The Influence of the 1997 Updated Classification Criteria for Systemic Lupus Erythematosus: Epidemiology, Disease Presentation, and Patient Management

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ABSTRACT. ***Objective.*** The 1997 update of the American College of Rheumatology classification criteria (ACR97) for systemic lupus erythematosus (SLE) has not been validated. We determined to what extent their introduction influenced the epidemiology and clinical characteristics of the disease in northern Norway.

Methods. Annual incidence and point-prevalence rates, clinical manifestations, and outcome were determined in an inception cohort of patients with SLE in northern Norway, included between 1996 and 2006, using ACR97 criteria (97acr). These findings were compared with a cohort from the same area enrolled 1978-1995 using the 1982 revised criteria ACR82 (82acr).

Results. The mean annual incidence of SLE was 3.00 for cohort 97acr (n = 58) versus 2.63 for cohort 82acr (n = 81) (p = 0.5). All patients in the 97acr cohort also fulfilled the 1982 criteria; however, significantly fewer patients presented with discoid rash [odds ratio (OR) 0.31)], arthritis (OR 0.24), renal (OR 0.28) or hematological disorder (OR 0.27), and significantly more with anti-dsDNA (OR 2.57) and antiphospholipid antibodies (OR 27.9). Initial treatment with intravenous pulse methylprednisolone (OR 9.23), azathioprine (OR 6.32), and low-dose aspirin (OR 20.9) was increased in cohort 97acr. Five- (95.2%) and 10-year survival (91.9%) rates were also improved for cohort 97acr.

Conclusion. The ACR97 criteria set has construct validity compared to the ACR82 criteria set. SLE incidence remains unchanged in northern Norway, but a significant reduction of renal disease and further improvements in survival rates occurred simultaneously with increased serological surveillance with ELISA-based assays and early immunosuppressive and anticoagulant therapy. (J Rheumatol First Release Jan 15 2009; doi:10.3899/jrheum.080574)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS EPIDEMIOLOGY
PATIENT CARE CLASSIFICATION CRITERIA DIAGNOSIS

Systemic lupus erythematosus (SLE) is one of the most common systemic autoimmune diseases, characterized by a highly variable clinical presentation and an unpredictable disease course[1,2]. There are considerable regional differences in the epidemiology of SLE, with the lowest incidence rates observed in Caucasian populations[3-6]. There has been a trend towards an increased incidence and prevalence of SLE for Caucasian cohorts in the USA[7-9], while the incidence has been stable in southern Sweden[10].

The 1982 revised criteria for the classification of SLE by the American College of Rheumatology (ACR) were modified in 1997[11,12], where the presence of LE cells was replaced with the presence of antiphospholipid antibodies (aPL). These recommendations reflected that few laboratories were still performing the LE cell assay. The recommendations for the 1997 update were consensus-based and the operating characteristics of the updated criteria set have never been validated. As persistent aPL can also be found in many other conditions[13-16], the inclusion of aPL in ACR97 could, in theory, change SLE incidence and prevalence, e.g., by including patients with undifferentiated connective tissue disease or antiphospholipid syndrome (APS). In the same way, the association between aPL and thrombosis[16,17] may affect the spectrum of disease manifestations by emphasizing vascular events in SLE. While the prognosis for patients with SLE has improved over time and standardized mortali-

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ty rates (SMR) have decreased in Caucasian SLE cohorts, mortality in patients with SLE remains higher than in matched controls with cardiovascular events as a major cause of death[7,18,19]. Our study compared the epidemiological and clinical characteristics of a recent SLE inception cohort defined by the 1997 update of the classification criteria of SLE (ACR97) with an existing cohort from the same region classified according to the 1982 revised ACR criteria (ACR82), where one criterion is presence of LE cells as opposed to ACR97.

MATERIALS AND METHODS

The catchments area for our study consisted of the 2 northernmost counties of Norway (population in 1993 was 224,724 inhabitants, population on January 1, 2007, 226,898) representing 5% of the Norwegian population (Statistics Norway; www.ssb.no). The Department of Rheumatology at University Hospital of Northern Norway is the only rheumatology center in this area, which otherwise has 3 local hospitals and no privately practicing rheumatologists. Data sources were hospital patient registries (in- and outpatients) for all departments in these 4 hospitals. Patients were identified through computerized diagnostic registry searches for International Classification of Diseases-10 codes for SLE (M32.0, M32.1, M32.8, and M32.9), Sjögren's syndrome (M35.0), unclassified connective tissue disease (M35.9), and discoid lupus (L93.0). All adult patients (16 yrs or older) who fulfilled 4 or more of the ACR97[12] criteria in the 11-year period prior to January 1, 2007, were included and designated cohort 97acr. Children with SLE were registered separately and included in prevalence data when reaching 16 years of age (during the study period). Cohort 82acr is a previously reported cohort of SLE incident cases defined by ACR82 during 1978–95[11], constituted in the same area and manner with a high case ascertainment[5]. Demographic data, clinical data, disease activity by SLE Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI) were collected by a single investigator and stored in a central database as described[5]. Missing data were considered to indicate negative findings. Scoring of both SLEDAI and SLICC/ACR DI have been validated[20,21].

Antinuclear antibody (ANA) screening was performed at a single clinical immunology department by immunofluorescence techniques until 1994 and by automated ELISA since then. All ANA-positive sera were routinely tested for the presence of antibodies (Ab) against double-stranded DNA (anti-dsDNA) by *Crithidia luciliae* immunofluorescence assay and ELISA (since 1995), as well as antibodies against Ro (anti-SSA), La (anti-SSB), Smith (anti-Sm), and anti-U1 small nuclear ribonucleoparticle (anti-U1-snRNP), all by ELISA techniques. Both IgG and IgM isotypes of anticardiolipin (aCL) antibodies were tested by commercial ELISA kits since 1992 (cutoff levels for positive findings > 16 IU), while lupus anticoagulant (LAC) was tested in a phospholipid-dependent coagulation assay[22].

Data reported are median values unless indicated otherwise. Continuous data were analyzed by Mann-Whitney U-test, Poisson distribution contingency tables, or Fisher's exact test in case of low numbers. Annual incidence rate (AIR) and point-prevalence (PP) are reported per 100,000. Survival rates were estimated by Kaplan-Meier method and compared by log-rank testing. Standardized mortality rates were calculated by randomly assigning each patient 5 controls, born in the same year and month and matched for sex and municipality identified by area code. The prognostic values of potential survival predictors were analyzed by Cox proportional hazards models. Hazard ratios (HR) are reported with 95% confidence interval (95% CI). All statistical analyses were performed with SPSS 11.0 and Epi-Info 4.1. The regional ethics board approved the study protocol and all patients gave written informed consent for the identified use of their data.

RESULTS

Incidence data. Inception cohort 97acr contained 58 patients with new-onset SLE and was similar to cohort 82acr with regard to age (39.4 vs 41.7 yrs; p = 0.6), sex (84.5% vs 85.2% female; p = 0.4), and ethnicity (1.7% vs 1.2% non-Caucasian; p = 0.8). The estimated average AIR was 2.8 (95% CI 2.2–3.3) for the whole study period (1978–2006), with no significant difference between the AIR for cohort 97acr (3.00, 95% CI 2.0–4.0) and cohort 82acr (2.63, 95% CI 1.9–3.7) (p = 0.5; Table 1). The overall AIR was highest among women 30–49 years of age in both cohorts (8.27 vs 5.79; p = 0.093; Table 1).

Prevalence data. As 16 patients migrated and 40 patients died during the whole study period they were excluded from prevalence analysis. Another 19 patients with SLE diagnosed before 1978 and 12 pediatric patients reaching 16 years of age during the observation period were included in the prevalence data for a total number of 114 adult patients. The crude point-prevalence at January 1, 2007, was 64.1 overall, 108.6 for women, and 20.0 for men per 100,000 (Figure 1). The disease prevalence increased gradually during the observation period, with the highest point-prevalence at 124.9 seen in women age 50 years or older (data not shown).

Clinical and laboratory manifestations. The time between onsets of the first SLE-related symptom and fulfilment of ACR criteria was 1 year in both cohorts, regardless of age and sex (data not shown). The mean number of classification criteria in cohort 97acr was significantly lower than in cohort 82acr [4.6 (range 4–7) vs 6.0 (range 4–9); p < 0.001]. In cohort 97acr, aPL antibodies occurred simultaneously with anti-dsDNA or anti-Sm antibodies in 93.3% at diagnosis; in 6.7% aPL presence was the only immunological criterion, but these patients fulfilled at least 4 other criteria at diagnosis. Overall, all patients in the 97acr cohort fulfilled at least 4 of the ACR82 criteria, even though the assay for LE cells was not available for the patients in this cohort. In cohort 82acr, 33% of the patients with SLE presented with positive LE cells, but only 6.2% as the fourth and only immunologic classification criterion. At diagnosis, SLEDAI scores were similar for both cohorts [8.3 (95% CI 6.6–10.0) vs 8.8 (95% CI 7.4–10.4); p = 0.445], but clinical features differed considerably (Table 2). In cohort 97acr significantly fewer presented with discoid rash (OR 0.31), arthritis (OR 0.24), proteinuria (OR 0.22), leukopenia (OR 0.35), or lymphopenia (OR 0.25). In contrast, the frequencies of anti-dsDNA antibodies and aPL antibodies were significant increased in cohort 97acr (OR 2.57 and 20.9, respectively), while no significant increase was seen for other autoantibodies such as anti-SSA (33% vs 20%), anti-SSB (10% vs 7%), rheumatoid factor (12% vs 17%), or anti-U1-snRNP (12% vs 9%) (data not shown).

To explore this increase in serological classification criteria further, we also compared the intensity of serological

Table 1. Mean annual incidence rates (AIR) for SLE per 100,000 at risk by age and sex, comparison between 2 cohorts in northern Norway. Patients in 97acr cohort were classified by ACR97, while ACR82 was used in 82acr cohort.

	Population	97acr Cohort, 1996–2006		82acr Cohort, 1978–1995		97acr vs 82acr, p	Whole Period 1978–2006	
		n	AIR (95% CI)	n	AIR (955 CI)		n	AIR (95% CI)
Children	47,084	5	0.9 (0.0–1.9)	6	0.7 (0.0–1.4)	0.494	11	0.8 (0.3–1.3)
Adults	177,640	58	3.0 (2.0–4.0)	81	2.6 (1.9–3.7)	0.500	139	2.8 (2.2–3.3)
Men	89,952	9	0.9 (0.0–1.8)	12	0.8 (0.4–1.1)	0.738	21	0.8 (0.4–1.2)
Women	87,688	49	5.1 (3.7–6.4)	69	4.6 (3.1–6.1)	0.208	118	4.8 (3.7–5.8)
Female age groups, yrs								
16–29	25,178	12	4.3 (1.8–6.9)	20	4.4 (1.6–7.2)	0.701	32	4.4 (2.5–6.3)
30–49	30,798	28	8.3 (5.4–1.1)	31	5.8 (3.2–8.4)	0.093	59	6.7 (4.9–8.6)
Over 50	31,712	9	2.6 (0.7–4.4)	18	3.2 (1.3–5.0)	0.848	27	2.9 (1.7–4.2)

Total number in population in 1993 was 224,724 inhabitants. Children: < 16 yrs; ACR: American College of Rheumatology; ACR97: 1997 update of criteria for systemic lupus erythematosus (SLE); ACR82: 1982 revised criteria. n : number of incident cases during the period.

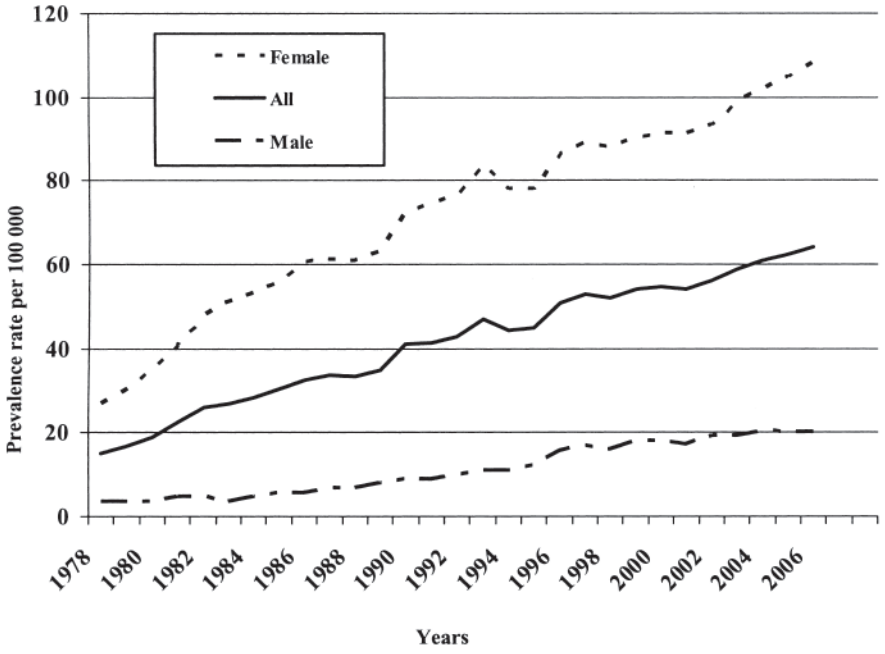

Figure 1. Prevalence rates of SLE in Northern Norway, 1978–2006.

surveillance. With the exception of ANA-negative patients, all patients in both cohorts were surveyed for anti-dsDNA Ab (98% vs 99%; p = 0.9). The annual number of anti-dsDNA assays performed was significantly higher in the 97acr cohort (2.32 vs 1.34; p < 0.001). As the assay for aCL antibodies was introduced in 1992, the data of aPL profiles at diagnosis were biased. When including all available data on the ever-presence of aPL, there was a slight, although not statistically significant, increase in the number of aPL-positive patients in the 97acr cohort (41 % vs 31%; p = 0.201), possibly because more 97acr patients were ever tested for aPL (97% vs 83 %; p = 0.014). The increase in the annual numbers of aPL tests performed in cohort 97acr (2.3 vs 1.4; p < 0.001) was similar to that for anti-dsDNA testing.

Disease course. Initial treatment: During the first 4 months of disease there was increased use of azathioprine (p = 0.011), intravenous pulse methylprednisolone (p = 0.015), and low-dose aspirin (p < 0.001) in cohort 97acr (Table 2). The number of patients treated with nonsteroidal antiinflammatory drugs, hydroxychloroquine, cyclophosphamide, methotrexate, cyclosporine A, plasmapheresis, oral corticosteroids, warfarin, or antihypertensive drugs showed no significant differences (data not shown).

Mortality: At the end of the observation period, 5 women in cohort 97acr had died, for a case fatality rate of 8.6%. At death, disease duration was 19 months (range 3–77) and age 50 years (range 19–75). The overall adjusted SMR was highest in cohort 97acr: overall 3.00 versus 1.88 and women

Table 2. SLE manifestations at diagnosis. Treatment during the first 4 months after diagnosis.

Criteria	97acr Cohort, n = 58 (%)	82acr Cohort, n = 81 (%)	OR	95% CI
Malar rash	35 (60)	43 (53)	1.35	0.7–2.7
Discoid rash	18 (31)	48 (59)	0.31	0.2–0.6
Photosensitivity	30 (52)	53 (65)	0.57	0.3–1.1
Oral ulcers	12 (21)	25 (31)	0.58	0.3–1.3
Arthritis	31 (54)	67 (83)	0.24	0.1–0.5
Serositis	11 (19)	21 (26)	0.67	0.3–1.5
Renal disorder	7 (12)	27 (33)	0.28	0.1–0.7
Proteinuria	5 (9)	24 (31)	0.22	0.1–0.6
Casts	6 (10)	16 (20)	0.47	0.2–1.3
Neurological disorder	1 (2)	5 (5)	0.27	0.0–2.4
Hematological disorder	27 (47)	62 (77)	0.27	0.1–0.6
Leukopenia	16 (28)	42 (52)	0.35	0.2–0.7
Lymphopenia	15 (26)	47 (58)	0.25	0.1–0.5
Immunological disorder	43 (74)	57 (70)	1.21	0.6–2.8
LE cells	0 (0)	27 (33)	—	—
Anti-DNA antibodies	39 (67)	36 (44)	2.57	1.3–5.2
Anti-Sm antibodies	6 (10)	8 (10)	1.05	0.4–3.2
False-positive syphilis test	5 (9)	7 (9)	1.00	0.3–3.3
aPL	15 (26)	1 (1)	27.9	3.6–218
Antinuclear antibodies	53 (95)	78 (96)	0.41	0.1–1.8
Azathioprine	8 (14)	2 (3)	6.32	1.3–31.0
Methylprednisolone	6 (10)	1 (1)	9.23	1.1–78.9
Low-dose aspirin	12 (21)	0 (0)	20.9	2.6–165.7

For abbreviations see Table 1.

3.75 versus 1.94 (Table 3). In cohort 82acr, 25 patients had died (case fatality rate 30.9%) after longer disease duration (98 months, range 1–209) and at higher age (66 yrs, range 19–81) than in cohort 97acr.

Survival: Ten-year survival for patients with SLE was significantly lower than in the general population ($p = 0.004$ for cohort 97acr, and $p < 0.001$ for cohort 82acr). Five- and 10-year survival estimates were higher in cohort 97acr (95.2% and 91.9%, respectively) than in cohort 82acr (90.8% and 80.5%), but this increase was not statistically significant (Figure 2).

Cox proportional hazard models identified potential predictors of survival within 10 years of diagnosis ($p < 0.1$ to enter, $p < 0.05$ to stay). In cohort 97acr, the initial presence of renal disease (HR 10.9; $p = 0.009$), initial treatment with pulse methylprednisolone (HR 1.5; $p = 0.012$), low-dose aspirin (HR 1.3; $p = 0.005$), and antihypertensive drugs (HR 1.3; $p = 0.001$) were associated with poorer survival by univariate analysis. The low number of events did not allow multivariate analysis of the interdependency of these predictors. In cohort 82acr, age > 50 years at diagnosis was the sole independent predictor for poorer survival (HR 12.2; $p \leq 0.001$; Table 4).

Table 3. Sex and age-adjusted standardized mortality ratio (SMR) for the various SLE cohorts and controls (C).

	97acr Cohort, 1996–2006				82acr Cohort, 1978–1995				Whole Period, 1978–2006			
	SLE, n = 58	Control, n = 290	SMR	95% CI	SLE, n = 81	Control, n = 405	SMR	95% CI	SLE, n = 139	Control, n = 695	SMR	95% CI
	No. Deaths				No. Deaths				No. Deaths			
Children	0	0	NC	—	0	0	NC	—	0	0	NC	—
Adults	5	5	3.00	1.6–5.8	25	55	1.88	1.3–2.7	30	60	2.00	1.4–2.8
Men	0	2	NC	—	5	13	1.67	0.7–4.1	5	15	1.50	0.6–3.5
Women	5	3	3.75	2.1–6.8	20	42	1.94	1.3–2.9	25	45	2.14	1.5–3.1
Age at death, yrs												
16–29	1	0	NC	—	1	1	3.17	0.6–17.9	2	1	4.06	1.6–10.5
30–49	1	1	3.00	0.7–12.5	4	4	2.72	1.3–5.9	5	5	2.87	1.5–5.6
50–69	2	2	3.04	1.0–9.2	8	5	3.32	1.9–5.7	10	7	3.28	2.0–5.3
70+	1	1	NC	—	7	32	1.44	0.6–3.2	8	32	1.54	0.7–3.3

NC: not calculated. Children < 16 years.

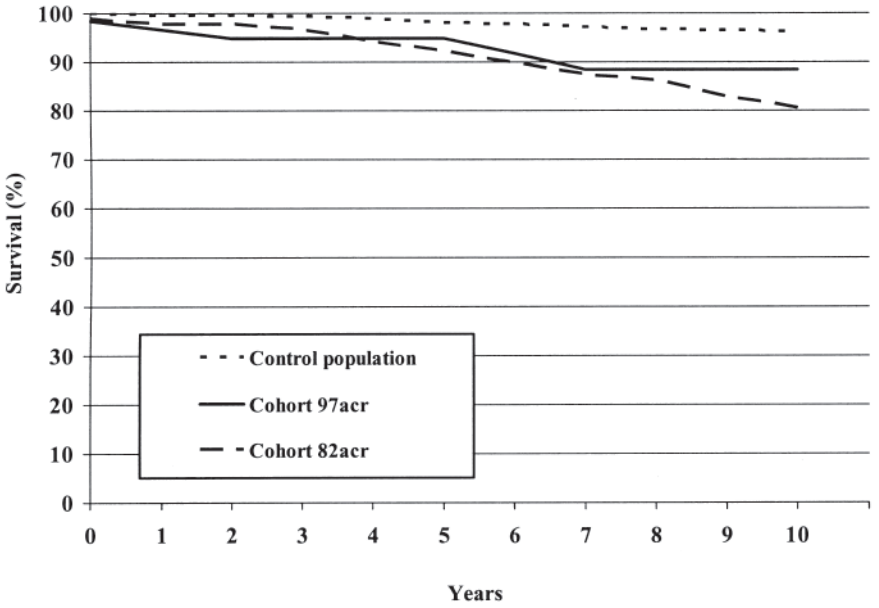

Figure 2. Survival among SLE patients in cohort 97acr (diagnosed by ACR97), cohort 82acr (diagnosed by ACR82), and control population. For cohort 97acr and controls p = 0.004 and for cohort 82acr and controls p < 0.001, by log-rank test.

Table 4. Predictors for mortality in SLE within 10 years after diagnosis, by univariate analysis (hazard ratio, both cohorts) and multivariate analysis (adjusted HR, cohort 82acr only). Clinical criteria reflect findings at scientific diagnosis, drug treatment during the first 4 months after diagnosis, SLICC/ACR DI > 0 one year after diagnosis, hypocomplementemia during first year of disease; and ever-positive test for aPL antibodies.

Criteria	97acr Cohort				82acr Cohort				Adjusted	
	Died, n = 5 (%)	Alive, n = 57 (%)	HR	95% CI	Died, n = 17 (%)	Alive, n = 70 (%)	HR	95% CI	HR	95% CI
Age ≥ 50 yrs	2 (40)	10 (18)	2.2	0.4–13.4	13 (77)	10 (14)	11.5	3.7–35	12.2	3.3–46
Malar rash	2 (40)	35 (61)	0.4	0.1–2.6	6 (35)	43 (61)	0.4	0.1–0.9	0.8	0.2–2.4
Photosensitivity	2 (40)	30 (53)	0.5	0.1–3.2	8 (47)	48 (69)	0.4	0.2–1.1		
Oral ulcers	0	21 (21)	0.04	0.0–651	2 (12)	26 (37)	0.2	0.1–1.0		
Renal disorder	3 (60)	5 (9)	10.9	1.8–66	7 (42)	24 (34)	1.3	0.5–3.5		
NSAID	3 (60)	23 (40)	1.8	0.3–10.7	5 (29)	40 (57)	0.4	0.1–1.0		
Methylprednisolone	2 (40)	4 (7)	1.5	1.1–2.0	0	3 (4)	0.6	0.1–3.6		
Cyclophosphamide	2 (40)	4 (7)	5.2	0.9–31	1 (6)	11 (16)	0.3	0.0–2.5		
Low-dose aspirin	4 (80)	8 (14)	1.3	1.1–1.5	0	0				
Antihypertensives	3 (60)	1 (2)	1.3	1.1–1.4	0	2 (3)				
SLICC/ACR DI > 0	2 (40)	17 (30)	1.4	0.2–8.1	5 (29)	7 (10)	2.8	1.0–8.0	1.7	0.6–5.0
Low C3	3 (60)	11 (19)	5.4	0.9–32	6 (35)	31 (44)	0.7	0.3–1.9		
Low C4	4 (80)	18 (32)	7.2	0.8–65	5 (29)	23 (33)	0.9	0.3–2.5		
aPL	4 (80)	21 (37)	7.0	0.8–63	4 (24)	24 (34)	0.6	0.2–1.7		

NSAID: nonsteroidal antiinflammatory drugs; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; aPL: antiphospholipid antibodies.

DISCUSSION

In an effort to determine the validity of the 1997 update of the ACR classification criteria for SLE, a longterm population-based study of SLE was performed. The use of the ACR97 criteria did not lead to changes in SLE incidence or demographics, as all patients fulfilled the ACR82 criteria as well. However, the clinical disease pattern did change over time, with a significant reduction in the frequency of renal disease and increased use of assays for lower avidity ds-DNA and aPL antibody as classification criteria. Concurrent increased use of early treatment with pulse methylprednisolone, azathioprine, and low-dose aspirin and more intense serological surveillance may have further contributed to this "prevention" of renal disease with subsequent improvements in overall 5- and 10-year survival rates for the whole cohort.

The negligible increase in SLE incidence during the last decade is in accord with earlier observations from southern

Sweden[10]. The average AIR (3.0 per 100,000 adults) remains within the range of reported Scandinavian incidence rates (1.5–4.8 per 100,000)[3,5,6,10,23]. Studies from other regions give conflicting data. In the French West Indies no changes in SLE incidence have occurred[24], while the Mayo Clinic in Rochester, MN, USA, describes a tripling of SLE incidence in the period 1950-92[9]. The Rochester population has a strong Nordic background and the overall incidence rate for the study was 3.0/100,000[9], similar to our data, so the increase observed in Rochester may be a catchup effect. The trend towards increasing AIR in women for the 30–49 age group (8.3) is in line with other studies[5,6,25], however, aside from the high AIR (14.1) seen in women 65–74 years old in southern Sweden[10]. SLE prevalence in Northern Norway was highest in postmenopausal women (1.3 per 1,000), making SLE a disease currently seen in 1 per 770 women in this age group. The increasing overall prevalence (64.1 per 100,000 as of January 1, 2007) is due to a stable disease incidence and improved survival.

While not a primary aim of our study, we observed a stable incidence and no case fatalities in children with SLE in northern Norway. The mean AIR was 0.9 per 100,000 for children, somewhat higher compared with other studies on Scandinavian cohorts[23,26].

Despite few changes in epidemiological characteristics, remarkable changes in the clinical presentation of SLE over time occurred. The average number of classification criteria at diagnosis decreased significantly, even though the time from the first symptom attributable to SLE was 1 year in both cohorts. Increased reliance on sensitive, although not necessarily specific, autoantibody assays for anti-dsDNA and aPL seems to have become an essential part of the diagnostic investigation and classification process. The fact that overall disease activity at diagnosis was similar is not in contradiction with this, as the SLEDAI incorporates several recognized disease manifestations not covered by the classification criteria (e.g., alopecia, vasculitis, cerebrovascular accidents, fever, and hypocomplementemia). These data thus imply that, currently, physicians with the use of sensitive assays recognize SLE at an earlier stage before severe and/or multi-organ presentation develops and also include serological surveillance more often in patient management[27].

The decrease in the number of patients with lupus nephritis in the 97acr cohort in our study is especially intriguing. Most studies link lupus nephritis to the presence of nephritogenic high avidity anti-dsDNA Ab as detected by *C. luciliae* immunofluorescence or the Farr radioactivity assay[28-30]. Anti-dsDNA Ab are, however, often present long before SLE is clinically apparent and they gradually obtain their nephritogenic potential through repeated antigenic stimulation[28,31,32]. Several short-term prospective studies have shown that intensive anti-dsDNA Ab surveillance can help prevent disease flares such as lupus nephritis[33,34]. In our study the 97acr cohort was surveyed more frequently for early serological disease markers, had increased early treatment with pulse steroids and azathioprine, and generally had milder lupus. Altogether this may lend support to the accumulated theory on lupus development. While our observational data only provide circumstantial evidence, they at least support the idea that severe lupus could be prevented by intervening in the mechanism behind the antibody maturation response and thereby reducing the risk of renal disease and attaining the goal of milder lupus.

It is, however, important to note that established renal disease remained a strong risk factor for reduced short-term survival (HR 10.9)[35-37]. Therefore, lupus nephritis remains a potentially severe, although now less frequent, complication of SLE in Caucasian patients, and the use of serological surveillance in the prevention of lupus nephritis deserves further study.

A similar case can be made for increased surveillance for aPL antibodies. aPL screening was reinforced by the ACR97 criteria, and aPL Ab are detectable in the serum of patients with SLE many years before diagnosis and prior even to anti-dsDNA Ab[32,38]. While the pathogenic characteristics of aPL are less well defined than for anti-dsDNA Ab, increased serological surveillance likely contributed to earlier identification of cases in the 97acr cohort, and clearly contributed to patient management measures as illustrated by the preventive treatment with low-dose aspirin in 21% of newly diagnosed patients[39].

Patients with SLE in northern Norway remain at risk of premature death, as indicated by the overall SMR of 2.00 for the whole study period. During the 1970s and 1990s, SMR for lupus cohorts ranged between 2.7 and 4.9 around the world[40-42]. Some studies from the last decade report decreasing SMR, with a study from Greece reporting a SMR of only 1.5[36,43]. In our study, SMR was higher in cohort 97acr (3.00) than in cohort 82acr (1.88). Mortality in SLE has been described as having a bimodal pattern, with an early mortality peak mainly due to active disease and a later peak associated to cardiovascular complications[44,45]. Given the disease duration of only 19 months at death in the 97acr cohort, this increased SMR can likely represent the first peak in the mortality curve. Alternatively, the increased SMR may reflect a larger reduction in mortality in the control group than in the SLE cohort due to improved general healthcare delivery and living standards. For the whole period, SMR was highest in women under 30 years of age and lowest in the elderly, similar to data from various other cohorts[36,40,41].

Both 5- and 10-year survival rates were improved for the 97acr cohort compared with 82acr cohort, in line with other single-center studies[10,46]. This development naturally reflects the combined effects of earlier case recognition with subsequent inclusion of patients with milder form of dis-

ease, advances in therapeutic modalities, and more judicious use of existing therapies such as hydroxychloroquine[47]. Cardiovascular disease is an increasingly important contributor to SLE mortality, and together with infections is the most frequent cause of death[19,41,48]; and while low numbers did not allow detailed analyses, causes of death in cohort 97acr were also mainly cardiovascular (40%) and infectious (40%), with 1 patient in a fatal accident (20%).

Of necessity, our study is observational and we are aware of the biases incurred by such study design and the relatively low number of patients. While the use of an earlier-inception cohort, the single-center setting, and the long followup time provided some measure of control, selection bias may nonetheless have influenced our conclusions, which will need further confirmation. The differences in observation times precluded any firm conclusions on mortality differences between the 2 cohorts, while low numbers did not allow us to perform statistically meaningful analyses of specific causes of death.

The ACR97 criteria set was found to have excellent construct validity compared to the ACR82 criteria. While the incidence of SLE in northern Norway remained constant between 1978 and 2006, an increase in the use of serological classification criteria coincided with a notable reduction in prevalence of lupus nephritis. The increased use of a sensitive ELISA for anti-dsDNA and aPL antibodies may thus have allowed earlier identification of patients at risk for severe disease. Together with a more aggressive therapeutic approach, this seems to have contributed to milder lupus in a number of patients, with subsequent improvements in survival.

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