Prolonged Serologically Active Clinically Quiescent Systemic Lupus Erythematosus: Frequency and Outcome

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ABSTRACT. ***Objective.*** Some patients with systemic lupus erythematosus (SLE) are clinically quiescent despite persistent serologic activity. We determined the frequency of serologically active clinically quiescent (SACQ) SLE and its outcomes in prospectively followed patients with SLE.

Methods. Patients with SLE followed between July 1970 and April 2008 with visits ≤ 18 months apart were identified. SACQ was defined as a ≥ 2-year sustained period without clinical activity with persistent serologic activity (increased anti-dsDNA and/or hypocomplementemia), during which antimalarials but neither steroids nor immunosuppressives were permissible. Characteristics of patients with an SACQ period and its features were analyzed. To determine flare predictors, anti-dsDNA and complement levels in SACQ patients who experienced flare were compared to levels in those who did not. Descriptive statistics were used; comparisons were made using t tests and chi-squared tests.

Results. Of the patients studied, 56/924 (6.1%) were SACQ. They differed significantly from the non-SACQ SLE population only in the presenting SLE Disease Activity Index 2000 (7.34 vs 10.1 in non-SACQ), and frequency of steroid use (33.9% vs 60.8% in non-SACQ) and immunosuppressive use (3.6% vs 19.4% in non-SACQ) at first visit. Median SACQ period was 158 weeks. Thirty-three (58.9%) patients who were SACQ experienced flare (at median 155 weeks), 6 (10.7%) became clinically and serologically quiescent (236 weeks), and 17 continued to be SACQ (159 weeks). Common flare manifestations were arthritis, mucous membrane involvement, and sterile pyuria. Fluctuations in anti-dsDNA or complement levels did not predict flare.

Conclusion. Fifty-nine percent of SACQ patients experienced flare, but after a median of 3 years. Fluctuations in complement and anti-dsDNA levels did not predict flare, thus treatment decisions in these patients must rely upon close clinical observation. Alternative predictive biomarkers warrant study. (First Release July 1 2010; J Rheumatol 2010;37:1822–7; doi:10.3899/jrheum.100007)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is an autoimmune disease with protean manifestations and morbidities. Diagnosis is based upon the presence of a combination of clinical features and laboratory abnormalities. Anti-dsDNA antibodies are recognized as highly specific diagnostic markers for SLE that are found in 60%–80% of patients, and have been included in the American College of Rheumatology (ACR) classification criteria since 1982[1,2,3]. Anti-dsDNA antibodies have been observed to be strongly correlated with SLE for over 50 years. In 1967, Koffler, *et al* observed deposition of DNA (anti-DNA immune complexes) in the glomeruli of 10 patients with nephritis of SLE, which supported the antigen-antibody complex hypothesis for renal injury in lupus[4]. Indeed, the presence of anti-dsDNA antibodies was, and to some extent still is, an essential element of renal lupus.

Many have observed concordance in levels of anti-dsDNA antibodies with disease activity in keeping with their presumed central role in SLE pathophysiology. Some have evaluated the role of fluctuations in anti-dsDNA antibody levels in prognostication and prediction of disease flare, with some success[1,5-11]. These studies have prompted prospective, randomized controlled trials that involved increasing steroid dosing prophylactically in response to anti-dsDNA fluctuations in the absence of clinical flare[12,13].

Although not as specific for SLE as anti-dsDNA antibodies, serum hypocomplementemia has been regarded as a

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sensitive indicator of SLE activity and has been found to be reliable in disease prognostication[6,9,13,14]. Its proposed pathophysiologic role (i.e., consumption by immune complexes) may similarly be invoked in SLE.

There exists a small subset of patients with SLE, first described by Gladman, *et al* in 1979, who evolve to persistent serologic activity, as evidenced by elevated anti-dsDNA antibody levels and/or hypocomplementemia, despite clinical quiescence[15]. While some patients remain serologically active clinically quiescent (SACQ) indefinitely or become serologically quiescent clinically quiescent (SQCQ), others' SACQ periods are terminated by disease flare, for which reliable predictors have yet to be identified[16]. The SACQ group challenges the conventional SLE pattern, which implicates anti-dsDNA antibodies in disease pathogenesis. While the existence of this cohort is widely acknowledged, its significance and clinical implications remain the subjects of debate.

SACQ represents an important divergence from the conventional SLE pattern. In one study, the SACQ cohort represented at least 12% of the total SLE population followed at a large center[16]. The prevalence of the reciprocal group, that is, the clinically active serologically quiescent cohort, determined some years later at the same center, was also 12%[17]. These 2 discordant cohorts combined have thus represented nearly one-quarter of the total SLE population in past studies. They compel us to explore more deeply the roles of anti-dsDNA and complement in SLE pathophysiology to better understand its pathogenesis and develop more effective management strategies, especially for this significant subset of patients with SLE.

Patients who present to the clinic with clinical serological discordance pose a particular management quandary. In our study, we determined the frequency of SACQ and its outcome in a large cohort of patients with SLE followed prospectively at a single center. We then focused on those patients whose SACQ period was terminated by disease flare, and analyzed the 2 SACQ visits prior to disease activity for potential predictors thereof.

MATERIALS AND METHODS

Setting. The University of Toronto Lupus Clinic at the Center for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital, was established in 1970 to study clinical-laboratory correlations in SLE. All patients entered fulfilled 4 or more of the 1971 or 1982 ACR 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 on maintenance therapy to patients in complete remission and off all therapy[18].

Patient selection. Patients with SLE were followed with clinical and laboratory information collected using a standardized protocol at clinic visits, typically at 2-month to 6-month intervals. These visits occur regardless of disease activity. Patients were identified who were registered in the Lupus Clinic database between July 1970 and April 2008 with visits no more than 18 months apart.

Definitions. SACQ was defined as at least a 2-year period without clinical activity and with persistent serologic activity [SLE Disease Activity Index 2000 (SLEDAI-2K) score 2 or 4, from positive anti-dsDNA antibody and/or hypocomplementemia only, at each clinic visit]. The patients could be taking antimalarials, but those receiving corticosteroids or immunosuppressive medications were excluded. Disease flare was defined as any increase in SLEDAI-2K score not accounted for by either hypocomplementemia or anti-dsDNA, or by the initiation of steroid or immunosuppressive treatment. SQCQ was defined as a SLEDAI-2K score of 0.

Laboratory measures. Serum complement (C3 and C4) levels were measured using nephelometry. Anti-dsDNA levels were measured by the Farr assay, since this assay best reflects disease activity[18]. Anti-dsDNA antibody levels were defined as normal (0–25 IU/ml), low (26–49 IU/ml), medium (50–74 IU/ml), and high (> 75 IU/ml), according to the Farr assay used until June 16, 1997. From that date onward, with the implementation of the new Farr assay, the categorical cutoffs were normal (0–7 IU/ml), low (8–20 IU/ml), medium (21–50 IU/ml), and high (> 50 IU/ml). Complement levels were analyzed both categorically (normal vs abnormal, as defined at the testing laboratory) and as continuous variables.

Statistical analysis. The SACQ cohort was divided into 3 groups, based on clinical outcome: those patients whose SACQ period terminated with disease flare, those who became serologically inactive (SQCQ), and those who remained SACQ at their last clinic visit. The SACQ period was calculated from the first SACQ visit to either the date of known flare or serologic inactivity, or to the most recent known SACQ clinic visit. In patients who had more than 1 SACQ period, only the first was analyzed. Results are presented using descriptive statistics. Comparisons were made using t tests and chi-squared tests.

In analyzing for potential predictors of flare, anti-dsDNA antibody and complement levels at the 2 visits immediately preceding flare (flare group) were compared to those drawn at the third-last and second-last visits in patients who remained SACQ or who became SQCQ at their last visit (non-flare group). By analyzing the anti-dsDNA antibody and complement levels at second-last and third-last visits (rather than the last 2 visits) in the non-flare group, we ensured that the latter visit recorded did not immediately precede a flare, as that patient would then rightfully belong in the flare group. The difference in anti-dsDNA antibody and complement levels between visits was then analyzed categorically as well as continuously.

RESULTS

As of April 2008, 1351 patients were registered in the Lupus Clinic database. Of these, 924 fulfilled the criterion of having all visits ≤ 18 months apart. We identified 56 patients (6.1%) who fulfilled the SACQ criteria as described, accounting for a total of 70 SACQ periods: 43 had 1 SACQ period; 12 patients had 2 discrete SACQ periods; 1 patient had 3. These patients differed demographically from the remainder of the SLE population only in terms of the presenting SLEDAI-2K score (7.34 vs 10.1 in non-SACQ; $p = 0.01$), and frequency of use of steroid (33.9% vs 60.8% in non-SACQ; $p < 0.0001$) and immunosuppressive (3.6% vs 19.4% in non-SACQ; $p = 0.0004$) at first clinic visit (Table 1). The difference in the number of patients who ultimately died in each group showed a trend in favor of the SACQ group, although it was not statistically significant (5.4% vs 14.2% in non-SACQ; $p = 0.06$). The frequency of SLE-related organ involvement in the SACQ cohort, from presentation at the Lupus Clinic until the start of the first SACQ period versus organ involvement in non-SACQ patients with SLE, followed over a comparable time period,

is outlined in Table 2. The SACQ patients had less musculoskeletal, skin, and central nervous system involvement compared to the non-SACQ patients. The mean (± SD) disease duration at the beginning of the SACQ period was 10.8 (± 9.2) years (median 8.6 yrs). The median duration between clinic visits was 6 months.

The SACQ period lasted an average of 182 weeks (median 158 wks). The SACQ period was characterized by both hypocomplementemia and elevated anti-dsDNA antibodies in 35 patients (62.5%). For our calculations, these patients need not have had both markers positive simultaneously at each clinic visit but rather have either hypocomplementemia and/or elevated anti-dsDNA at each visit during the SACQ period. Thirteen patients in the cohort (23.2%) had isolated hypocomplementemia defining SACQ, with the remaining 8 (14.3%) having elevations in anti-dsDNA antibodies only.

We then subdivided the 43 patients with elevated anti-dsDNA antibodies at some point during the SACQ period categorically, as described, into low, moderate, and high levels of anti-dsDNA. The median anti-dsDNA level was normal in 5 (11.6%, that is, in patients in whom anti-dsDNA was at some point elevated, but normalized during the SACQ period while they were hypocomplementemic), low in 25 (58.1%), moderate in 9 (20.9%), and high in 4 (9.3%).

Of the 56 patients' first SACQ episodes, 33 (59%) ended in disease flare at a median 155 weeks, 6 patients (10.7%) became clinically and serologically inactive at a median 236 weeks, and 17 (30.4%) remained SACQ at their most recent clinic visit.

Symptoms and signs heralding flare were arthritis in 8 patients; mucous membrane involvement in 6; sterile pyuria in 6; alopecia, headache, or urine casts in 3 patients each; hematuria, new rash or proteinuria in 2 patients each; and leukopenia or thrombocytopenia each in 1 patient. Some patients presented with more than 1 of these simultaneously at flare onset.

Patients were divided into 2 groups, flare [33 (58.9%)] and non-flare [23 (41.1%)], according to their outcomes. We

Table 1. Comparison of SACQ vs non-SACQ patients. Numbers are mean ± SD or n (%).

Characteristics	SACQ	Non-SACQ	p
Age at diagnosis, yrs	28.8 ± 14.9	31.1 ± 13.3	0.22
SLEDAI-2K at presentation	7.34 ± 7.68	10.1 ± 8.0	0.01
Disease duration at presentation, yrs	3.72 ± 6.24	3.77 ± 5.60	0.95
Female	49 (87.5)	764 (88.0)	0.91
Race			
White	46 (83.6)	631 (73.6)	0.10
Black	0 (0)	85 (9.9)	(White vs all other)
Chinese	4 (7.3)	83 (9.7)	
Other	5 (9.1)	58 (6.8)	
Deceased	3 (5.4)	123 (14.2)	0.06
Medications at presentation			
Steroid	19 (33.9)	527 (60.8)	< 0.0001
Antimalarial	16 (28.6)	285 (32.9)	0.50
Immunosuppressive	2 (3.6)	168 (19.4)	0.004

SACQ: serologically active clinically quiescent; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

Table 2. Frequency of SLE-related organ involvement in SACQ cohort (from presentation until first SACQ period) compared to the control group (evaluated at a followup interval with the same distribution as in the SACQ group).

Organ System	Frequency in SACQ, n = 56 (%)	Frequency in Controls, n = 868 (%)	p*
Musculoskeletal	28 (50.0)	587 (67.6)	0.007
Skin	41 (73.2)	764 (88.0)	0.001
Vasculitis	15 (26.8)	256 (29.5)	0.67
Renal	39 (69.6)	661 (76.2)	0.27
Central nervous system	16 (28.6)	420 (48.4)	0.004
SLE cardiac	11 (19.6)	221 (25.5)	0.33
Atherosclerotic cardiac	3 (5.4)	126 (14.5)	0.07
Thromboembolic (data missing from 14)	4 (9.5), n = 42	70 (11.0), n = 636	1.00

* Chi-square or Fisher's exact test. SLE: systemic lupus erythematosus; SACQ: serologically active clinically quiescent.

compared the 2 SACQ visits preceding the flare to the second-last and third-last visits in the non-flare group. There was no difference between groups in terms of change in SACQ serologic profile over the 2 visits analyzed (p = 0.83): that is, in analyzing whether anti-dsDNA levels and/or complement levels changed to or from normal between the 2 studied visits, we found no significant difference between the pattern in those who experienced flare and those who did not.

Five patients (15.2%) in the flare group, versus 2 (8.7%) in the non-flare group, had categorical changes in their anti-dsDNA levels (p = 0.69); 2 patients in each of the flare and non-flare groups (6.1% and 8.7%, respectively) became hypocomplementemic between the 2 visits (p = 1.00).

Similarly, when analyzed as continuous variables, both the anti-dsDNA antibody and complement levels did not differ between flare and non-flare groups.

DISCUSSION

SACQ patients constitute a subset of about 6% of patients with SLE whose serologic discordance presents a clinical dilemma in that changes in anti-dsDNA titers and/or complement levels are not associated with clinical disease nor are they predictive of imminent flare of disease activity. Thus in these patients these biomarkers are less helpful in disease management. SACQ patients are not necessarily SACQ throughout their course. In fact, the mean (± SD) disease duration at the start of the SACQ period was 10.8 (± 9.2) years. At the time of referral to the Lupus Clinic, they differed from the non-SACQ SLE population only in terms of a lower mean SLEDAI-2K (7.34 ± 7.68 vs 10.1 ± 8.0 in non-SACQ), achieved with fewer patients using steroids (33.9% vs 60.8% in non-SACQ) or immunosuppressives (3.6% vs 19.4% in non-SACQ). Most SACQ patients had renal involvement prior to their SACQ period. Further, among those in the SACQ group, nearly 60% ultimately flared, but did so after an average of 182 weeks.

Previous studies have investigated fluctuations in anti-dsDNA levels just prior to a flare, with incongruent results. Ter Borg, *et al* first observed that a significant increase in anti-dsDNA antibody levels preceded an SLE exacerbation by 8–10 weeks, while Swaak, *et al* determined that a sharp drop in anti-dsDNA, usually preceded by a rise, was related to a serious exacerbation[8,9,10]. In Swaak's group, laboratory investigations were performed at least monthly for this correlation to be made. Regardless, a prevailing notion remains that anti-dsDNA and/or complement play a pathophysiologic role in lupus, and that their changing levels should thus reflect disease activity.

To ascertain whether there were predictors of flare following SACQ periods, we compared fluctuations in anti-dsDNA and complement levels in the visits immediately preceding flare to the second-last and third-last visits in the non-flare groups, and found no difference between these groups. While it might have been anticipated that there would be a further increase in anti-dsDNA or a further decrease in complement prior to flare, we found that there was no significant difference between the flare and non-flare groups in the number of patients whose anti-dsDNA changed categorically (either upward or downward), or in the median change in anti-dsDNA when analyzed as a continuous variable. Similarly, there was no significant difference in the number of flare versus non-flare patients whose complement levels changed to or from normal between the studied visits. Thus it was not possible to predict flare in the SACQ population based upon laboratory investigations drawn at routine preceding clinic visits.

Clearly, in Ter Borg and Swaak's studies, anti-dsDNA levels were drawn far more frequently than in our cohort, in which the average duration between visits was 6.7 months (median 6.0 mo). On average, patients had 8 clinic visits during their SACQ period (median 6 visits). We thus cannot ensure that our results would have differed had we applied their protocol. We feel a particular strength of our study, however, lies in its practical applicability. The frequency of laboratory investigations in our study is reflective of routine visits by patients with SLE who are clinically well.

In our cohort, more than 6% of patients were SACQ. This is considerably lower than in other studies, in which the frequency of SACQ was up to 12%–15%[15]. This may be due to the more stringent criteria by which we defined SACQ. Specifically, the minimum SACQ period to meet inclusion criteria was months longer than the longest SACQ period in some studies[9,16]. Further, in our study the SLEDAI-2K score was either 2 or 4, based upon positive anti-dsDNA and/or hypocomplementemia only, while in other studies, mild stable disease was included. The use of any steroid and/or immunosuppressive ended the SACQ period in our study, while others allowed low-dose or maintenance-dose steroid use[13]. To our knowledge, this is the most stringently applied definition of SACQ to date.

The lack of close association of disease activity with anti-dsDNA antibodies in SACQ patients calls into question the pathogenic role of these antibodies in these patients. Relative sensitivities and specificities of assays for anti-dsDNA antibodies and the pathogenic importance of various anti-dsDNA isotypes and idiotypes, and high-affinity versus low-affinity anti-dsDNA antibodies, have all been investigated in lupus pathogenesis[1,2,5,7,19]. A strength of this study lies in the use of the Farr assay for anti-dsDNA antibody detection. While previous studies investigating the predictive role of anti-dsDNA antibodies have used other assays, the Farr is best correlated with global disease activity, and with renal and vasculitic involvement. It predominantly detects high-avidity (and thus the most pathogenic) anti-dsDNA and has the highest sensitivity, thus making it the choice assay in predicting SLE exacerbation[7,10,20].

Mostoslavsky, *et al* performed an experiment distin-

guishing pathogenic versus nonpathogenic anti-dsDNA antibodies by their cross-reactivity with a major structural component of glomerular podocytes and mesangial cells[21]. By invoking molecular mimicry with this component, α-actinin, which has been shown by some to have a central role in several experimental glomerulonephropathies, they advance the prevailing concept that not all anti-dsDNA antibodies are created equal. This theory, however, has not been consistently supported: another study longitudinally evaluated anti-dsDNA, anti-nucleosome, and anti-α-actinin antibodies in 16 patients with SLE with new-onset lupus nephritis. While levels of the 2 former antibodies were correlated with urine protein/creatinine ratio, serum albumin, and remission status, the same was not true of anti-α-actinin antibodies[22].

More recently, the role of antinucleosome antibodies has been investigated. Autoantibodies against nucleosomes in sera of lupus mice and patients with SLE were detected with high frequency and specificity[23,24]. It is theorized that, rather than binding to "naked" DNA, antibodies are actually binding to the nucleosome, specifically DNA coiled around an octamer of histone proteins. Once bound to the antinucleosome antibody, the positively charged histone component binds the negatively charged components of the kidney glomerular basement membrane, linking the antibody to renal tissue[2].

Antinucleosome autoantibodies have been found to be more sensitive than anti-dsDNA antibodies for both active SLE and active nephritis, and to be correlated with damage[23,25,26,27,28]. Of relevance to our study, these antibodies thus far have proven more sensitive than anti-dsDNA antibodies for the diagnosis of SLE[21,23]. Ng, *et al* recently investigated the frequency and predictors of flare in SACQ patients in their SLE cohort of 290 patients, of whom 9% were SACQ. They found that time to first flare after a SACQ period was significantly correlated with the presence of antinucleosome antibodies[29]. Antinucleosome antibodies may thus prove critical in monitoring disease in the SACQ patients; further investigation into the role of these antibodies in the SACQ cohort is required.

SACQ patients represent a small but clinically important group within our SLE population. Although 59% of SACQ patients experience flare, they do so after an average of 3 years. Changes in complement and anti-dsDNA antibody levels drawn at routine clinic visits are not predictive of flare in SACQ patients and levels of anti-dsDNA and complement during SACQ periods are not predictive of subsequent flare. Thus the decision to treat in these patients must be based on close clinical observation, and alternative predictive biomarkers must be studied.

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