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TRENDS IN THE INCIDENCE AND MORTALITY OF SYSTEMIC LUPUS ERYTHEMATOSUS, 1950–1992

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Objective. **To describe trends in systemic lupus erythematosus (SLE) incidence and mortality over the past 4 decades.**

Methods. **Using the Rochester Epidemiology Project resources, medical records were screened to identify all Rochester, Minnesota residents with any SLE-associated diagnoses, discoid lupus, positivity for antinuclear antibodies, and/or false-positive syphilis test results determined between January 1, 1980 and December 31, 1992. Medical records were then reviewed using a pretested data collection form in order to identify cases of SLE according to the American College of Rheumatology 1982 revised criteria for SLE. Drug-induced cases were excluded. All identified SLE patients were followed up until death, migration from the county, or October 1, 1997. These data were combined with similar data from the same community obtained between 1950 and 1979, and trends in the SLE incidence and mortality over time were calculated.**

Results. **Of the 430 medical records reviewed, 48 newly diagnosed cases of SLE (42 women and 6 men) were identified between 1980 and 1992. The average incidence rate (age- and sex-adjusted to the 1970 US white population) was 5.56 per 100,000 (95% confidence interval [95% CI] 3.93–7.19), compared with an incidence of 1.51 (95% CI 0.85–2.17) in the 1950–1979 cohort. The age- and sex-adjusted prevalence rate as of January 1, 1993 was ~1.22 per 1,000 (95% CI 0.97–1.47). Survival among SLE patients was significantly worse than in the general population ($P = 0.017$ compared with the 1980–1992 cohort, and $P < 0.0001$ compared with the 1950–1979 cohort, by log-rank test). Cox proportional hazards modeling demonstrated a statistically significant improvement in the survival rate over time ($P = 0.035$).**

Conclusion. **Over the past 4 decades, the incidence of SLE has nearly tripled, and there has been a statistically significant improvement in survival. These findings are likely due to a combination of improved recognition of mild disease and better approaches to therapy.**

Systemic lupus erythematosus (SLE) is a disease that can affect many different organ systems. Preliminary criteria for the classification of SLE were first defined by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) in 1971 (1) and were subsequently revised by the ACR in 1982 (2).

Using the 1982 ACR criteria for the classification of SLE (2,3), we assembled a population-based inception cohort of SLE patients from Rochester, Minnesota (1980 through 1992). We combined the associated data of this cohort with data from a previously assembled cohort (1950 through 1979) in the same community (4) in order to assess trends in SLE incidence and mortality over the past 4 decades.

PATIENTS AND METHODS

The Rochester Epidemiology Project (REP) is a unique system that allows the identification and retrieval of virtually all inpatient and outpatient medical records of residents of Olmsted County, Minnesota (including the city of Rochester) (5). Medical diagnoses made at clinics, hospitals, and nursing home visits or at autopsy are entered into this computerized index system, and all pertinent medical records can be retrieved for detailed review.

In this study, we screened the inpatient and outpatient medical records of all Rochester, Minnesota residents who had

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a diagnosis of SLE and associated diagnoses, discoid lupus, positive test for antinuclear antibodies (ANA), and/or false-positive test result for syphilis that was determined between January 1, 1980 and December 31, 1992. A pretested data collection form was used to collect information on demographics, clinical manifestations, laboratory findings, treatment (corticosteroids, antimalarials, cyclophosphamide, azathioprine, and other immunosuppressive agents), and outcome. All SLE patients were followed up until death, migration from the county, or October 1, 1997. These data were then combined with similar data from a 1950–1979 cohort in the same community (4), and trends over time were calculated.

An incidence case was defined as the diagnosis of SLE in an individual who had been a resident of Rochester, Minnesota for at least 1 year prior to diagnosis and had fulfilled the 1982 ACR criteria for the classification of SLE between January 1, 1980 and December 31, 1992. Drug-induced cases were excluded. A prevalence case was defined as a diagnosis of SLE in any individual who was a resident of Rochester, Minnesota as of January 1, 1993 and who, prior to that date, fulfilled the 1982 ACR criteria for SLE. The date of diagnosis was defined as the date of fulfillment of the fourth ACR criterion. ANA levels were considered positive if the titer was 1:40 or higher. All possible and definite cases of SLE from the 1950–1979 SLE incidence cohort were reabstracted using the 1982 ACR criteria and the above definition for ANA positivity, thus ensuring that the same methods were used to assemble both incidence cohorts.

Incidence rates were estimated by dividing the number of incidence cases, as defined above, by the Rochester population as obtained from the decennial censuses, with linear interpolation for the intercensal years. Prevalence rates were estimated by dividing the number of prevalence cases on January 1, 1993, as defined above, by the estimated Rochester population on that date. Overall rates were age- and sex-adjusted to the 1970 US white population. Survival rates were estimated using the Kaplan-Meier method. Cox proportional hazards modeling was utilized to analyze trends in survival over the 43-year time period.

RESULTS

Patient characteristics. Of the 430 medical records reviewed, we identified 48 cases of SLE (42 women and 6 men) that were first diagnosed between 1980 and 1992. The remaining 382 patients were excluded for the following reasons: lupus was drug-induced (n = 8), <4 ACR criteria were fulfilled (127 patients had 1–3 criteria and 100 had no criteria), the fourth criterion occurred before 1980 or after 1992 (n = 33), another connective tissue disease was present (n = 14), or residency was outside of Rochester, Minnesota (n = 100).

The mean age at diagnosis was 49.2 years (range 10.7–85.6) and 46.4 years (range 17.8–74.2) in the 1980–1992 and 1950–1979 incidence cohorts, respectively. The average length of followup was 6.58 years (range 0.24–14.83) for the 1980–1992 cohort and 7.20 years (range 0.25–34.4) for the 1950–1979 cohort.

Table 1. Manifestations of systemic lupus erythematosus at diagnosis

Criteria	1980–1992 cohort, no. (%) (n = 48)	1950–1979 cohort, no. (%) (n = 21)
Malar rash	13 (27)	5 (24)
Discoid rash	10 (21)	4 (19)
Photosensitivity	18 (38)	8 (38)
Oral ulcers	3 (16)	1 (5)
Arthritis	20 (42)	17 (81)
Serositis	12 (25)	10 (48)
Renal disorder	23 (48)	8 (38)
Casts	21 (44)	7 (33)
Proteinuria	8 (17)	3 (14)
Nephritis	10 (21)	7 (33)
Neurologic disorder	1 (2)	1 (5)
Hematologic disorder	39 (81)	16 (76)
Immunologic disorder	27 (56)	17 (81)
Antinuclear antibodies	37 (77)	9 (43)

Clinical manifestations. The SLE criteria at diagnosis in the 2 cohorts were compared (Table 1). Arthritis and serositis were more common in the 1950–1979 cohort than in the 1980–1992 cohort. Although renal disease in general was slightly more common in the 1980–1992 cohort, our data indicate that more patients in the 1950–1979 cohort had nephritis (diagnosed by a physician and/or confirmed by biopsy), while more patients in the 1980–1992 cohort had urinary casts. The frequency of ANA was, as expected, higher in the 1980–1992 cohort due to the increased availability and utilization of serologic testing for ANA over time. The higher frequency of immunologic disorders in the previous time period reflects the increased use of the lupus erythematosus cell test during that time.

Treatment. The treatment of SLE over the followup period was compared between the 1980–1992 and 1950–1979 cohorts (Table 2). The percentage of patients treated with corticosteroids and immunosuppressives decreased over time, while the use of antimalarials increased.

Table 2. Treatment of systemic lupus erythematosus

	1950–1979 cohort, no. (%)	1980–1992 cohort, no. (%)
Corticosteroids	13 (62)	23 (48)
Antimalarials	3 (14)	23 (48)
Cyclophosphamide	12 (57)	1 (2)
Azathioprine	6 (29)	3 (6)
Other immunosuppressives	–	5 (10)

Table 3. Incidence of systemic lupus erythematosus

	1950–1979	1980–1992	1950–1992
Males	0.50	1.54	0.91
Females	2.47	9.40	5.11
Total	1.51*	5.56	3.06
95% confidence interval	0.85–2.17	3.93–7.19	2.32–3.80

* Recalculated using the 1982 revised criteria of the American College of Rheumatology (2).

Incidence, prevalence, and survival rates. The average incidence rate, age- and sex-adjusted to the 1970 US white population, was 5.56 per 100,000 (95% confidence interval [95% CI] 3.93–7.19) in 1980–1992 (Table 3). In contrast, an incidence of 1.51 per 100,000 (95% CI 0.85–2.17) was found in the 1950–1979 SLE cohort (recalculated from the original report by applying the 1982 ACR criteria and the updated definitions for positive ANA). The average incidence rate in Rochester, Minnesota during the entire period, 1950–1992, was 3.06 per 100,000 (95% CI 2.32–3.80). The incidence rate was ~5–6-fold higher in women than in men in both cohorts.

The age- and sex-adjusted prevalence rate on January 1, 1993 was ~1.22 per 1,000 (95% CI 0.97–1.47). Survival of SLE patients was significantly worse than in the general population ($P = 0.017$ for the 1980–1992 cohort, and $P < 0.0001$ for the 1950–1979 cohort, by log-rank test) (Figures 1 and 2). Cox proportional hazards modeling demonstrated a statistically significant improvement in the survival rate over time ($P = 0.024$). The standardized mortality ratio was 2.70 (95% CI 1.65–4.18) among the SLE patients between 1950 and 1992.

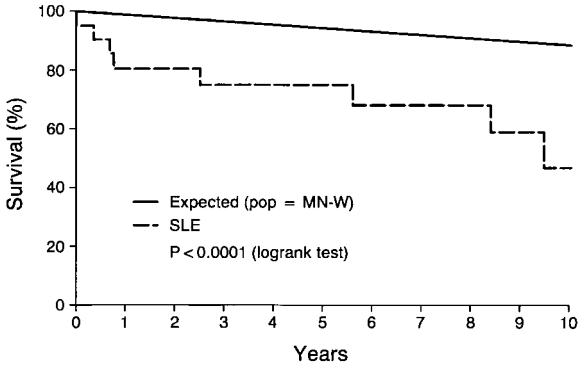

Figure 1. Survival among systemic lupus erythematosus (SLE) patients in the 1950–1979 cohort. pop = population; MN-W = Minnesota whites.

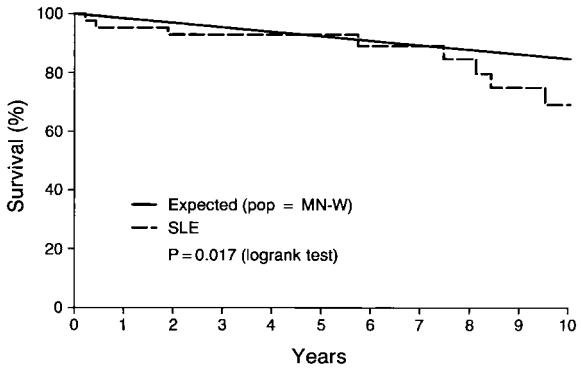

Figure 2. Survival among SLE patients in the 1980–1992 cohort. See Figure 1 for definitions.

DISCUSSION

Our results indicate that the incidence of SLE in the same community has more than tripled over the past 4 decades, and that the rate of survival for individuals with this condition (while still poorer than expected for the general population) has significantly improved. A likely explanation for the increase in incidence is improved recognition of mild disease. On the other hand, the percentages of neurologic and hematologic manifestations were similar in the 2 cohorts (Table 1), which suggests that SLE may not, in fact, have been more benign in the 1980–1992 cohort compared with the earlier cohort. Other possible explanations for an increase in incidence of SLE over time include an increased exposure to hormones such as oral contraceptives (6) and estrogen replacement therapy (7), exposure to ultraviolet light (8,9), and smoking (10). The increased utilization of the ANA test as a screening tool may have contributed to the increased ascertainment of SLE. A higher proportion of patients with mild disease could, in part, explain the observed improvements in survival. However, better approaches to the treatment of SLE and its complications are also contributing factors.

Previous studies have reported SLE incidence rates that are between 1.5 and 7.6 per 100,000 (3,11). Our incidence rate falls within this range. However, those rates are not all directly comparable with ours. For example, the incidence rate of 7.6 per 100,000 reported by Fessel (11) was calculated using the ACR preliminary criteria for SLE (not the 1982 revised criteria, which was used in our study), and the population in that study was more ethnically diverse than the primarily white population of Rochester, Minnesota. In general, the studies with the higher incidence rates utilized more comprehensive case-retrieval methods, rather than simply ac-

cepting a physician's diagnosis of SLE from outpatient or hospital sources (12–15).

An interesting characteristic of incidence cases in our study was the mean age at diagnosis of SLE. While the mean age at diagnosis was similar in both cohorts, it was higher than the mean ages reported in some other studies (12,16–18). However, Hopkinson et al (14) reported a similar mean age at diagnosis (47 years for women and 55.5 years for men) in a population-based cohort in the UK. Population-based data resources such as ours and those used by Hopkinson et al commonly result in a higher mean age at diagnosis because they include elderly incidence cases from the community, which may not be included in referral cohorts.

Our prevalence rate of 1.22 per 1,000 (130 per 100,000) was higher than other reported prevalence rates. Previously reported prevalence rates in the continental US have ranged between 14.6 and 50.8 per 100,000 persons (19). However, 2 recent studies on self-reported diagnosis of SLE indicated that the actual prevalence of SLE in the US may be much higher than previously reported (20,21). One of these studies validated the self-reported diagnosis of SLE by reviewing available medical records (20). The prevalence rate in that study was 124 cases per 100,000 persons, which is similar to the prevalence rate in our study. The increased prevalence in our study may also have been due to the improved survival rate among SLE patients in the recent time period (Figures 1 and 2).

The survival of SLE patients has improved significantly over time in Rochester, Minnesota. This improved survival has been reported in the literature, when studies from 1950 were compared with studies in the 1990s (5-year survival 50% in 1950 versus 80–90% in the 1990s) (22,23) . However, some of these previous studies compared survival rates of patients who lived in different cities and, in some cases, even different countries. A recent study compared the SLE-related mortality rates in a single referral center over time and also found improved survival over a 24-year period (1970–1994) (23). Ours is the first population-based study to compare survival rates in the same community over 4 decades.

Explanations for the improved survival include earlier diagnosis of SLE, recognition of mild disease, and better approaches to therapy. Unfortunately, evidence to support or refute these possible explanations is scarce. One study demonstrated no significant difference between the age at diagnosis and the interval between the onset of symptoms and diagnosis in patients diagnosed with SLE over the past 20 years, suggesting that SLE is not currently being diagnosed earlier than it was in the past (16). Another study showed that the activity of SLE, as measured by the SLE Disease Activity Index, was similar over 24 years (23). Therefore, these authors concluded that the improved survival of SLE patients over time was not due to earlier diagnosis or recognition of milder disease. In our cohort, the average age at diagnosis was similar over time, which supports those conclusions. Compared with the earlier cohort (Table 1), the percentage of renal disease in the 1980–1992 time period was increased. Differences in treatment over time were observed in our study, with use of more antimalarials and less cyclophosphamide and corticosteroids in 1980–1992 compared with 1950–1979. Although this finding supports the hypothesis that the disease observed in these patients in 1980–1992 may have been less severe than it was during the earlier time period, it may also reflect changing practice patterns.

As with any other study, our results must be interpreted in light of our study limitations. With medical records review, underascertainment of cases is possible. In order to ensure complete case ascertainment, we carried out several measures. First, a pretested data collection form was used. Any questions of diagnosis were reviewed with the physician co-investigators and resolved by consensus. Second, the unique medical records retrieval system of the REP was utilized, which provides virtually complete access to cases of any disease diagnosed since the turn of the century (24,25). Third, medical records were retrieved for 1 year before and after the study time period (1979 and 1993) to ensure capture of all cases. Fourth, we rescreened the REP database in April 1997 to ensure that all diagnostic coding and data input were updated. Because of these reasons, we believe that underascertainment of cases was unlikely in our study.

With the use of the REP database, other possible limitations exist. In order for a disease or disorder to be identified in the database, it must be recognized by a physician, recorded, and then retrieved. Therefore, disorders that do not come to medical attention or for which there is no documentation would not be identified. Furthermore, certain racial and ethnic groups are underrepresented in Rochester, Minnesota. According to the 1990 US Census, the population of Rochester, Minnesota was 94% white, 4% Asian, 1% Hispanic, and 1% African American or other ethnic group. Therefore, our population-based study is generalizable only to the US white population.

In summary, the incidence of SLE has tripled over the past 4 decades in Rochester, Minnesota, and the survival of SLE patients has improved significantly. The

increased incidence and improved survival of patients with SLE is likely due to a combination of improved recognition of mild disease and better approaches to therapy.

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