Prolonged Clinical Remission in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Systemic lupus erythematosus (SLE) is typically a relapsing/remitting disease. However, some patients experience prolonged remission. These patients may provide further insights into SLE pathophysiology. In this study we characterize their clinical course.

Methods. Prolonged remission was defined as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) = 0, = 2, or = 4 (based on serology) for ≥ 5 consecutive years, with visits ≤ 18 months apart. The patients could be taking antimalarials, but not corticosteroids or immunosuppressives. Flare was defined as clinical activity on SLEDAI-2K, or by corticosteroid/immunosuppressive initiation. Each patient's preremission course was classified as monophasic, relapsing/remitting, or chronic active. These patients were compared to matched SLE controls and patients achieving remission on medications.

Results. A total of 38/1613 (2.4%) patients achieved prolonged remission while taking no medications. The mean duration was 11.5 ± 6.4 years. Twenty-seven patients (71.0%) had relapsing/remitting disease, 11 (28.9%) had monophasic illness, and none had chronic active disease prior to remission. They differed from matched controls in ethnicity, disease activity at first visit, and cumulative organ damage. There were 34/1613 patients (2.1%) who achieved prolonged remission while taking steroids and/or immunosuppressives, with mean duration 8.5 ± 2.9 years. Twelve patients (35.3%) experienced disease flare. They were younger at diagnosis, with more disease activity prior to remission than patients taking no medications.

Conclusion. Prolonged remission is an infrequent outcome among patients and is preceded by an atypically monophasic clinical course in a significant minority. Those taking medications represent a heterogeneous group: those who will tolerate eventual taper, and those whose disease activity was merely suppressed by ongoing immunosuppression. Prolonged remission may reflect unique pathophysiologic mechanisms, and warrants further investigation. (First Release Aug 1 2014; J Rheumatol 2014;41:1808–16; doi:10.3899/jrheum.131137)

Key Indexing Terms:
SLE DISEASE ACTIVITY OUTCOMES SEROLOGIC ACTIVITY

In early reports, systemic lupus erythematosus (SLE) was classically described as an unrelenting disease that would often culminate in death[1]. However, the disease has been increasingly recognized as a chronic, albeit potentially fatal, relapsing-remitting disease. Given the increased risk of organ damage with disease activity over time, remission is a very desirable outcome. Studies have revealed that the propensity for flare or remission in the initial years of disease are predictive of longterm outcome, with those remitting earlier having a more favorable disease course[2,3]. Substantial variability exists, however, in the nature and duration of remission, likely attributable to differences in patient cohorts and inconsistent remission definitions (Table 1).

One important discrepancy between studies is that of the significance of isolated, potentially pathogenic serologic activity, that is, elevation in anti-dsDNA antibodies and/or hypocomplementemia, in the setting of clinical quiescence. A description of these patients, termed "serologically active clinically quiescent," can first be found in the literature in 1979, when Gladman, *et al* described 14 patients who were clinically quiescent, but had persistently positive SLE preparations and antinuclear antibodies, hypocomplementemia, and high levels of DNA binding[4]. These patients had displayed typical SLE features in the past, including

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Table 1. Past remission studies.

Authors, (ref)	Yr of Publication	Remission Definition	Serologic Activity Permissible	Treatment Permissible	Remission Achieved, % (total n)	Remission Duration
Dubois (10)	1956	N/D	N/D	N/D	38 (156)	Up to 26 yrs
Dubois & Tuffanelli (11)	1964	N/D	N/D	N/D	35 (520)	Up to 26 yrs
Gladman, *et al* (4)	1979	Asymptomatic	Yes (all patients)	None	7.8 (180)	4.25 yrs (mean), 2–11 yrs (range)
Tozman, *et al* (12)	1982	Absence of clinical manifestations of disease	No	None	2.5 (160)	75 mos (median)
Heller & Schur (33)	1985	Asymptomatic without active organ involvement	No	AM, "low dose" CS	4 (305)	0.5–13 yrs (range)
Walz LeBlanc, *et al* (34)	1994	Clinical SLEDAI = 0 over ≥ 3 consecutive clinic visits	Yes (all patients)	Any	N/D	N/D
Drenkard, *et al* (3)	1996	≥ 1 yr during which lack of clinical disease activity permitted withdrawal of all SLE treatment	Yes	None	23 (667)	4.6 ± 3.6 yrs (mean ± SD), 1–17.3 yrs (range)
Barr, *et al* (35)	1999	Clinical SLEDAI or PGA = 0 for ≥ 1 yr (1 PGA to < 1.0 permissible)	Yes	N/D	16 of patient-yrs of followup (204)	2.3 ± 1.1 yrs (mean ± SD), 1.0–5.7 yrs (range)
Formiga, *et al* (24)	1999	≥ 1 yr during which lack of disease activity permitted SLE treatment withdrawal	Yes	None	24 (100)	55 mos (mean)
Swaak, *et al* (36)	1999	Absence of disease-related signs with no need for treatment	N/D	None	0 (187)	N/A
Urowitz, *et al* (16)	2005	Clinical SLEDAI = 0 for ≥ 5 yrs	Yes	None	1.7 (703)	7.1 ± 5.3 yrs (mean ± SD), 5–17 yrs (range), 6 yrs (median)
Nossent, *et al* (37)	2010	"By PGA" not otherwise defined, within 1st yr of SLE diagnosis	N/D	N/D	27.5 (200)	N/D; 49% achieving remission maintained over 5-yr followup
Steiman, *et al* (18)	2010	Clinical SLEDAI-2K = 0 for ≥ 2 yrs	Yes (all patients)	AM	6.1 (924)	182 weeks (mean), 158 weeks (median)
Conti, *et al* (38)	2012	Clinical SLEDAI-2K = 0 for ≥ 2 yrs	Yes (all patients)	AM	2.2 (45)	N/D

N/D: not described; AM: antimalarials; CS: corticosteroids; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLE: systemic lupus erythematosus; PGA: physician global assessment; N/A: not applicable.

major organ manifestations, such as renal or central nervous system involvement.

Serologically active clinically quiescent patients present a clinical conundrum of reconciling the presence of potentially pathogenic serologic activity with the clinical picture of complete quiescence. Are these patients similar to those who are both serologically and clinically quiescent, and thus could be spared exposure to corticosteroids and immunosuppressive medications and their associated side effects? A method to distinguish which serologically active clinically quiescent patients will remain quiescent versus those who will ultimately flare would be clinically beneficial.

Another important group of potentially remitted patients are those who have evolved to clinical quiescence, with or without serologic quiescence, while being treated with corticosteroids and/or immunosuppressive medications. While such patients are in a disease-free state, they do so under the coverage of medications, which bear significant associated risks. In these patients, it is only with medication taper and withdrawal that the clinician can determine whether the patient has truly remitted or, alternatively, whether their disease is merely suppressed by a quantity of corticosteroid or immunosuppressive medication. If the former, then drug discontinuation is the goal to minimize treatment-associated damage; however, if the latter, medications must be maintained to minimize disease-associated morbidity. Thus, these patients comprise a mixed group of 2 disease states necessitating very different approaches to management.

To gain insights into the nature and extent of prolonged remission among patients with SLE, we have defined remission as at least 5 years of clinical quiescence in patients with and without active serologic markers, and those taking and not taking corticosteroids and immunosuppressive medications.

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 classification criteria, or 3 criteria and a typical biopsy lesion of SLE. The lupus clinic is a tertiary care facility affiliated with the University of Toronto. It also serves as a primary and secondary care

facility in downtown Toronto. The clinic's patients range from those with acutely active disease of variable manifestations, to patients with inactive disease who are taking maintenance therapy, to patients in complete remission, who are not taking any therapy[5]. All patients sign informed consent to allow their clinical, serologic, and genetic material to be studied and reported.

Patient selection. Patients with SLE are followed with clinical and laboratory information collected using a standardized protocol at clinic visits, typically at 2- to 6-month intervals, which occur regardless of disease activity. Patients registered in the clinic database between July 1970 and October 2011 were identified. Serologically and clinically quiescent, and serologically active clinically quiescent patients with SLE were selected from this population.

Definitions. Serologically and clinically quiescent was defined as at least a 5-year period without clinical and serologic activity [Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI), SLEDAI-2K score = 0], where clinic visits were no more than 18 months apart. Serologically active clinically quiescent was defined as at least a 5-year period without clinical activity and with persistent serologic activity (SLEDAI-2K score = 2 or 4, from positive anti-dsDNA antibody and/or hypocomplementemia only, at each clinic visit) where clinic visits were no more than 18 months apart. A mixed remission period was defined as one during which a patient's serology fluctuated between serologically and clinically quiescent, and serologically active clinically quiescent status. Patients were then divided into those taking no corticosteroids or immunosuppressives for the duration of quiescence (No Medication group), and those who continued to take one or both of these classes of medications (Medication group). Patients in all groups could be taking antimalarials.

Disease flare was defined as any increase in SLEDAI-2K score not accounted for by either hypocomplementemia or anti-dsDNA, or the initiation of (No Medication group) or increase in (Medication group) corticosteroid and/or immunosuppressive therapy.

Disease course was defined as either monophasic, relapsing-remitting, or chronic active. A monophasic disease course was defined as a single flare [clinical SLEDAI-2K activity at ≥ 1 consecutive visit(s)] followed by clinical quiescence, as defined above.

A relapsing-remitting course was defined as at least 2 discrete episodes, separated by periods of clinical quiescence.

A chronic active course was defined as persistent clinical activity, without any intervening period of quiescence.

Organ manifestations were defined by SLEDAI-2K descriptors; diagnosis of "cardiac — atherosclerotic", "thrombotic", and "pulmonary" manifestations were made clinically and through the use of imaging modalities.

Serologic studies. Anti-dsDNA antibodies were quantified by the Farr assay (normal ≤ 7 U/ml)[6]. Serum complement factor 3 and 4 (C3 and C4) were evaluated by nephelometry (normal range C3 0.9–1.8 g/l; C4 0.1–0.4 g/l, Siemens Healthcare Diagnostics Inc.)[7].

Analysis. Patients in the No Medication group were matched 1:3 to SLE controls on the bases of sex, age at first clinic visit, decade of entry into the clinic, length of clinic followup, and disease duration at first remission visit. A second, unmatched control group was selected from the remainder of the SLE cohort (with sole criterion for inclusion being > 5 years of followup in clinic) to ensure that matching criteria of the first control group were not, in fact, driving the rare outcome. Adjusted mean SLEDAI (AMS), a validated measure accounting for variable duration between clinic visits in reporting SLE disease activity over time[8], was calculated for each patient from clinic entry until remission; in matched controls, AMS was calculated from clinic entry to a visit of matched duration. Descriptive statistics were used. Comparisons were made using t-tests and McNemar's test. Logistic regression analysis was pursued, guided by the findings of the univariate analysis. Charts were reviewed to elucidate the rationale for continued corticosteroid and/or immunosuppressive use among those patients in the Medication group.

RESULTS

No Medication group. There were 1613 patients with visits identified in the SLE clinic database. Thirty-eight of 1613 patients (2.4%) achieved prolonged, medication-free remission. One patient experienced 2 discrete prolonged medication-free serologically active clinically quiescent remission periods (with about 8 years between the end of the first and start of the second remission period). For this patient, only the first prolonged remission was included in the analysis. Thirty-two patients (84%) were women.

Mean duration of SLE clinic followup was 21.8 ± 10.3 years, and the mean time to remission from clinic entry was 9.1 ± 8.8 years. The mean prolonged remission duration was 11.5 ± 6.4 years. Seventeen remission periods were serologically and clinically quiescent, 10 were serologically active clinically quiescent, and 11 were mixed serologically and clinically quiescent/serologically active clinically quiescent. When subdivided by type, mean remission duration was 9.8 ± 5.7, 9.2 ± 3.3, and 16.5 ± 6.4 years for those who were serologically and clinically quiescent, serologically active clinically quiescent, and mixed remissions, respectively. All but 1 of the 28 patients who continue to be followed contemporarily were in remission at their last clinic visit. Antimalarials were used by 16 patients (42%) at remission onset, with a further 5 (13%) using them at some point during their remission.

Twenty-seven patients (71%) had had relapsing/remitting disease, 11 (29%) had monophasic illness, and none had chronic active disease prior to remission. The clinical manifestations in those patients with a monophasic course are outlined in Table 2. Mean AMS from clinic entry until remission onset was 3.02 ± 1.93.

Case-control analysis. There were more white cases than controls (82% vs 72%, p = 0.02). Cases had significantly lower SLEDAI-2K at first clinic visit (8.03 ± 9.47 vs 10.6 ± 9.04, p = 0.02), and their AMS until remission onset (vs clinic visit of matched duration from clinic entry) was similarly significantly lower (3.02 ± 1.93 vs 5.95 ± 3.56, p < 0.0001). Among those patients with organ damage, significantly less had accrued in cases (1.08 ± 1.32 vs 1.60 ± 2.06, p = 0.03). There were significantly fewer skin, central nervous system, and pulmonary manifestations over the patients' disease courses among cases. There was no difference in antimalarial use between groups, but overall prednisone use and cumulative dose was significantly lower among cases at the start of their prolonged remission period, as was the use of immunosuppressive agents (Table 3).

Logistic regression models were built comparing cases to matched and unmatched controls. In a model where all potential risk factors were included, no associations were statistically significant between presence of remission and sex, age at diagnosis, disease duration at first visit, race, disease activity (by SLEDAI-2K) at first visit, or renal, pulmonary, or dermatologic involvement. A stepwise regres-

Table 2. SLEDAI-2K clinical characteristics of flare in patients with monophasic course.

Patient	Clinical Characteristics in Flare	Remission Type	Remission Duration to Most Recent Visit, yrs	Race	Age at Diagnosis, yrs	Ever CS	Ever AM	Ever IS
1	Arthritis, fever, headache, pericarditis, pleurisy	SQCQ	25.1	White	41.5	Yes	No	No
2	Organic brain syndrome, fever, mucosal ulcers, pleurisy	Mixed	22.3	White	60.6	Yes	No	No
3	Fever, rash	SACQ	7.1	White	83.1	No	No	No
4	Leukopenia, mucosal ulcers, pericarditis, rash, renal	Mixed	27.7	White	50.4	No	No	No
5	Alopecia, rash, renal	SQCQ	8.7	White	52.4	Yes	No	Yes
6	Alopecia, fever, headache, organic brain syndrome, rash, renal	Mixed	25.1	Asian	22.1	Yes	No	No
7	Arthritis, rash	SQCQ	11.0	White	52.1	No	Yes	No
8	Arthritis, leukopenia	Mixed	12.1	Other	31.9	No	Yes	No
9	Alopecia, arthritis, pleurisy, rash, renal, vasculitis	SACQ	8.0	Other	16.8	Yes	Yes	No
10	Arthritis, fever, rash, thrombocytopenia	Mixed	11.5	White	12.1	No	Yes	No
11	Leukopenia, renal	SQCQ	5.8	Other	36.2	Yes	Yes	No

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; CS: corticosteroids; AM: antimalarials; IS: immunosuppressives; SQCQ: serologically and clinically quiescent; SACQ: serologically active clinically quiescent.

Table 3. No Medication group matched case-control analysis.

	Cases, n = 38 (%)	Controls, n = 114 (%)	Matched p
Demographics			
Sex (F)	32 (84.2)	96 (84.2)	N/A
Age at diagnosis, yrs	36.1 ± 15.2	36.6 ± 14.9	N/A
Length of followup at remission onset, yrs	9.13 ± 8.79	8.89 ± 8.50	N/A
Race			
White	32 (82.4)	82 (71.9)	0.02 (white vs all others)
Black	0 (0)	16 (14.0)	
Asian	2 (5.3)	10 (8.8)	
Other	4 (10.5)	6 (5.3)	
SLEDAI-2K at first clinic visit	8.03 ± 9.47	10.6 ± 9.04	0.02
AMS (from clinic entry to remission onset)	3.02 ± 1.93	5.95 ± 3.56	< 0.0001
SLICC Damage Index			
Score > 0	20/37 (54.1)	67/109 (61.5)	0.37
Mean score	1.08 ± 1.32	1.60 ± 2.06	0.03
Organ involvement (ever), by SLEDAI-2K, from clinic entry to remission onset (or matched visit)			
Musculoskeletal	16 (42.1)	50 (43.9)	0.73
Skin	28 (73.7)	104 (91.2)	0.0004
Vasculitis	10 (26.3)	42 (36.8)	0.08
Renal	26 (68.4)	88 (77.2)	0.12
Central nervous system	14 (26.8)	65 (57.0)	0.002
Cardiac — SLE-related	12 (31.6)	34 (29.8)	0.74
Cardiac — atherosclerotic*	4 (10.5)	19 (16.7)	0.16
Thrombotic*	3/25 (12.0)	10/84 (11.9)	0.59
Pulmonary*	5 (13.2)	34 (29.8)	0.0009
Medication use from clinic entry			
Corticosteroids	22 (57.9)	91 (79.8)	< 0.0001
Antimalarials	23 (60.5)	73 (64.0)	0.55
Immunosuppressives	9 (23.7)	54 (47.4)	0.0003
Cumulative corticosteroid dose (g)	(n = 22)**, 20.7 ± 17.2, (n = 38)***, 12.0 ± 16.6	(n = 90)** 42.7 ± 37.8 (n = 113)*** 34.0 ± 37.9	< 0.0001, < 0.0001

* Diagnosed clinically and/or radiographically, not a component of SLEDAI-2K; ** Cumulative corticosteroid dose in patients on corticosteroids at some point; *** Cumulative corticosteroid dose all patients (assume = 0 in patients never taking corticosteroids). SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; AMS: adjusted mean SLEDAI; SLICC: Systemic Lupus International Collaborating Clinics; SLE: systemic lupus erythematosus; N/A: not applicable.

sion suggested remitted patients were less likely to have dermatologic involvement [OR 0.27 (0.10, 0.71), p = 0.008]. Including all risk factors in a model using the unmatched controls was similarly unrevealing for any association with sex, age at diagnosis, disease duration, or disease activity at first visit, and race with remission status. The stepwise regression associated older age at diagnosis with remission status [OR 1.03 (1.00, 1.05), p = 0.02].

To further characterize the remitted patients, we then embarked upon analyses comparing demographic and clinical characteristics of the cohort to the Medication group, and to both matched and unmatched controls, at several timepoints, to provide a measure of disease evolution over time (Supplementary Tables 1,2,3,4,5 available online at jrheum.org). Given that the goal of the paper was descriptive, and that multiple comparisons were made in these analyses, we focused upon only those results that were highly significant. With this lens we found the No Medication patients had lower disease activity, by SLEDAI-2K, at various timepoints in their disease course, and that steroid use was less prevalent than in both matched and unmatched controls. They had less renal disease than matched and unmatched controls at 5 years from clinic entry (p = 0.003 for both), but this difference did not persist at other timepoints studied.

Medication group. Thirty-four patients who achieved prolonged remission while taking corticosteroids and/or immunosuppressives were identified among the 1613

Table 4. Clinical characteristics of Medication (MED) compared to No Medication (NO MED) groups at remission start.

	MED, n = 34 (%)	NO MED, n = 38 (%)	p
Sex (F)	33 (97.1)	32 (84.2)	0.11
Age at diagnosis, yrs	27.9 ± 11.7	36.1 ± 15.2	0.01
Length of followup at remission onset, yrs	9.13 ± 8.74	9.13 ± 8.79	1.00
Race			
White	25 (73.5)	32 (84.2)	
Black	4 (11.8)	0 (0)	0.27 (white vs
Asian	4 (11.8)	2 (5.3)	all others)
Other	1 (2.9)	4 (10.5)	
SLEDAI-2K at first clinic visit	8.15 ± 7.72	8.03 ± 9.47	0.95
AMS (from clinic entry to remission onset)	4.24 ± 2.67	3.02 ± 1.93	0.03
Damage Index*			
Score > 0	18/31 (58.1)	20/37 (54.1)	
Mean score	1.68 ± 1.87	1.08 ± 1.32	0.14
Organ system involvement (ever), by SLEDAI-2K, from clinic entry to remission onset			
Musculoskeletal	11 (32.4)	16 (42.1)	0.39
Skin	28 (82.4)	28 (73.7)	0.38
Vasculitis	6 (17.7)	10 (26.3)	0.38
Renal	19 (55.9)	26 (68.4)	0.27
Central nervous system	18 (52.9)	14 (36.8)	0.17
Cardiac – SLE-related	9 (26.5)	12 (31.6)	0.63
Cardiac – atherosclerotic*	4 (11.8)	4 (10.5)	1.00
Thrombotic*	4/28 (14.3)	3/25 (12.0)	1.00
Pulmonary*	10 (29.4)	5 (13.2)	0.09

* Diagnosed clinically and/or radiographically, not a component of SLEDAI-2K. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; AMS: adjusted mean SLEDAI; SLICC: Systemic Lupus International Collaborating Clinics; SLE: systemic lupus erythematosus.

Table 5. Medication use from clinic entry in Medication (MED) compared to No Medication (NO MED) group.

	MED, n = 34 (%)	NO MED, n = 38 (%)	p
Corticosteroids	34 (100)	22 (57.9)	**< 0.0001**
Antimalarials	21 (61.8)	23 (60.5)	0.91
Immunosuppressives	18 (52.9)	9 (23.7)	**0.01**
Cumulative corticosteroid dose (g)	(n = 34)*	(n = 22)*	
	42.9 ± 39.7	20.7 ± 17.2	
	(n = 34)**	(n = 38)**	**0.006**
	42.9 ± 39.7	12.0 ± 16.6	**0.0001**

*Cumulative corticosteroid dose in patients taking corticosteroids at some point; **Cumulative corticosteroid dose all patients (assume = 0 in patients never receiving corticosteroids). P values in bold face are statistically significant.

eligible patients (2.1%). The mean duration of prolonged clinical quiescence in this group was 8.5 ± 2.9 years (range 5.1–16.3). This prolonged clinically quiescent period was terminated by flare in 12 patients (35%). In the remaining 22 patients (65%) whose prolonged clinically quiescent period did not end in flare, medications were eventually successfully discontinued in 5 (15%). Medications were being tapered in 6 patients (18%) and were being maintained in 2 (6%), with organ transplants necessitating ongoing immunosuppression. Six patients (18%) were maintained on a stable regimen, with no standardized drug withdrawal algorithm specified. Three patients (9%) were lost to followup (Figure 1).

Comparison of No Medication versus Medication groups. When the groups were compared, patients within the Medication group were younger at diagnosis (27.9 ± 11.7 vs 36.1 ± 15.2, p = 0.01), and required more immunosuppressives (53% vs 24%, p = 0.01) and corticosteroid (100% vs 58%, p < 0.0001) at higher cumulative doses [42.9 ± 39.7 vs 20.7 ± 17.2 g (among those requiring corticosteroids; n = 22), p = 0.006] from clinic entry to the onset of prolonged clinical quiescence. Their disease was more active prior to remission onset (AMS 4.24 ± 2.67 vs 3.02 ± 1.93, p = 0.03). There were no between-group differences in ethnicity, SLEDAI-2K at presentation, antimalarial use, time to prolonged clinical quiescence, organ manifestations to remission onset, or Systemic Lupus International Collaborating Clinics damage index (Tables 4 and 5). The 2 groups did not differ in terms of hematologic involvement or autoantibody profiles (Supplementary Tables 2,3,4,5 available online at jrheum.org).

DISCUSSION

Remission is an elusive and often ill-defined goal in SLE. The generalizability of the SLE remission literature is limited by differences in definition, with duration, disease activity measure used, the inclusion of treatment, and serologic activity all being variables that may significantly affect the result. Further, given the heterogeneity of lupus presentation, and the effect of ethnicity upon disease manifestations, severity, and prognosis[9], differences inherent to a cohort itself may prove central to the type and duration of remission achieved. Regardless of how it is defined, remission remains a desirable outcome in SLE, but is rarely achieved. Table 1 summarizes past studies exploring remission in SLE, highlighting the similarities and differences between these efforts.

Dubois provided one of the first descriptions of remission in a cohort of 163 patients with SLE in his 1956 paper[10]. He reported that an astounding 38% of the patients experienced at least 1 "spontaneous remission" prior to treatment with antimalarials or corticosteroids, including 1 patient with a 26-year remission, and up to 16% with multiple remissions. He admitted, however, that most of these patients "did not have the full picture of systemic lupus erythematosus," but rather had a rheumatoid arthritis-like presentation. There was no definition of remission offered in this historic paper, but it seemed to be based upon the physician's global clinical impression. In 1964, Dubois and Tuffanelli then corroborated the considerable remission rate, reporting that 35% of 520 patients with SLE experienced "spontaneous remission," lasting up to 26 years in 1 case[11]. The definition of remission was similarly vague in this study.

By contrast, and highly consistent with our study's findings, Tozman, *et al* determined that the rate of "prolonged complete remission" in SLE, defined as the absence of clinical manifestations of disease and without immunosuppressive therapy, was 4/160 (2.5%)[12]. They used

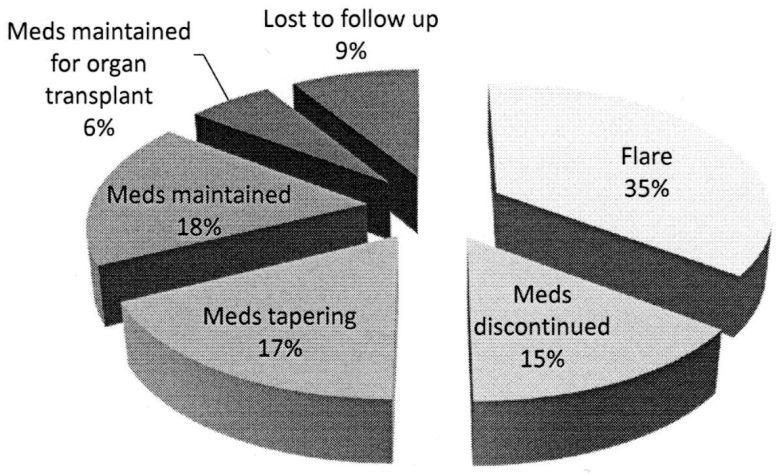

Figure 1. Medication group remission outcomes.

both clinical and laboratory variables in their assessment, including for the first time in the setting of remission the absence of anti-DNA antibodies and C3 hypocomplementemia, both of which are known to run a concordant course with disease activity in some patients with SLE[13,14,15]. These patients had remitted from previously severe disease, with median remission duration of 75 months. Thus, considerable disparity in duration, definition, and frequency of remission existed in the earlier literature.

In 2005, Urowitz, *et al* addressed the inconsistencies that had plagued the SLE remission literature by quantifying and describing disease quiescence using incrementally less restrictive criteria[16]. They defined prolonged remission as at least a 5-year period without disease activity (SLEDAI-2K = 0), while not taking corticosteroids, immunosuppressives, or antimalarials. They found that remission, thus defined, was a rare event, occurring in only 12 of 703 patients (1.7%) in their cohort. As would be expected, when progressively less stringent criteria were applied to the remission definition, encompassing 1 to 5 years' disease quiescence, permitting the presence of hypocomplementemia and/or anti-dsDNA positivity, and permitting the use of antimalarials, corticosteroids, and immunosuppressive medications, remission prevalence increased as stringency decreased. When defined as clinical quiescence (by SLEDAI-2K) for 1 year, permitting active serology, and permitting the use of medications (the least restrictive definition), remission prevalence was 24.5%. Thus, as demonstrated by this paper, the important issue to be decided is the type of remission to be quantified.

In our study, our goal was to describe those patients who had achieved prolonged remission, which we defined as at least a 5-year period without clinical activity. While any remission definition is somewhat arbitrary, we felt this cutoff, borrowed from the oncology literature where 5-year survival rates abound and cancers quiescent for 5 years are presumed cured, was clinically significant. Further, 5 years provides a considerable window for damage accrual secondary to disease or medication use, and therefore reprieve of this duration would likely yield an appreciable difference compared to a patient with active disease requiring treatment with corticosteroids[17].

While prolonged complete remissions were rare, durable remission of a decade or more can be anticipated, even among those whose anti-dsDNA and/or complement levels fluctuated from normal range. In fact, the mixed remission group had the longest average remission duration of nearly 17 years. Thus, in patients whose serology proves discordant, fluctuations from normal range during prolonged remission may simply be observed without the introduction of corticosteroids or immunosuppressive medications, because remission can persist in spite of these changes. This finding is consistent with past studies, which reveal that, among serologically active but clinically quiescent (SACQ) patients, fluctuations in anti-dsDNA and/or complement levels were not predictive of disease flare[18].

It should also be emphasized that these patients fundamentally differ from those described by Tseng, *et al*, who were serologically active and clinically stable[19]. In their study, those with serologic evidence of flare, namely 25% elevation in anti-dsDNA and 50% elevation in C3a, were randomized to receive either a 3-week course of prednisone, with starting dose 30 mg per day, or placebo. They found that significantly more flares occurred in the placebo group than in the treatment group (6 vs 0 among 41 patients who experienced serologic flare, $p = 0.007$). Severe caution must be exercised, however, in extrapolating these findings to our SACQ patients, because Tseng's patients could have had active disease requiring up to 15 mg of prednisone daily and still have met inclusion criteria. Because this cohort included patients who continued to have evidence of active disease despite treatment with corticosteroid, as well as patients whose clinical manifestations may have been merely suppressed by their baseline corticosteroid dosing, they were fundamentally different from the serologically active clinically quiescent patients as we had defined them.

Monophasic course is a rare outcome among the rheumatic diseases; review of the literature yields rare description thereof in few disease entities (systemic juvenile idiopathic arthritis, myositis, adult-onset Still's disease, and polyarteritis nodosa)[20,21,22,23]. Thus, a unique finding of this study was the significant subset of patients, representing nearly one-third of the No Medication group, whose illness was atypically monophasic. None of these patients' SLE diagnosis was thought to be attributable to drug use, thus they did not appear to have a reversible etiology. To our knowledge, there are no other studies that report this unusual pattern of disease activity in this classically relapsing-remitting disease. These patients may provide unique pathophysiologic insights into SLE, if not autoimmunity, more generally, and thus warrant further investigation at genotypic and phenotypic levels.

We noted disease duration of nearly a decade at remission onset, in keeping with past observations that likelihood of remission increases with disease duration[3]. Our case-control analysis also demonstrates that the remitted patients had milder disease, with less need for corticosteroids and/or immunosuppressives, and less resultant damage accrual early on. This is consistent with the notion that early disease activity is the harbinger of what is to come: Formiga, *et al* studied remissions among those with high disease activity early in their disease course[24]. They defined remission as disease activity permitting the withdrawal of all SLE-related treatment over at least 1 year, and asymptomatic serologic fluctuations were permissible. Twenty-four percent of their exclusively white cohort (of 100 patients) achieved such a remission, at mean 64 months after diagnosis, and the remissions persisted, on average,

over more than 4.5 years. While there were differences in baseline SLEDAI value between those who achieved remission and those who did not (with those with higher initial SLEDAI scores less likely to remit), these did not attain statistical significance. Thus, they observed remissions in patients with all disease manifestations, including major organ involvement, and found a significant correlation between SLEDAI values and time to remission onset: remission occurred later among those with more severe baseline disease. We acknowledge that, as in Formiga's cohort, there were no blacks among our cases. This may limit the generalizability of our findings, but may also indicate an important and defining phenotypic clue to prolonged remission, which may be borne out in future, multicentered, collaborative studies.

We found that cases did not differ from controls with respect to prevalence of renal manifestations at the start of their remission period. This is consistent with past investigations of serologically active clinically quiescent patients, revealing no difference in nephrologic involvement compared to a large group of SLE controls (n = 868)[18], and commensurate with widely cited renal SLE prevalence[25]. We did find that they differed from matched and unmatched controls at 1 timepoint (5 years from clinic entry; Supplementary Table 3 available online at jrheum.org). We observed a lower prevalence of central nervous system manifestations in cases than controls at the start of the remission period. However, this difference was not reflected at other timepoints investigated. While these findings may be suggestive of differing organ involvement in those patients with SLE achieving prolonged remission, they should be borne out in a larger sample of remitted patients, ideally over multiple centers, internationally, especially given the notoriously variable prevalence reported in these organ systems[25,26,27].

Our logistic regression findings of difference between cases compared to matched and unmatched SLE controls were equivocal: while forced models were unrevealing, stepwise modeling yielded an association with less skin involvement and older age at diagnosis, and the achievement of prolonged remission. The weight and significance of these results, while of interest, should be assigned with caution. The disparity between the forced and stepwise models suggests that a larger sample size would be required to confirm these findings. Alternatively, both skin disease (specifically in the form of subacute cutaneous lupus, as reviewed[28]) and later age at disease onset[29,30] are known to be associated with a relatively mild SLE course, thus rendering our findings biologically plausible and consistent with past observations. However, our definition of "dermatologic involvement" by SLEDAI-2K combines all forms of dermatologic involvement, which are not uniformly associated with good outcomes, further highlighting the potential benefit for multicenter collaboration to bolster power in studies of this rare and unique remitted cohort. The practical implication remains that the phenotype of skin involvement in a patient with SLE of relatively late onset is neither adequately sensitive nor specific to reassure the patient or physician of remission — or even a mild course — *a priori*, and should thus not affect a practitioner's approach to any individual patient.

Our analysis of patients who had remitted while taking corticosteroids and/or immunosuppressives is suggestive of 2 subsets within this cohort: those patients in true remission, for whom medications being successfully tapered will be withdrawn, and those patients in whom disease was merely suppressed by treatment. In fact, a significant minority of these patients were evolving to the No Medication group, but had not yet fulfilled the 5-year duration criterion for drug-free remission. Comparison of these remitted/suppressed subsets at genetic and/or biochemical levels may yield important differences that may be applied in the future to disease prognostication and treatment.

The pathophysiology of SLE remission, in general, and especially in the face of persistent, purportedly pathogenic serologic activity is not understood. A pilot study comparing autoantibody levels in patients with serologically active clinically quiescent disease who ultimately flared compared to those who did not failed to elucidate a difference between groups[31]. A fascinating experiment performed by Pau, *et al* involved an SLE-prone mouse phenotypically resembling serologically active clinically quiescent patients, and explored the centrality of interferon (IFN)-α expression in SLE. They found that, despite marked plasmacytoid dendritic cell expansion, there was decreased IFN-α production peripherally, even in the face of Toll-like receptor stimulation[32]. Inspired by these unique findings, we plan to explore the IFN response in this rare and perhaps instructive cohort.

Prolonged clinical remission without corticosteroids and/or immunosuppressive medication is an infrequent outcome among patients with SLE, occurring in only 2.4%. It lasts more than a decade, and is preceded by an atypically monophasic clinical course in a significant minority. These occurrences may reflect unique pathophysiologic mechanisms, and warrant further investigation.

About 2% of our cohort achieves prolonged clinical quiescence while taking medication. This group, however, appears heterogeneous: those who flared, representing a group whose disease activity is merely suppressed by ongoing medication use, and those who tolerated/were tolerating medication withdrawal, reflective of true prolonged clinical quiescence (as in the No Medication group).

Remission in SLE may be reflective of unique pathophysiologic mechanisms, and thus warrants further investigation.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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