Monophasic Disease Course in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Disease course in systemic lupus erythematosus (SLE) is primarily relapsing-remitting. Long quiescent and chronically active patterns are less frequent. We recently described an atypical "monophasic" course in a small number of patients. The aim of the present study was to assess the prevalence and characteristics of such patients in a defined SLE cohort.

Methods. The inception patients of the University of Toronto Lupus Clinic (enrolled within 18 mos of diagnosis) were investigated. No time interval > 18 months was allowed between consecutive visits. A monophasic course was defined as Systemic Lupus Erythematosus Disease Activity Index 2000 = 0 (serology excluded), achieved within 5 years since enrollment and maintained for ≥ 10 years. Descriptive statistics were used.

Results. Of 267 inception patients, 27 (10.1%) achieved prolonged clinical remission (≥ 10 yrs) and 20 (7.5%) sustained remission for the entire followup (18 yrs on average). Twelve patients were receiving no maintenance treatment 10 years after achieving remission. Clinical manifestations at diagnosis (apart from skin and musculoskeletal involvement) included 25% in each of central nervous system involvement and lupus nephritis (LN). Half the patients were serologically active. Ten years after achieving remission, two-thirds of the patients had discontinued glucocorticosteroids; the remaining were treated with 5 mg/day on average. Seven patients relapsed after 10 years, 4 with arthritis, 2 LN, and 1 catastrophic antiphospholipid syndrome.

Conclusion. A monophasic disease course was observed in 7.5% in this inception cohort. Patients sustained remission for 18 years on average, eventually without medications. Further study of such patients may provide unique pathophysiologic insights for SLE. (First Release June 1 2018; J Rheumatol 2018;45:1131–5; doi:10.3899/jrheum.171319)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS PROLONGED REMISSION MONOPHASIC DISEASE

Systemic lupus erythematosus (SLE) is primarily a relapsing-remitting disease with unpredictable flares interspersed with periods of clinical quiescence of varying duration. Initial studies from the Hopkins Lupus Cohort on the patterns of disease activity over time described 3 different subgroups of patients: long quiescent, relapsing-remitting, and chronically active in 4.5 years of followup[1]. Chronically active disease was the most common pattern, accounting for 58% and 40% of the cumulative patient-years, as evaluated by the physician's global assessment (PGA) and the modified Systemic Lupus Erythematosus Disease Activity Index (SLEDAI; excluding serology), respectively[1]. A more recent study from the same center, where all patients with at least 1 year of followup were included, yielded different results applying the same definitions[2]. Relapsing-remitting disease was the most prevalent pattern (54% and 50%, as assessed by the PGA and modified SLEDAI, respectively), followed by long quiescence (31% by the modified SLEDAI)[2].

Steiman, *et al* described an unusual course of "monophasic" disease in a small subset of patients (11/1613, 0.7%) who achieved prolonged remission[3]. In that study, the proportion of patients who achieved a state of complete remission for > 5 years without medications reached 2.4% of the entire cohort. The monophasic patients sustained complete remission for an average of 11.5 years, eventually without medications.

Although these studies provided valuable insights into the

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patterns and fluctuation of disease activity over time in SLE, they all enrolled prevalent patients, many in the late stages of the disease[1,2,3]. Thus, the disease course from diagnosis (inception) onward could not be specified. Given that disease duration has a significant effect on disease activity[4], the prevalence and characteristics of the different patterns of disease activity might have been affected. Further, those patients had already accumulated damage, which is one of the strongest predictors of subsequent damage[5,6]. In addition, the length of followup (1–5 yrs) may have been too short to define the course of a chronic disease such as SLE[1,2,3].

The aim of our present study was to assess the prevalence and characteristics of a monophasic disease course in a defined inception SLE cohort over 10 years of followup after achieving remission.

MATERIALS AND METHODS

Using the database of the University of Toronto Lupus Clinic, we retrieved 883 inception patients who were enrolled in the clinic within 18 months since diagnosis. Patients were followed regularly at 2–6 months intervals according to a standard research protocol, which identified demographic, clinical, immunological, and therapeutic variables [including all variables necessary for the calculation of the SLEDAI 2000 (SLEDAI-2K)]. All patients fulfilled the revised American College of Rheumatology (ACR) criteria for SLE classification[7] or had 3 criteria and a supportive biopsy. All patients have provided written informed consent for studies being conducted at the University of Toronto Lupus Clinic and approved by the University Health Network Research Ethics Board (UHN/REB: 14-7975 AE).

Inclusion criteria consisted of a minimum followup of 10 years (from the time of achieving clinical remission to last clinic visit) and a time interval between visits of < 18 months. The choice of inception patients and prolonged followup (≥ 10 yrs) was deemed most appropriate for describing the disease course of SLE. Patients were considered to be in prolonged complete remission if they had achieved a clinical SLEDAI-2K[8] of 0 [serology excluded (anti-dsDNA antibodies and low complements C3 or C4)] within the first 5 years since enrollment (index date), and had maintained this status for 10 consecutive years. Serological activity was defined as abnormal anti-dsDNA antibodies and/or low levels of complement C3 or C4. Clinical quiescence between visits was ensured by the lack of any treatment escalation (medications had to be stable or could include decreasing doses of antimalarials, glucocorticosteroids, and immunosuppressives). A monophasic disease course was defined based on the maintenance of complete clinical remission for the entire length of followup (until the last clinic visit).

Patients with prolonged complete remission are described regarding demographic (age, sex, ethnicity), clinical (manifestations according to the ACR classification criteria), immunological [anti-dsDNA antibodies, C3/C4, anti-extractable nuclear antigen antibodies (anti-ENA)], and therapeutic (antimalarials, glucocorticosteroids, immunosuppressives) variables at enrollment. Immunological variables, cumulative damage (as expressed by the Systemic Lupus International Collaborating Clinics/ACR Damage Index; SDI), and certain comorbidities (atherosclerotic cardiovascular events, avascular necrosis, and advanced chronic kidney disease) are described at 10 years after the index date. Mortality and flare rate were also analyzed after that 10-year period.

Measurements of continuous variables are represented as mean ± SD, and categorical variables as count (percent). Comparisons were made using unpaired t tests for continuous, chi-square/exact chi-square tests for binary, and the Cochran-Armitage trend test for multilevel categorical variables. Statistical analysis was performed with SAS 9.3; $p < 0.05$ was considered significant.

RESULTS

Of the 267 patients who fulfilled the inclusion criteria, 27 (10.1%, 24 females) achieved prolonged remission (≥ 10 yrs). Clinical manifestations at diagnosis included mucocutaneous involvement in 19 (70.4%), arthritis in 16 (59.3%), myositis in 2 (7.4%), serositis in 5 (18.5%), nephritis in 7 (25.9%), central nervous system (CNS) involvement in 7 (25.9%), cytopenias in 15 (55.6%, leukopenia in 14/15), and vasculitis in 1 patient (3.7%). Lupus nephritis (LN) on biopsy was Class II in 3, Class III in 1, and Class IV in 3 patients. CNS involvement consisted of seizures in 2 patients, organic brain syndrome in 3, multiple strokes (in the context of CNS vasculitis) in 1, and retinal vasculitis in 1. Serologic activity at enrollment was documented in 13 patients (48.1%); 9 had both increased anti-dsDNA titers and decreased C3/C4 whereas 4 patients had only the former. The demographic, SLEDAI-2K, immunological, and therapeutic variables of these patients at baseline (first clinic visit) and at 10 years after remission are shown in Table 1.

A comparison between these patients and the remaining 240 individuals (who followed a more typical relapsing-remitting course) revealed no statistically significant differences regarding the demographic (age at onset, sex distribution, race/ethnicity), clinical (according to the 1997 ACR classification criteria), immunological (anti-dsDNA and anti-ENA antibodies, complement C3/C4), and therapeutic variables (glucocorticosteroids and daily dose, antimalarials, immunosuppressives; Table 2).

Complete clinical remission was achieved within 1.2 years (median, range 0–4.1 yrs) of enrollment. Concerning the alterations in immunological variables over 10 years, anti-dsDNA positivity was decreased (from 48.1% to 22.2%), while that was less pronounced for abnormal C3/C4 (from 33.3% to 29.6%). There were no significant differences regarding the anti-ENA positivity (Table 1). From a therapeutic perspective, antimalarial usage was decreased (from 59.3% to 40.7%; in 3 patients owing to prolonged remission and in 2 owing to ocular toxicity), as well as the use of immunosuppressives (from 33.3% to 11.1%; azathioprine in all 3 patients). Ten years after the index date, about one-third of the patients who were initially treated with glucocorticosteroids were still taking prednisone (from 63% to 22.2%). Mean daily prednisone dose was decreased from 16.8 ± 9.5 mg to 5.3 ± 3.2 mg.

Their SDI was increased from 0.26 ± 0.53 at 1 year after enrollment to 0.96 ± 1.06 at 10 years after remission. Of note, of the 16/27 patients who accumulated damage, 8 did so within the first year of disease and another 8 during the 10 years of remission. In 6 patients, damage was deemed independent of glucocorticosteroids, while that was related to these medications in 10/16 patients. During that period, 1 patient had a cardiovascular event (myocardial infarction), 1 developed advanced chronic kidney disease owing to LN (estimated glomerular filtration rate < 45 ml/min), and 4 patients developed avascular necrosis.

Table 1. Characteristics of the patients at enrollment and 10 years after achieving remission. Values are n (%) unless otherwise specified.

Variable	At Enrollment	At 10 Yrs after Remission
Females	24 (88.9)	
Age at SLE diagnosis, yrs, mean ± SD	39.03 ± 14.06	
Ethnicity		
White	21 (77.8)	
Black	2 (7.4)	
Others	4 (14.8)	
SLEDAI-2K, mean ± SD	10.67 ± 11.57	1.2 ± 1.6
C3/C4	9 (33.3)	8 (29.6)
Anti-dsDNA+	13 (48.1)	6 (22.2)
Anti-SSA/Ro	8 (29.6)	7 (25.9)
Anti-SSB/La	3 (11.1)	2 (7.4)
Anti-Sm	2 (7.4)	2 (7.4)
Anti-RNP	3 (11.1)	4 (14.8)
Glucocorticosteroids	17 (63)	6 (22.2)
Prednisone dose, mg/day, mean ± SD	16.8 ± 9.5	5.3 ± 3.2
Antimalarials	16 (59.3)	11 (40.7)
Immunosuppressives	9 (33.3)	3 (11.1)
SLICC/DI, at 1 yr, mean ± SD	0.26 ± 0.53	0.96 ± 1.06
SLICC/DI > 0, at 1 yr	8 (29.6)	16 (59.3)

SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/DI: Systemic Lupus International Collaborating Clinics/Damage Index.

Beyond the 10-year period, 20/27 patients (7.5% of the initial group of 267 patients) maintained their remission status for the entire duration of followup (17.8 ± 6.7 yrs). Twelve of them (60%) were not taking any medications at 10 years after entering remission.

Concerning the 7 patients who relapsed in the long term (at an average of 15.2 ± 3.8 yrs since diagnosis), 4 exhibited musculoskeletal and/or skin involvement. Major flares (with visceral involvement) were documented during or shortly after pregnancy in 2 patients who developed new-onset LN (1 Class III, 1 Class V) and 1 with catastrophic antiphospholipid syndrome (pulmonary embolism, retinal vein occlusion, and multiple cerebral infarcts). Of note, 6/7 patients had persistently active serology over the 10-year period; 5 of whom with both abnormal anti-dsDNA and C3/C4, and 1 with decreased complement only. Regarding the major flares, there was deterioration in both variables (increasing anti-dsDNA titers and decreasing C3/C4) shortly before the clinical relapse. On the contrary, 2/20 patients who did not relapse had active serology at 10 years after remission.

Concerning mortality, 3 patients died 22 years after diagnosis (average): 1 from lung cancer, 1 from myocardial infarction, and 1 from an unknown cause.

DISCUSSION

In our present study we identified a subgroup of patients with SLE (10.1%) who achieved a prolonged complete remission

Table 2. Comparison of the demographic, clinical, immunological, and therapeutic variables at baseline (first visit) between patients who achieved prolonged remission and those who did not. Values are % (n) unless otherwise specified.

Variable	Patients with Prolonged Remission, n = 27	Patients without Prolonged Remission, n = 240	p
Age, yrs, mean ± SD	39 ± 14.1	35.3 ± 13.1	0.143
Females	88.9 (24)	86.3 (207)	0.703
Ethnicity			
White	77.8 (21)	73.3 (176)	0.895
Black	7.4 (2)	13.3 (32)	
Others	14.8 (4)	13.3 (32)	
Malar rash	44.4 (12)	43.3 (104)	0.912
Discoid rash	11.1 (3)	10 (24)	0.856
Photosensitivity	29.6 (8)	34.6% (83)	0.607
Oral ulcers	14.8 (4)	28.8 (69)	0.123
Arthritis	59.3 (16)	55 (132)	0.881
Serositis	18.5 (5)	22.9 (55)	0.604
Renal involvement	25.9 (7)	27.1 (65)	0.898
CNS involvement	7.4 (2)	7.9 (19)	0.926
Hematologic abnormalities	55.6 (15)	57.1 (137)	0.879
Immunologic abnormalities	88.9 (24)	86.3 (207)	0.894
Antinuclear antibodies	100 (27)	100 (240)	1.000
No. ACR criteria, mean ± SD	4.4 ± 1.4	4.6 ± 1.7	0.613
SLEDAI-2K score, mean ± SD	10.7 ± 11.6	9.8 ± 8.2	0.635
Low complement C3/C4	33.3 (9)	44.2 (106)	0.717
Abnormal anti-dsDNA	48.1 (13)	50.4 (121)	0.974
Anti-SSA/Ro	29.6 (8)	23.3 (56)	0.68
Anti-SSB/LA	11.1 (3)	8.8 (21)	0.904
Anti-Sm	7.4 (2)	15 (36)	0.523
Anti-RNP	11.1 (3)	19.2 (46)	0.535
Glucocorticosteroids	63 (17)	66.7 (160)	0.835
Antimalarials	59.3 (16)	61.7 (148)	0.794
Immunosuppressives	33.3 (9)	45 (108)	0.728

CNS: central nervous system; ACR: American College of Rheumatology; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000

(≥ 10 yrs) after an initial period of clinical activity. Most of these patients (7.5% of the initial cohort) maintained their remission for the entire length of followup (18 yrs on average); some of them did so with no maintenance treatment in the long term. Therefore, prolonged remission for 10 years may serve as a strong prognostic factor for a monophasic course. Despite its rarity, this finding demonstrates that a lifelong remission is achievable, even in cases with severe disease at presentation, such as proliferative nephritis and neuropsychiatric lupus. Our prior observations of monophasic patients were based on non-inception cases and a different study design and thus might have been influenced by the prolonged disease duration[3,4].

Previous attempts to define the patterns of disease activity in SLE failed to identify monophasic patients[1,2,9,10]. This should be attributed to the relatively short followup (1–5 yrs) of those studies. In this context, severe disease manifesta-

tions, such as LN with nephrotic range proteinuria, may be resolved in up to 5 years since induction therapy[11]. Therefore, in the appropriate clinical setting (i.e., when signs of partial remission are evident), it seems reasonable to allow sufficient time for remission to occur. That was the rationale for allowing a 5-year period to achieve remission in our present study.

The reasons for this uncommon disease course are not known. However, it seems possible that, in monophasic patients, the clinically relevant autoimmune response was suppressed promptly (1.2 yrs on average) and irrevocably. Although anti-dsDNA titers were normalized in about two-thirds of these patients, there were no significant changes regarding the anti-ENA antibodies and the levels of complement. Nonetheless, clinical disease did not relapse despite the persistence of these immunologic abnormalities (hence the continuous activation of the immune system). Similarly, Touma, *et al* showed that the burden of autoantibodies (defined as the number of positive antinuclear, anti-dsDNA, antiphospholipid, and anti-ENA antibodies) was not associated with time-adjusted disease activity (as expressed with adjusted mean SLEDAI-2K) or damage after 5 years of followup[12].

Another explanation for this favorable disease course can be sought in genetic factors that may suppress the effective arm of the immune response or enhance immune regulation (or both)[13,14]. Epigenetic variables may also be involved in the attenuation of the pathogenetic process[15]. Further investigation at the genetic level may provide unique pathophysiologic insights for this subset of SLE. Prompt identification of these monophasic patients by a set of gene markers will allow for early de-escalation of therapy, thus avoiding adverse side effects and damage accumulation in the long term. In our present study, half of the patients who accumulated damage did so in the first year after enrollment (during active disease). However, an equal number of patients developed irreversible impairment in the decade after achieving remission.

About a quarter of these patients relapsed despite their 10-year remission. In most of them (and in all who had major flares), there was persistent serologic activity (both anti-dsDNA and low C3/C4) throughout the disease course. Steiman, *et al* showed that about 60% of the serologically active clinically quiescent patients would relapse after 3 years[16]. In that study, fluctuations in the anti-dsDNA titers or complement levels were not associated with the subsequent flare. Further, these patients did not accrue more damage than patients in clinical and serological remission and thus do not warrant active treatment, but close surveillance[17]. In this context, solely increased anti-dsDNA titers and/or decreased C3/C4 (without concomitant clinical activity) are accepted by most investigators for inclusion into the definition of remission[18,19]. Nevertheless, serology monitoring may be particularly indicated in periods with increased risk for disease relapse, such as in pregnancy, even in the absence of clinical activity[20].

From a therapeutic perspective, most patients had discontinued all medications by 10 years after remission. The remaining were taking mainly antimalarials, whereas about a quarter were still treated with glucocorticosteroids (5 mg/day on average). In all these cases, the physician's or patient's reluctance prevented glucocorticosteroid withdrawal. However, in most patients who accrued damage, it could be attributed to glucocorticosteroids (10/16), implying that even low doses may be harmful in the long term.

Limitations of our present study include the relatively small number of patients, which did not allow for further stratification according to certain medications (use of glucocorticosteroids or not) or serological activity. However, to our knowledge, it is the first study to provide evidence that a monophasic disease course pattern exists in SLE based on the strict definition and the duration of followup.

Monophasic disease course was documented in 7.5% of our inception patients. These patients sustained complete clinical remission for the entire length of followup (18 yrs on average), eventually without maintenance treatment. Further investigation of these patients may provide answers for the accurate prognosis of SLE.

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