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Clinical significance of fever in the systemic lupus erythematosus patient receiving steroid therapy

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Background. Active systemic lupus erythematosus (SLE) can cause fever. Steroids (glucocorticoids) suppress SLE fever; however, the extent to which steroid therapy affects SLE fever not previously been rigorously studied.

Methods. Study A is a prospective study of recurrently active SLE patients ($N = 92$, 60 renal SLE and 32 nonrenal SLE) who recorded daily oral evening temperatures while participating in a longitudinal study of risk factors for SLE flare. Study B is a retrospective study of consecutive febrile SLE patients ($N = 22$) who received steroids initially because SLE was suspected. At final analysis 11 had SLE fever and 11 had infection fever.

Results. In study A during a mean follow-up of 13.2 ± 8.1 months, 51 of the 92 patients experienced 73 SLE flares. In only one patient was SLE fever associated with SLE flare. In the other 50 patients who flared, there was no significant trend to develop fever prior to or at the onset of SLE flare. Prednisone, median dose 10 mg, was being received at 82% of the study visits at which an SLE flare was declared. In study B, prednisone 28 mg (range 20 to 40 mg) completely suppressed SLE fever, usually within 24 hours. In contrast, infection fever persisted despite prednisone 35 to 300 mg/day. Of those with infection fever, three developed fatal sepsis when high-dose steroid therapy was continued.

Conclusion. In SLE patients receiving prednisone at maintenance doses or greater, SLE fever is rare. When fever does develop, it is usually due to infection. Continuing high steroid dose steroid therapy in those with infection fever may increase the risk of severe sepsis.

Fever is believed to be a common manifestation of active systemic lupus erythematosus (SLE) fever. In the report of Harvey et al [1] from the early 1950s, fever attributed to active SLE occurred in 86% of patients. However, over the ensuing decades the reported incidence of fever attributed to SLE has declined progressively (reviewed in [2]). For example, in SLE patients studied between 1980 and 1989, only 41% reported fever as a sign of active SLE [3]. Wallace [2] suggests that the recent decline in the incidence of SLE fever may result from the more frequent use of nonsteroidal anti-inflammatory drug (NSAID) therapy. The present work tests the hypothesis that glucocorticoid (steroid) therapy also can contribute to the declining incidence of SLE fever. Study A tested this hypothesis prospectively in a cohort with recurrently active SLE in which, at any given time, an average of 75% were receiving steroid therapy. Study B tested this hypothesis retrospectively by determining whether steroid therapy suppressed SLE fever better than the fever of infection (infection fever).

Previous work has studied fever in SLE [4–6]. However, none of these studies specifically addressed the hypotheses of study A or study B. Furthermore, our experience and that reported by others [7–9] suggests that fatal sepsis can result when high-dose steroids are continued in the persistently febrile SLE patients. The reason for continuing high-dose steroid therapy in the persistently febrile SLE patients was not stated in the reports; however, in the patients reported here the managing physicians justified the high-dose steroid therapy because they assumed that the fever was a sign of active SLE. Thus, there is a need to better understand the relation of fever to steroid therapy in the management of SLE. Study A and study B were undertaken to address this unmet need.

The most rigorous test of the effects of steroid therapy on SLE fever versus infection fever would be a placebo-controlled randomized trial. We suggest, however, that such a study design would be unethical because it would withhold proven therapy from seriously ill patients. We suggest that an observational trial design such as that of study A and study B is the only feasible means to adequately test the study hypotheses regarding the effect of steroid therapy on SLE fever versus infection fever.

Key words: SLE, fever, steroid therapy.

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METHODS

Setting and procedures

Study A. The patients are the first 92 enrolled in the Ohio SLE Study (OSS), also titled "Pathogenesis of SLE relapse." The OSS is the clinical component of the NIH Program Project entitled "Genetic and clinical risk factors of human SLE nephritis." The OSS is a prospective longitudinal study in which SLE patients with four or more American College of Rheumatology (ACR) criteria for SLE and recurrently active SLE (two or more SLE flares requiring an increase in therapy in the previous three years) or persistently active disease (≥4 months of active SLE despite therapy consisting of at least prednisone ≥20 mg daily). The patients either had renal SLE defined as major renal manifestations past or present with the following characteristics: 24-hour urine protein/creatinine ratio ≥1.0, serum creatinine ≥1.1 mg/dL (females) or ≥1.3 mg/dL (males) or both, and attributable to World Health Organization (WHO) Class III, IV, or V SLE glomerulonephritis, or nonrenal SLE defined as never having shown major renal manifestations. The OSS protocol is as follows.

First, daily testing, which includes a daily log completed consisting of seven items, including daily evening oral temperature using an electronic oral thermometer (Vicks), which was shown to be accurate within +0.5°F over the range of 99 to 102°F by calibration in an electronic thermocycler (data not shown). Each thermometer was tested when it was replaced after each 6 to 9 months of use. The daily log also recorded whether the patient experienced an infection or other illness that day.

Second, monthly testing, in which a first-voided morning urine specimen (midmonth for males and amenorrheic females) or between days 17 and 25 after the start of the previous menstrual cycle.

Third, testing each 2 months, which involves the completion of a systemic lupus activity measure (SLAM), acute illness report (if illness occurred since the last study visit), update of the medication list, problem list and procedure list, and laboratory testing to assess general status and SLE activation, as follows: 24-hour urine for protein, creatinine, urea, sodium, semiquantitative urinalysis by a study physician (renal SLE patients only), or dipstick urinalysis (nonrenal SLE patients only), complete blood count with differential and platelet count, basic metabolic profile, serum albumin (if renal SLE), standard plasma chemistries, complement C3 and C4, antidouble-stranded DNA antibodies, erythrocyte sedimentation rate, C-reactive protein, and collection of research specimens frozen at −70°F (plasma, serum, urine, urine sediment, and T cell and B cell fractions).

Fourth, testing each 6 months, including a comprehensive metabolic profile.

Finally, annual testing provides a detailed thrombotic tendency profile, 24-hour urine for protein, creatinine, urea, sodium (nonrenal SLE), C-peptide, intact parathyroid hormone (PTH), blood lipids, and homocysteine.

Adjudication and classification of SLE relapse. After all clinical testing results were assessed from each 2-month study visit, the OSS Conclusion Form was completed by the patient's study physician (L.A.H., K.V.H., B.H.R., S.L-W., or D.S.). This form included an assessment of whether an SLE flare (relapse) occurred, and whether it was renal, nonrenal, or both, and whether the flare was mild, moderate, or severe. Confirmation of the flare or no-flare status by independent review of the data by another study physician was required. Renal relapses were defined as previously reported [10, 11] as follows.

First, minor relapse, an increase in glomerular hematuria from <5 to >15 red blood cells/high-power field with at least two acanthocytes/high-power field, or recurrence of one or more red cell casts, leukocyte casts (in the absence of infection), or a combination of red cell/leukocyte casts.

Second, moderate relapse is an increase in serum creatinine, proteinuria, or both, attributable to the nephropathy of SLE. If baseline serum creatinine is <2.0 mg/dL, an increase in serum creatinine of 0.3 to 1.0 mg/dL. If baseline serum creatinine is ≥2.0, an increase in serum creatinine of 0.4 to 1.5 mg/dL. Proteinuria relapses were based on measurement of the protein/creatinine ratio of a 24-hour urine collection [12] as follows. If baseline protein/creatinine ratio is <0.5 an increase to ≥1.0. If baseline urine protein/creatinine ratio is 0.5 to 1.0, an increase to ≥2.0. If baseline urine protein/creatinine ratio is >1.0, a doubling of the urine protein/creatinine ratio but the absolute increase in protein/creatinine ratio is <5.0.

Third, major relapse is an increase in serum creatinine, urine protein/creatinine ratio, or both and attributable to the nephropathy of SLE, as follows. If baseline serum creatinine is <2.0 mg/dL, an increase in serum creatinine of >1.0 mg/dL. If baseline serum creatinine is ≥2.0 mg/dL, an increase in serum creatinine of >1.5 mg/dL. Finally, if there is an absolute increase of >5.0 in urine protein/creatinine ratio.

A nonrenal relapse was declared if the patient developed symptoms or signs of nonrenal SLE and they were of sufficient severity that the managing study physician increased therapy. The method for classifying severity of nonrenal relapses is as we have previously reported [10, 11] and as supplemented by the British Isle Lupus Assessment Group (BILAG) index, which ranked nonrenal SLE manifestations as categories A through C[13] as follows. Minor nonrenal relapse consists in one or more of the following and attributable to SLE: typical rash, symmetric mild to moderate arthralgias, fever, thrombocytopenia 50,000 to 100,000/mm^3, significant fatigue, oral ulcers, and mild to moderate hair loss. Moderate nonrenal