a strong positive correlation between SDI values and cumulative glucocorticoid doses in the whole cohort of SLE patients ($R = 0.307$, respectively, $p < 0.001$). Moreover, adjusted odds ratios (ORs) by multiple logistic regression analysis showed that cumulative doses were significantly and independently related to SDI (OR 0.05, respectively, $p = 0.027$).

Interestingly, the mean SDI value of patients treated with chloroquine ($N = 158$) was significantly lower than that of lupus patients not receiving chloroquine (1.64 ± 4.54 vs. 2.1 ± 1.82, respectively, $p = 0.024$). In the cases of cyclophosphamide, azathioprine, methotrexate, cyclosporine A and

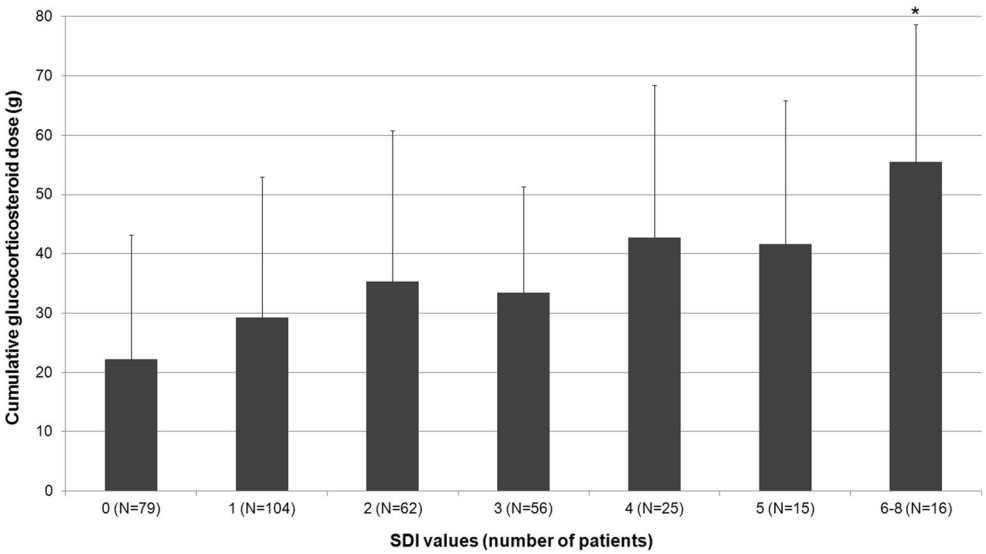

Fig. 3 The effect of long-term glucocorticoid therapy on SDI values. Patients with the highest SDI values (6–8) had a significantly higher average cumulative glucocorticoid dose compared to patients with lower SDI values (0–5) (*$p < 0.001$)

other investigated therapies, there was no significant difference between the mean SDI values of treated and non-treated patients. We did not find any associations between serological parameters and SDI values.

Disease outcome

During the whole follow-up period, 42 (32 women and 10 men) of our patients died. Mortality of the whole patient population was 11.76%; of note, mortality values differed significantly between male and female patients (30.3 vs. 9.88%, respectively, $p = 0.002$). As to the distribution by age groups, we lost 20 (17 female and 3 male), 18 (13 female and 5 male) and 4 (2 female and 2 male) patients, from the >60 years, the 40–59 years and the <40 age groups, respectively. When evaluating the causes of death, infections ($N = 15$) and cardiovascular events, such as myocardial infarction ($N = 11$) and stroke ($N = 3$), were the leading causes, being followed by heart failure ($N = 3$) and tumours including lung ($N = 3$), breast ($N = 2$), liver ($N = 1$) and brain cancers ($N = 1$), as well as malignant melanoma ($N = 1$) and non-Hodgkin's lymphoma ($N = 2$).

The overall 5-year survival rate was 99%, the 10-year survival rate was 98%, and the 15-year survival rate was 95%. The mean survival was 37.21 years [95% confidence interval (CI), 35.33–39.1]. Male patients and patients with 5 or more SDI score could be characterized with significantly worse survival ratios. The mean survival of male patients was significantly worse, compared to the values of female patients [28.78 years (95% CI, 24.82–32.74) vs. 38.19 years (36.24–40.15), respectively, $p < 0.001$]. Moreover, patients with 5 or more SDI score had significantly shortened mean survival time than patients with 4 or less SDI score [24.05 years (95% CI, 20.75–27.35) vs. 43.79 years (42.66–44.93), respectively, $p < 0.0001$] (Fig. 4a, b).

Cox regression analyses revealed three independent prognostic factors: male gender, >4 SDI score and higher cumulative glucocorticoid doses have significant negative effect on disease outcome [male gender: hazard ratio (HR), 2.785 (95% CI, 1.35–5.719), respectively, $p = 0.005$; >4 SDI score: HR, 55.12 (95% CI, 19.15–158.63), respectively, $p < 0.001$; cumulative glucocorticoid doses: HR, 1.02 (95% CI, 1.006–1.035), respectively, $p = 0.005$].

Discussion

In SLE, chronic organ damage has become an increasingly important factor beyond disease activity. Many factors such as geographic and ethnic determinants can affect the severity and course of the disease as well as the development of organ damage. In spite of the wealth in international data, our information on chronic organ damage and understanding of its determinants in SLE patients in East-Central Europe is incomplete, and the results measured by various centres diverge on several points.

Our results show that the patient's gender does not influence the development of chronic organ damages. Yee et al. and Estevez del Toro et al. obtained similar results in British and Cuban patients, respectively [17, 18]. In contrast, Andrade et al. found that male patients developed chronic organ damage faster and in larger numbers [19]. The incidence of the most common damages can vary. Among our patients, the most frequent damages were found in the cardiovascular and neuropsychiatric organ systems. The largest numbers of chronic organ damage were found in the renal and musculoskeletal systems [20], the musculoskeletal and dermal systems [18] and the neuropsychiatric system [21].

We made the assumption that among patients with longer disease duration, the number of chronic organ damages may

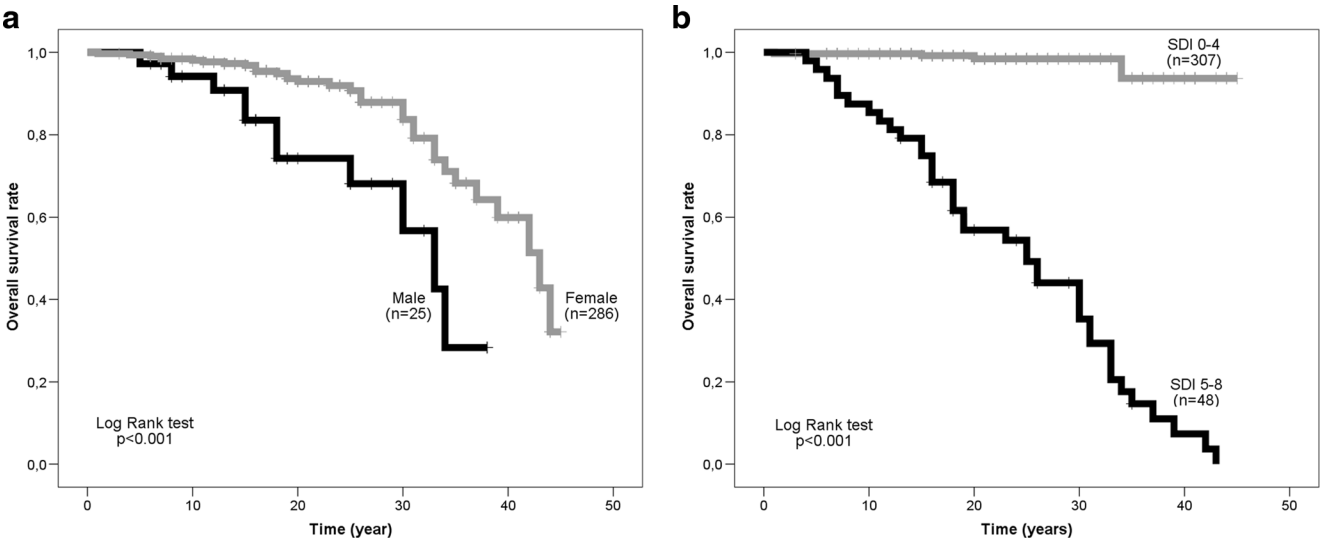

Fig. 4 Kaplan-Meier survival plots for patients subgroups. **a** Male and female patients. **b** Patients with SDI value >4 and <5

be increased. An additional complicating factor was that these patients might have been treated with several types of immunosuppressive therapies. Duration of disease has been designated as a factor in chronic damage by several centres [21]. There is disagreement in the results as to whether SDI value shows a linear increase with disease duration. A gradual increase was found by Cassano [22] in the Argentinian SLE population, and a similar linear increase was measured by Gladman et al. [23]. In agreement with our results, a gradual increase followed by a "plateau phase" after certain duration of disease was described by Becker-Merock and Nossent [24]. Interestingly, we found that the prevalence of chronic damage was 77.9% in our Hungarian SLE cohort, which is higher compared with other European cohort [5, 17]. This difference can be explained by our results, since the follow-up of our patients was longer, compared with the other cohorts, and based on our observations, a significant increase in SDI values develops typically 10 years after diagnosis.

During the course of SLE, chronic damage may develop with a higher frequency among patients with increased disease activity. As described earlier by Lopez et al., disease activity measured by BILAG predicted later damages [25]. In their 5-year prospective study, Stoll et al. found that disease activity defined the development of chronic damages [26]. Although we did not detect a significant difference in the course of the present study, the number of patients showing active disease during the prior 10 years was higher among SLE patients with higher SDI values.

Similar to our results, Maddison et al. described the role of mean age at the time of diagnosis. Higher SDI values were found among patients who were diagnosed after the age of 40 years than those diagnosed under 40 [27]. In contrast, Morgan et al. found that young and adolescent SLE patients sustain more damage over time [28]. In his study of Chinese lupus patients, Feng compared damages in patients with SLE diagnosed in childhood (under 18 years of age), youth (between 18 and 45 years of age) and old age (above 45 years of age); no difference was found in the damage indexes [29].

Various aspects of the effects of glucocorticoids on chronic organ damage were evaluated. Some publications examined cumulative doses of glucocorticoids [30], while others studied the average daily doses [20] or the potential effect of parenteral glucocorticoid therapy [31]. Mae Thaner et al. found that the risk of irreversible damage increased with an increase of the glucocorticoid dose. However, there was no significant difference in the development of damage with administration of low-dose (<180 mg/month) prednisolone [30]. Gladmann et al. found that the amount of glucocorticoid administered had an unequivocal effect on the development of cataracts and a likely effect on cardiovascular events [23]. We also found a strong association with high-dose glucocorticoid therapy cataract and osteoporosis. Cumulative glucocorticoid dose influenced also the cerebrovascular events, myopathy, lower extremity claudication and avascular necrosis of the femoral head, but the difference was not significant.

Regarding immunosuppressive agents, we described the beneficial effect of chloroquine. Data from the Lumina cohort found that the SDI values of patients given initial chloroquine therapy were lower [32]. According to Akhavan et al., in the case of patients treated with chloroquine, less damage could be expected during the 3 years after diagnosis [33].

Several other groups described that SLE patients treated with cyclophosphamide had higher mean SDI values [20, 34]. However, we did not detect any direct correlation between this and other immunosuppressive agents and the frequency of chronic organ damage among our patients. In contrast, Mok and Akhavan described a significant correlation between azathioprine and chronic damage in Chinese and Canadian patients with SLE [33, 35]. A recent study demonstrated the possible role of anti-phospholipid antibodies in the development of organ damage [36]. We did not reveal any associations between serological features and SDI; however, the more careful assessment of anti-phospholipid antibody-positive patients is undoubtedly necessary.

Significant gender differences were found in survival ratios; moreover, elevated SDI scores and higher cumulative doses of glucocorticoids increased mortality risk. This is in accordance with the fact that mortality ratios can improve and toxic adverse effects of glucocorticoids can be decreased by the usage of newer drugs with reduced glucocorticoid doses [37].

Our results demonstrate that as long-term survival in SLE improves, it becomes increasingly important to survey the results and to identify the determinants of chronic organ damage. Our data confirmed that disease duration, age at diagnosis and chronic high-dose glucocorticoid therapy have significant effects on the development of chronic organ damage in the Hungarian patients with SLE. Our data are representative of East-Central European SLE population as well. Additionally, we confirmed the protective effect of chloroquine. Most of the chronic organ damage occurs in the cardiovascular and the neuropsychiatric systems; thus, regular follow-up, screening and adequate therapy are essential for the best clinical outcome.

Compliance with ethical standards All experiments carried out in the study were in compliance with the Declaration of Helsinki.

Disclosures None.

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