Recommendations for Frequency of Visits to Monitor Systemic Lupus Erythematosus in Asymptomatic Patients: Data from an Observational Cohort Study

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ABSTRACT. ***Objective.*** The aim of our study was to determine the optimal frequency of followup visits in patients with systemic lupus erythematosus (SLE).

Methods. Patients followed in the lupus clinic over a 2-year period who had at least 3 visits and at least 18 months of followup were included. At each visit patients undergo a complete history, physical examination, and laboratory evaluation. The following variables that would not have been recognized by the patient were identified: proteinuria, hematuria, pyuria, casts, low hemoglobin, leukopenia, thrombocytopenia, elevated serum creatinine, positive anti-DNA antibodies, and low complement. When one of these variables was detected, it was determined whether it was new, and whether other features of activity were present. Thus isolated new variables of interest were identified. Descriptive statistics were used.

Results. A total of 515 patients (89% female, 61% white) met the inclusion criteria, with an average of 6.1 ± 1.5 for a total of 3126 visits. The average length of time between visits was 3.8 ± 1.0 months. In the 515 patients, the variables of interest were the sole manifestation of SLE in 126 (24.5%) patients (in a total of 175 visits). The commonest manifestations were renal, low complement, and DNA antibodies followed by thrombocytopenia, low hemoglobin, and elevated creatinine.

Conclusion. One in 4 patients with SLE seen over a 2-year period will have a solitary silent variable of interest that could be detected only by routine laboratory followup. Patients with mild or inactive disease should be followed with clinical and laboratory measures at 3–4 month intervals. (J Rheumatol First Release March 1 2013; doi:10.3899/jrheum.121094)

Key Indexing Terms:

LUPUS | MONITORING | OBSERVATIONAL COHORT
DISEASE ACTIVITY | SILENT MANIFESTATIONS

The American College of Rheumatology (ACR) ad hoc committee on systemic lupus erythematosus (SLE) guidelines suggest that "the cornerstone of managing SLE is lifelong patient monitoring to detect flares of disease early and to institute prompt, appropriate therapy"[1]. They suggest that the frequency of followup visits is determined by the activity and severity of the disease and its complications. Although no formal studies to determine a definitive interval between assessments were available, the committee recommended that patients with very mild stable disease be reviewed at 3-month to 6-month intervals. Patients with more severe disease or complications would require more frequent followup.

The European League Against Rheumatism (EULAR) developed a series of quality indicators necessary to evaluate the monitoring of patients with SLE in routine clinical practice[2]. They recommended that in patients with no activity, no damage, and no comorbidity, clinical and laboratory assessments be performed every 6–12 months. These recommendations were based on expert opinion because no data were available from which to derive evidence-based monitoring intervals[3].

Our aim therefore was to determine the optimal frequency of followup visits in patients with SLE.

MATERIALS AND METHODS

Setting. The University of Toronto Lupus Clinic at the Toronto Western Hospital has followed patients prospectively according to a standard protocol since 1970. Patients are followed at 2–6 month intervals regardless of disease activity[4]. Half the patients registered in the clinic are newly diagnosed, while prevalent patients are referred by family physicians, general internists, or other rheumatologists. Thus the range of disease varies from very mild to very severe.

Patient selection. Patients followed in the Lupus Clinic from January 1,

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2009, to December 31, 2010, who had at least 3 visits and at least 18 months of followup were included. At each visit patients underwent a complete history, physical examination, and laboratory evaluation.

Assessments. All items needed to complete the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) are collected prospectively, and the adjusted mean SLEDAI-2K can be calculated for any interval[5,6]. Items necessary for the calculation of the Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index are also collected yearly[7].

Solitary silent new features. A number of disease manifestations would not be obvious to a patient without evaluation by a physician or laboratory testing. These include proteinuria (> 500 mg per 24 h); hematuria (> 5 red blood cells per high power field); pyuria (> 5 white blood cells per high power field); both hematuria and pyuria in the absence of infection, menses, or stones; casts (heme granular or red blood cell); low hemoglobin (< 100); leukopenia (< 3000); thrombocytopenia (< 100,000); elevated serum creatinine (> 120); positive anti-DNA antibodies (> 7 units by Farr); and low complement (< 0.10 for C4 and < 0.9 for C3). At each visit in which one of these variables was detected, it was determined whether it was new, and whether other features of activity were present. Thus, isolated new variables of interest were identified as a new feature at a visit with no other SLEDAI feature present, and were termed "solitary silent new feature," because these would be unknown to the patient.

The implication of finding these solitary silent new features might lead to the following changes in management: new or increased therapy; additional investigations; earlier followup; notation of concern; or acknowledgment that this has occurred in the past without consequence.

Statistical analysis. Our study identifies the frequency of solitary silent new features within a 2-year window. Statistical analysis is limited to descriptive statistics of the study population (mean ± SD, sample size, and proportions). Comparisons of patients' features between patients who achieved a solitary silent new feature to patients who did not were made using chi-square tests and t tests for categorical and continuous variables, respectively.

RESULTS

Five hundred fifteen patients met the inclusion criteria; 89.5% were female and 61.2% were white. Age at study was 42.2 years and disease duration was 14.2 years. The SLEDAI-2K at study entry was 4.1 and the SLICC Damage Index was 1.51 (Table 1).

In the 2-year study period, there were a total of 3126 visits. The average number of visits per patient was 6.1 ± 1.5. The average length of followup was 1.8 ± 0.2 years. The average time between clinic visits was 3.8 ± 1.0 months. The adjusted mean SLEDAI-2K score in the followup period was 3.9 ± 3.4.

Solitary silent new features were found at 175 (5.6%) clinic visits. Solitary new features were found at least once in the study period in 126 different patients (24.5%). Table 1 provides a comparison between patients with and those without solitary silent new features in the 2-year study period. As can be seen, patients with solitary silent new features had the same degree of disease activity at presentation to clinic, but at the study start had lower SLEDAI-2K scores. This is expected, as the definition of the study outcome includes no clinical features and only silent new lesions.

Table 2 depicts the frequency of solitary silent new features within visits and within patients, as well as the ranges of abnormal values. As shown, the renal measures, casts, hematuria, proteinuria, and pyuria were the most frequent. Low complement and anti-DNA antibodies were also common. Less frequent manifestations were hematologic indicators, including thrombocytopenia, leukopenia, and anemia.

The discovery of these solitary silent new features led physicians to adopt a number of different management approaches. In the majority of cases concern was expressed and further laboratory tests were undertaken. For example, instances of pyuria, hematuria, casts, proteinuria, or elevated serum creatinine led to further tests, such as urine cultures or 24-h urine collections. In 18 patients, steroids, antimalarials, and/or immunosuppressives were added or doses increased within the 12 months following the identification of a silent solitary new feature. In cases of anemia, leukopenia, or thrombocytopenia, patients were called, and

Table 1. Characteristics of the patient population at first study visit.

Characteristic	All 515 Patients	No SSNF, n = 389	SSNF, n = 126	p
Female, n (%)	461 (89.5)	350 (90.0)	111 (88.1)	0.55
Ethnicity, n (%)				
White	315 (61.2)	235 (60.4)	80 (63.5)	0.54
Black	82 (15.9)	64 (16.5)	18 (14.3)	(white vs
Asian	54 (10.5)	40 (10.3)	14 (11.1)	all others)
Other	64 (12.4)	50 (12.9)	14 (11.1)	
Age at SLE diagnosis, yrs	28.0 ± 12.6	27.3 ± 12.6	30.1 ± 12.4	0.03
Age at study start, yrs	42.2 ± 15.1	41.1 ± 15.1	45.5 ± 14.8	0.004
Disease duration, yrs	14.2 ± 10.6	13.8 ± 10.4	15.5 ± 11.3	0.12
SLEDAI-2K at clinic entry	8.8 ± 7.2	8.8 ± 7.0	8.7 ± 7.8	0.96
SLEDAI-2K	4.1 ± 4.5	4.8 ± 4.7	2.1 ± 3.1	< 0.0001
SLICC Damage Index	1.51 ± 1.89	1.41 ± 1.83	1.83 ± 2.06	0.05

SSNF: solitary silent new features; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC: Systemic Lupus International Collaborating Clinics.

Table 2. Frequency of solitary silent new features (SSNF) in visits and in patients.

Feature (ranges)	No. Visits with SSNF (out of 175)	No. Patients with ≥ 1 Visit with SSNF (out of 126)
Casts (2)	16	16
Hematuria (10–30)	10	9
Proteinuria (0.550–2.26 g/24 h)	15	15
Pyuria (10–50)	42	35
Low complement C4 0.06–0.09; C3 0.7–0.89	55	45
Positive anti-DNA antibodies (8–55)	36	32
Thrombocytopenia (21–99 × 10^9/l)	8	7
Leukopenia (2–2.9 × 10^9/l)	7	7
Elevated serum creatinine (121–155)	9	8
Low hemoglobin (82–99)	10	9

tests repeated and in some cases cytotoxic drugs were discontinued. With regard to abnormal serology, tests were repeated and as in other features closer followup was arranged in many cases.

DISCUSSION

Quality indicators for SLE have been proposed, but do not provide information on monitoring patients with SLE[8]. Recommendations for monitoring of patients with SLE have been based primarily on expert opinion. The ACR recommendations were based on the nature of the protean clinical and laboratory features of SLE and the variety of treatments required to control these features[1]. It was recommended that patients with mild stable disease be followed at 3–6 month intervals, while patients with more severe disease would necessarily be followed more frequently as appropriate. The EULAR recommendations were based on the development of quality indicators to evaluate the monitoring of patients with SLE[2]. These indicators included assessment of disease activity, damage accumulation, quality of life, drug toxicity, and comorbidities. Specific ophthalmologic assessment for drug complications, laboratory assessment, screening for chronic infection, and documentation of vaccination were also included. The recommendations concluded that the use of these quality indicators to establish the cutoff that properly defines good clinical practice still needs to be discussed. EULAR recommends 6–12 months for frequency of assessment for patients without active disease, damage, or comorbidities. The level of evidence for this recommendation was 5 (expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles") and the grade of recommendation was D (level 5 evidence or troublingly inconsistent or inconclusive studies of any level)[9].

Our study is the first, to our knowledge, to address the appropriate interval for monitoring in asymptomatic patients with SLE. We used data collected prospectively from our longitudinal cohort, where patients are carefully monitored at 2–6 months regardless of disease activity. We selected patients who had appropriate followup (at least 3 visits and at least 18 months of followup), with an average of 6 visits over a 2-year period. Clinical features discernible by the patients would trigger a visit to the physician. We specifically sought features that would not be recognized by a patient, such as proteinuria, hematuria, pyuria, casts, low hemoglobin, leukopenia, thrombocytopenia, elevated serum creatinine, positive anti-DNA antibodies, and low complement. We further defined a solitary silent new feature as one of the above items in the absence of any other manifestation of SLE. By this definition, it is not surprising that they were found to occur more commonly among patients with a lower level of disease activity at the study start. Moreover, there was no difference in the prevalence of organ-specific manifestations prior to the study start between those with and those without silent solitary new features (data not shown). Such new solitary silent features were identified in almost 5% of the visits, and in a quarter of the patients during the 2-year followup period. These new features triggered either further investigation or a change in therapy, or suggested more frequent followup. The frequency of visits in these patients was 3.8 months, suggesting that patients with inactive SLE should be followed at intervals of at least 3–4 months to identify these important silent manifestations. It is possible that if patients in our study had been seen more frequently, such as monthly, the frequency of abnormalities might have been higher, lending weight to our conclusion that at least every 3–4 months is appropriate. Whether a specialist or a primary care physician supervises the monitoring will depend on the different jurisdictions and healthcare provisions. Patients with more active or severe disease would be followed more frequently as indicated by their clinical status. Similarly, patients with comorbid conditions such as heart disease, osteonecrosis, osteoporosis, and infection should be monitored appropriately.

Based on the Oxford Center for Evidence Based Medicine – levels of evidence, our study fits with level of evidence category 2b and grade of recommendation B. Thus it is recommended that both the ACR and EULAR recommendations be amended to reflect this evidence-based finding: that patients with mild or inactive disease be followed at intervals of 3-4 months.

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