Prolonged Remission in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the frequency of prolonged remission in systemic lupus erythematosus (SLE) using strict criteria for remission and to define disease characteristics and prognosis of patients achieving this state. To also determine the frequency of remission utilizing less restrictive definitions, such as allowing shorter period of disease quiescence, persistence of serological activity, or treatment in the absence of clinical disease.

Methods. Patients registered in the Lupus Clinic database between 1970 and 1997 with visits no more than 18 months apart were identified. Prolonged remission was defined as a 5-year consecutive period of no disease activity (SLE disease activity index, SLEDAI = 0) and without treatment (corticosteroids, antimalarials, or immunosuppressants). Prolonged serologically active, clinically quiescent (SACQ) was defined as active serology (elevated anti-dsDNA by Farr assay or hypocomplementemia) but no clinical activity on SLEDAI and no treatment.

Results. Seven hundred and three patients fulfilled inclusion criteria. Of the 703 patients 46 (6.5%) achieved complete remission for at least 1 year, whereas only 12 patients (1.7%) had prolonged complete remission of at least 5 years on no treatment. Although the frequency of disease manifestations was similar to the patients not in remission, the 5-year remission group was distinguished by lower overall disease activity as measured by adjusted mean SLEDAI, lower prevalence of anti-DNA antibodies, and lower use of steroids and antimalarials.

Conclusion. Prolonged complete remission in lupus is rare. Therefore with current therapies continued vigilance for disease recurrence is necessary. (J Rheumatol 2005;32:1467–72)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS REMISSION SLE DISEASE ACTIVITY INDEX

Systemic lupus erythematosus (SLE) is a chronic disease characterized by a fluctuating disease course. Although morbidity and mortality have been the subject of extensive research[1-3], there are relatively few reports of prolonged remission.

A number of indices of disease activity in SLE have been developed and validated, but these have not yet led to uniform criteria for disease quiescence or remission. These disease indices include the SLE disease activity index (SLEDAI)[4], systemic lupus activity measure[5], and British Isles Assessment Group index[6]. Of these, the SLEDAI showed the most sensitivity to change over time[7]. In addition, outcome studies have tended to focus on the significant longterm morbidity and mortality of lupus, which has led to the development of a damage index. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index measures damage resulting from both disease and treatment in lupus[8].

In contrast, the poor agreement on the definition of disease remission is reflected in the varying criteria for remission in SLE in reports to date. Most concur that no clinical signs of activity should exist and that patients should be receiving no treatment. The importance of serological and laboratory abnormalities varies[9-12]. With respect to duration of disease inactivity, experience would suggest that while SLE may be quiescent for several months to a year, this may simply represent a transition phase of the disease and may not be of longterm clinical importance, whereas prolonged inactivity of 5 or more years would on the other hand signify an important disease-free period. Since one of the advantages of prolonged inactive disease is the ability to withdraw potentially harmful disease modifying therapy, it is important also to assess the number of patients, regardless of serological activity, who are able to stop therapy for such a prolonged period.

As discussed by Schneider[13], the purest definition of complete remission should incorporate normal markers of disease activity such as complement and autoantibodies. Since antinuclear antibodies (ANA) and extractable nuclear antigens are less likely to vary with disease activity, seroconversion of these antibodies is not relevant to this definition; anti-dsDNA antibodies may be more reliable in this

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regard and are particularly associated with renal disease, but are not present in all lupus patients[14]. Adding to the complexity of the issue of active serology in SLE is the subset of lupus patients who present with serological activity and clinical quiescence for a prolonged period. First described by Gladman, *et al*[15], these patients may present a management dilemma until they declare themselves over a longer period as being truly without occult clinical disease, despite active serology. As a potentially treatment free subset, they represent a clinically important group.

A further issue in the concept of remission is that treatment practice may have been altered with the finding that antimalarial drugs can reduce flares of lupus with an acceptable risk-benefit ratio[16]. This translates in reality to patients without evidence of active disease potentially remaining on longterm therapy.

Our aim was to determine the frequency of prolonged remission in SLE using strict criteria for remission and to define disease characteristics and prognosis of patients achieving this state. We also determined the frequency of remission utilizing less restrictive definitions, such as allowing shorter period of disease quiescence, persistence of serological activity, or treatment in the absence of clinical disease.

MATERIALS AND METHODS

Setting. The University of Toronto Lupus Clinic at the Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital was established in 1970 to study clinical-laboratory correlations in SLE. All patients entered fulfill 4 or more of the 1971 or 1982 American College of Rheumatology (ACR) classification criteria, or had 3 criteria and a typical lesion of SLE, such as a renal or skin biopsy[17]. The Lupus Clinic serves as a tertiary care facility associated with the University of Toronto. It also serves as a primary and secondary care facility in downtown Toronto. The Clinic contains a broad spectrum of patients with SLE including patients with acutely active disease with varying manifestations, patients with no current disease activity on maintenance therapy, and patients in complete remission off all therapy.

Patient selection. Patients with SLE were registered in a database and followed prospectively in a longitudinal cohort study at the University of Toronto Lupus Clinic. Patients are followed with clinical and laboratory information collected using a standardized protocol at clinic visits at 2 to 6-month intervals. Patients registered in the Lupus Clinic have regular visits scheduled regardless of disease activity. Patients were included in this study if clinic visits were no more than 18 months apart, for a minimum 5-year period. The average period between visits was 4 months.

Definitions. Our primary objective was to look at prolonged complete remission defined as a period of at least 5 years with clinical and laboratory quiescence (SLEDAI-2K = 0) and the absence of pharmacotherapy for lupus, specifically no corticosteroids, antimalarials, or immunosuppressants. Nonsteroidal antiinflammatory therapy was permitted.

To examine broader definitions of remission of SLE, we identified the frequency of remission as defined by the following criteria: (1) clinical and serological inactivity allowing medications and (2) persisting serological activity (anti-DNA antibodies and low complement) with clinically quiescent disease (SACQ) on at least 3 consecutive visits, no more than 18 months apart. We looked at SACQ with and without medications. For each of these definitions a different duration (1, 2, 3, 4, and 5 years) was examined.

Disease activity. Disease features as listed in the SLEDAI-2K[4] were assessed. The adjusted mean SLEDAI (AMS), recently validated, was utilized as a measure of disease activity over time[18]. AMS is based on a mathematical formula that reflects the average level of SLEDAI-2K over time. AMS is likely to be very close to the mean SLEDAI-2K if patients are followed at exact set intervals, but more accurately accounts for varying time intervals between visits, such as occur in the usual clinic setting. Anti-dsDNA antibody levels were evaluated by the Farr assay; complements C3 and C4 were evaluated by standard methods.

Definitions for organ involvement. Arthritis: inflammatory arthritis in at least 2 joints. Cutaneous: inflammatory type rash, alopecia, mucous membrane ulcers. Vasculitis: ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, biopsy or angiogram proof of vasculitis. Renal: hematuria, pyuria, (attributed to lupus), casts, proteinuria > 0.5 g/24 h, elevated serum creatinine, renal replacement therapy, renal biopsy showing WHO class 2-6. Biopsies are offered to all our patients at presentation regardless of clinical evidence of renal disease, or at presentation with renal disease. Central nervous system (CNS): seizures, psychosis, organic brain syndrome, retinal changes of SLE, cranial or peripheral neuropathy, lupus headache, stroke syndrome, transverse myelitis.

Statistical analysis. Patients were classified in one of 3 groups: those who achieved complete remission for at least 5 years, those who achieved complete remission for only one year, and those who did not achieve remission of at least one year. Disease characteristics and therapy present prior to the time of remission in the remission groups and up to December 2001 in the non-remission group were analyzed. Analysis of variance was used to compare the 3 groups overall. Pairwise comparisons between remission groups were done using Wilcoxon rank sum test in the presence of continuous variables and Fisher's exact test for binomial data.

RESULTS

Prior to January 1st, 1997, 850 patients were identified in the SLE cohort. Of these 703 patients had visits no more than 18 months apart for at least a 5-year period and were the subject of the following analyses. Of the 703 patients 46 (6.5%) achieved complete remission for at least 1 year, whereas only 12 patients (1.7%) had prolonged complete remission of at least 5 years with no treatment. To examine broader definitions of remission we identified the frequency of remission as defined by clinical and serological inactivity but allowing medications, and persisting serological activity with clinical quiescence with and without medications (Figures 1 and 2). Figure 1 depicts the number of patients achieving different levels of remission, from clinical serological remission on medications to complete remission off medications. The number of patients in any remission decreased with time (from 1 year to 5 years). Importantly, by year 2 the number decreased by at least half and by year 5 by three-quarters. Moreover, the number of patients in remission decreased with progressive restriction of medication use in the definition. Thus remissions were more common when all drugs (steroid, immunosuppressives and antimalarials) were allowed, and became less frequent as only immunosuppressives and antimalarials, then antimalarials alone, and then no medications were allowed. Similar observations can be seen in Figure 2 for patients in remission with serological activity (SACQ). Progressive dramatic reduction in number of remissions occurs with increasing time and excluding medication use.

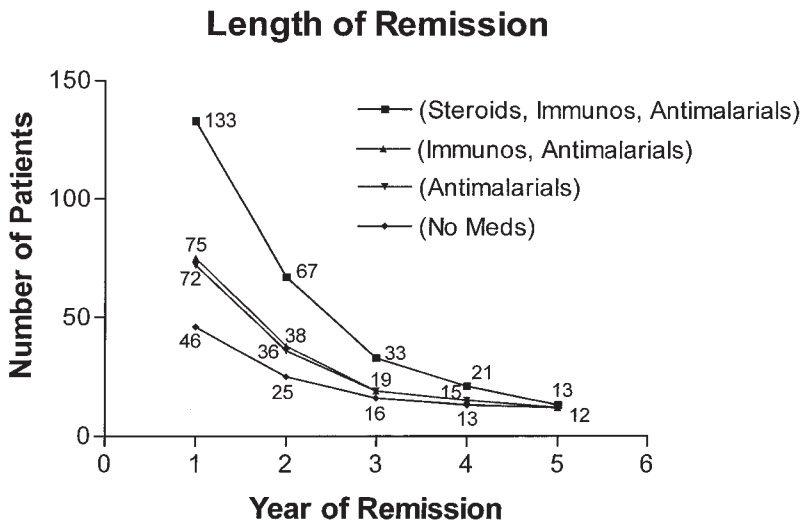

Figure 1. Number of patients achieving different levels of remission, from clinical serological remission on medication to complete remission with no medication. Immunos: immunosuppressive agents.

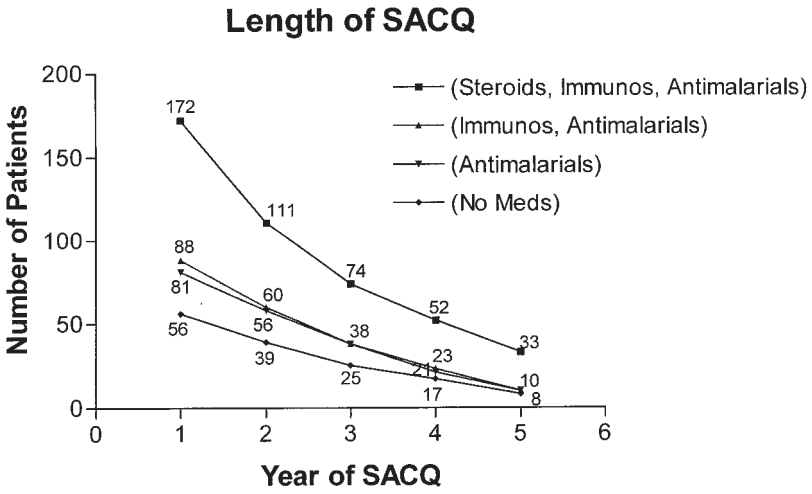

Figure 2. Number of patients with different periods of serologically active, clinically quiescent disease with or without medication. Immunos: immunosuppressive agents.

Table 1 describes the demographic features of the 46 patients who achieved complete remission for 1 or 5 years and the 570 patients who did not achieve any remission. Twelve patients (1.7%) fulfilled the requirement for prolonged complete remission. Their mean duration of remission was 7.1 ± 3.5 years (range 5 -17 yrs, median 6 yrs). An additional 34 patients achieved a complete remission of one year but less than 5 years. The mean duration of remission in this group was 1.8 ± 0.9 years. Patients who never achieved remission were younger at diagnosis and had longer disease duration at study.

Table 2 shows disease characteristics and therapy present prior to remission in the 1 and 5-year complete remission groups and up to December 2001 in the non-remission group. Patients who never achieved remission had a higher frequency of cutaneous and CNS manifestations than patients who achieved a 1-year remission. Although the frequency of renal manifestations in the 5-year remission group was the same as the non-remission group, the nature of the renal pathology differed. Of patients with 5-year remission 6 had biopsies with 2 (33%) being proliferative. In the non-remission group, 69% of 164 biopsies had proliferative glomerulonephritis. In the 1-year remission group 4 (66%) had proliferative glomerulonephritis. AMS was significantly higher in the non-remission group compared to both remission groups, even when adjusted for disease duration. As expected, AMS was higher in the 1-year remission compared to the 5-year remission group. SLICC/ACR DI

Table 1. Demographics for patient groups.

	Remission			p		
	5 yrs, n = 12	1 yr, n = 34	Never, n = 570	5 yrs vs 1	5 yrs vs Never	1 yr vs Never
Sex, F	10 (83.3%)	30 (88.2%)	510 (89.5%)	0.6435	0.3716	0.7742
Age at diagnosis	37.9 ± 14.0	35.8 ± 13.5	32.0 ± 13.1	0.6616	0.1241	0.0452
Age at 1st visit	40.2 ± 13.8	37.8 ± 12.9	35.1 ± 13.3	0.5235	0.1660	0.1801
Disease duration at 1st visit	2.3 ± 4.5	1.9 ± 3.3	3.1 ± 4.6	0.6388	0.1291	0.0682
Age at study, yrs	48.7 ± 15.1	45.2 ± 12.2	45.4 ± 13.9	0.3482	0.3139	0.7903
Disease duration at study entry, yrs	10.9 ± 10.3	9.3 ± 7.1	13.4 ± 8.5	1.00	0.1752	0.0065

Table 2. Disease characteristics. Values are n (%) unless otherwise stated.

	Remission			p		
	5 yrs, n = 12 (%)	1 yr, n = 34 (%)	Never, n = 570 (%)	5 yrs vs 1	5 yrs vs Never	1 yr vs Never
Organ						
Arthritis	6 (50.0)	22 (64.7)	426 (74.7)	0.4949	0.0871	0.1942
Cutaneous	11 (91.7)	26 (74.5)	526 (92.3)	0.4092	1.00	0.0055
Vasculitis	4 (33.3)	10 (29.4)	221 (38.8)	1.00	0.7742	0.2753
Renal	11 (91.7)	22 (64.7)	444 (77.9)	0.1345	0.4781	0.0752
CNS	6 (50.0)	12 (35.3)	318 (55.8)	0.4949	0.7731	0.0197
AMS	2.54 ± 0.99	3.70 ± 2.44	6.25 ± 3.61	0.0481	< 0.0001	< 0.0001
Adjusting for disease duration				0.1038	0.0002	< 0.0001
SLEDAI-2K at 1st visit, mean ± SD	10.4 ± 12.7	8.6 ± 7.5	10.7 ± 8.5	0.8309	0.3386	0.1815
SLICC at study entry, mean ± SD	1.25 ± 1.14	0.85 ± 1.52	1.92 ± 2.13	0.0593	0.5504	0.0006
Low complement	9 (75.0)	25 (73.5)	489 (85.8)	1.00	0.3947	0.0511
DNA binding	5 (41.7)	19 (55.9)	427 (74.9)	0.5077	0.0159	0.0142
Abnormal PTT	8 (66.7)	22 (66.7)	371 (65.4)	1.00	1.00	0.8847
Abnormal ACL	1/2 (50.0)	2/12 (16.7)	255/395 (64.6)	0.3956	1.00	0.0012
Steroids	7 (58.3)	20 (58.8)	481 (84.4)	1.00	0.0306	0.0001
Antimalarials	3 (25.0)	10 (29.4)	380 (66.7)	1.00	0.0043	< 0.0001
Immune suppressants	3 (25.0)	6 (17.7)	276 (48.4)	0.6777	0.1460	0.0005

CNS: central nervous system, AMS: adjusted mean SLEDAI. SLICC: Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index. SLEDAI-2K: SLE Disease Activity Index.

score at study was higher in patients who did not achieve remission compared to patients who achieved a 1-year remission.

With regard to laboratory manifestations, anti-cardiolipin antibodies were significantly more frequent in the non-remission group compared to the 1-year remission group. Anti-DNA antibodies were significantly more frequent in the non-remission compared to both the 1 and 5-year remission groups. Both the 1-year and the 5-year remission groups were significantly less likely to have been on corticosteroid or antimalarial therapy. Immunosuppressive therapy was significantly lower only in the 1-year group compared to the non-remission group. In general, patients who sustained at least a 1-year remission had less severe disease and were taking less therapy than patients who remained active throughout their course (Tables 1 and 2).

Thus the 5-year remission group was distinguished from the non-remission group by lower overall disease activity as measured by the AMS, lower prevalence of anti-DNA antibodies, and lower use of steroids and antimalarials. Of the 12 patients who had 5-year remission, 3 were lost to followup while still in remission. Of the 9 patients continuing to be followed at the clinic following their period of remission, none required corticosteroid or cytotoxic treatment in the 12 months following remission and 2 remain in remission for 5 and 17 years, respectively. In 7 of the 9 patients, remission was broken by clinical manifestations in 4, and laboratory abnormalities in 3. The clinical features included nasal ulceration (1) and renal manifestations (3). Renal features included microscopic hematuria (2) and proteinuria combined with sterile pyuria (1). The 3 patients with serological features ending remission all had an elevated anti-dsDNA antibody and normal complement levels.

Eight patients were identified who fulfilled the criteria for a 5-year period of clinical quiescence but with some serological activity. Two patients were identified on antimalarial therapy alone who would otherwise satisfy the definition of prolonged remission and 2 patients on antimalari-

al therapy alone who showed clinical quiescence but with some serological activity.

DISCUSSION

Remission in SLE defined as prolonged (5 years) and complete remission (clinical, laboratory, and no treatment) is rare, occurring in only 12 of 703 patients (1.7%) followed prospectively. Even if complete remission is defined as at least 1 year, only 46 of the 703 patients (6.5%) achieved remission. As well, when remission was defined more broadly as prolonged SACQ, or when antimalarial therapy is added to these definitions, prolonged remission was rare, occurring in 8 additional patients. This is in contradistinction to a number of other studies[9-12], usually because their definitions of remission were not as stringent. We have modeled our definition after that used in oncology (5 years disease-free).

Other studies have shown varying results. The previous evaluation of prolonged remission in this cohort published in 1982[9] found, among a cohort smaller in number, that 4/160 (2.5%) achieved remission as defined by absence of clinical activity, no treatment, normal complement levels, and negative anti-dsDNA antibody for a median period of 75 months. At that time no standardized measure of disease activity had yet been defined and validated.

In one of the earliest reports of remission, in 1964, Dubois[19] described a high rate of spontaneous remission occurring in 183 (35%) patients in a cohort of 520. These 183 had multiple spontaneous remissions of varying lengths of time. In 9 patients the remissions were between 10-20 years' duration. This frequency of 9 out of 520 (1.7%) is identical to our prolonged complete remission rate.

In 1985, Heller and Schur[12] defined patients in clinical and serological remission as those showing no clinical activity, seroconverting from positive to negative ANA, and being either on or off therapy. Thirteen (4%) of 305 patients achieved these criteria, with duration ranging from 6 months to 13 years. Complement levels determined in 12 of the 13 patients were all normal at the time of clinical and serological remission. There was a somewhat lower prevalence of renal and neuropsychiatric manifestations in those achieving remission. The 5 patients continuing on therapy at the time of remission were receiving low dose corticosteroids (3) and hydroxychloroquine (2). This frequency of remission on therapy (4%) is similar to the 6.5% rate for the minimum 1-year remission on therapy in our study.

In contrast to these low frequencies, Formiga, *et al*[11] found 24/100 (24%) of inception patients achieved remission, defined as absence of clinical activity, permitting withdrawal of therapy for at least 1 year. In this retrospective study serological activity was allowed. This compares with a frequency of 8% (56/703) in our study considering patients with persistent serological activity on no therapy. In the Formiga study the group of 24 remained in remission for a mean of 55 ± 40 months (range 16-56). The mean followup in this group was 140 ± 75 months. There were no statistically significant differences between the remission and non-remission groups.

Drenkard, *et al*[10] defined remission as at least 1 year during which clinical disease activity was absent, permitting withdrawal of all treatment for lupus, including nonsteroidal antiinflammatory drugs. Patients with mild symptoms on no treatment were excluded. A disease activity scoring system was not used and serological activity was not uniformly evaluated. Of 667 patients, 156 (23.4%) achieved this definition at least once during followup. Changes in laboratory variables were permitted in this period of remission, as long as clinical features were absent. This rate of remission is much higher than that observed in our cohort, for patients without clinical activity on no therapy but with serological activity.

In our study, even when we relaxed our definition to allow serological activity only 102 of 703 patients (14.5%) were found to have no clinical activity on no therapy for 1 year. We anticipated that there might be a group of patients with clinically quiescent disease, with or without active serology, who remain on antimalarial therapy. Since hydroxychloroquine may prevent flares of lupus[16], there is a rationale for maintaining patients on therapy despite their being clinically well. Furthermore, these drugs have additional therapeutic effects in lupus, beneficial at times of apparent disease quiescence. These include the positive effect on lipid profiles[20,21] particularly when corticosteroids are concomitantly used[22,23] and also potential anti-thrombotic effects[24,25]. When we allowed antimalarial therapy in the definition of remission, we found a 5 year disease-free state was still rare. We did not find significant numbers of patients in this category perhaps because our study dates back 2 decades, prior to the accepted use of antimalarials for prophylactic purposes. It is also possible that at the time of this study physicians were reluctant to prescribe antimalarial drugs to patients who had not received therapy for a prolonged period and remained without clinical disease. A survey of treatment practice in the last decade would therefore be of interest in this regard.

In this small group of patients with prolonged remission there was a lower AMS, less frequent presence of anti-dsDNA antibodies, and lower likelihood of treatment with corticosteroids and immunosuppressive agents prior to the period of remission. On the other hand, patients who achieved only a 1-year remission had multiple associated factors (Tables 1 and 2). Most of these factors were no longer associated with remission when examined for 5-year remission. These features identify this group of patients as having milder overall disease. Nevertheless, major organ involvement was similar in the prolonged complete remission patients as in the entire cohort. In fact 11 of the 12 patients with prolonged remission had renal manifestations

prior to their remission. Similarly, when remission was broken in 7 of these 12 patients, the recurrent manifestations could either be serological only (3), minor clinical manifestations (mucous membrane ulcers in 1 patient), or major clinical manifestations (3). Therefore the nature of the organ involvement characterizing disease prior to and after a period of remission does not distinguish these patients. Only careful longterm surveillance of patients will identify those destined to go into remission and similar careful followup of those in remission will detect relapse of their disease. Obviously newer treatment strategies are required to alter this prognosis.

To compare incidence/prevalence of remission among centers it will be necessary to develop consensus on the definition of remission and its duration. It is likely that remission will be defined in a number of ways including complete clinical and serological remission, clinical remission with persistence of serological abnormalities, and either of these with or without therapy.

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