Published in final edited form as:

Semin Arthritis Rheum. 2008 August ; 38(1): 41–54. doi:10.1016/j.semarthrit.2007.09.005.

High-Sensitivity C-Reactive Protein as an Associate of Clinical Subsets and Organ Damage in Systemic Lupus Erythematosus

Shin-Seok Lee, MD, PhD^{*}, Sukhminder Singh, MD[†], Kimberly Link, ScM[‡], and Michelle Petri, MD, MPH[§]

^{*}Visiting Scholar, Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; Assistant Professor of Medicine and Chief, Department of Rheumatology, Chonnam National University Medical School, Gwangju, South Korea. [†]Researcher, Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland. [‡]Researcher, Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland. [§]Professor of Medicine, Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Abstract

Objective—C-reactive protein (CRP) may play an anti-inflammatory role during the acute phase of inflammation, and is also used as a marker of inflammation associated with cardiovascular disease. In the present study, we investigated the association between high-sensitivity CRP (hsCRP) and systemic lupus erythematosus (SLE) manifestations, autoantibodies, and organ damage.

Methods—In this cross-sectional study, 610 SLE patients from a prospective cohort had more than one hsCRP measurement. Organ damage was assessed using the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index. Multiple linear regression models were used to adjust for age, gender, ethnicity, disease duration, body mass index, education, disease activity, current prednisone dose, statin use, and estrogen use.

Results—After adjusting for confounders, hsCRP was associated with myocarditis, cardiac murmur, interstitial pulmonary fibrosis, pulmonary hypertension, gastrointestinal lupus manifestations, and anemia. Anti-dsDNA antibodies and lupus anticoagulant were associated with hsCRP in unadjusted models, and these associations remained significant after adjustment for confounders. hsCRP levels were significantly higher in patients with pulmonary, musculoskeletal, and endocrine damage, and a total SLICC Damage Index score ≥ 1 . After adjustment, hsCRP was associated with pulmonary, musculoskeletal, and total damage, but no longer with endocrine damage.

Conclusions—hsCRP is associated with a broad range of clinical features and organ damage in SLE, particularly in the pulmonary and musculoskeletal systems. This association holds true independent of sociodemographic, disease activity, and treatment factors, and may be useful to identify high-risk SLE patients who would benefit from additional screening and surveillance studies.

Address correspondence and reprint requests to Michelle Petri, MD, MPH, Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7500, Baltimore, MD 21205. Tel: (410) 955-3823; Fax: (410) 614-0498; E-mail: E-mail: mpetri@jhmi.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Cardiovascular risk factors; C-reactive protein; systemic lupus erythematosus; inflammation

INTRODUCTION

C-reactive protein (CRP) is a major acute-phase reactant produced in the liver in response to infection, inflammation, and trauma. Although CRP is widely used as a marker of inflammation in various rheumatologic diseases, the biological function of CRP remains uncertain, particularly because it exerts either pro- or anti-inflammatory action depending on the level and type of Fcγ receptor expressed on cells at the site of CRP interaction (1).

Although earlier studies have suggested that active systemic lupus erythematosus (SLE) patients do not have elevated CRP levels (2–4), recent studies using a sensitive method have revealed that most SLE patients have elevated CRP levels during the evolution of the disease process, irrespective of concomitant active infection (5,6). Similarly, earlier investigators found no association between CRP levels and the patterns of organ involvement in SLE (4, 7). However, investigators have recently described an association between CRP and musculoskeletal (8), pulmonary (9), and renal involvement in SLE (10). To our knowledge, no study has been published to date that assesses the relationship between high-sensitivity CRP (hsCRP) and organ damage that has occurred since the onset of SLE, i.e., resulting from either the disease process or its sequelae. In the present study, we investigated the role of hsCRP in SLE patients, in a well-organized prospective cohort, by assessing the relationships between hsCRP levels and clinical features, autoantibodies, and organ damage.

METHODS

Patients

As previously described (11), the Hopkins Lupus Cohort is a prospective cohort study of predictors of lupus flare, atherosclerosis, and health status in SLE. The study cohort includes all patients who have a clinical diagnosis of SLE and give informed consent to participate in the study. Subjects enrolled in the cohort are followed quarterly, or more frequently if clinically necessary. The clinical features, laboratory testing, and damage accrual data are recorded at the time of entry into the cohort and are updated at subsequent visits. The Hopkins Lupus Cohort has been approved by the Johns Hopkins University Institutional Review Board and complies with the Health Insurance Portability and Accountability Act.

In this cross-sectional study, we measured hsCRP levels in 610 serial SLE patients between January and December 2005, all of whom fulfilled 4 or more of the American College of Rheumatology (ACR) 1982 revised classification criteria for SLE (12). During this period, 830 patients in the Hopkins Lupus Cohort visited the clinic, but 220 patients were not enrolled in the study because of refusal to participate and/or enrollment in other studies. The patients enrolled in this study had shorter disease duration, were less often depressed, and more often had positive anticardiolipin antibodies compared to those not enrolled (data not shown). Otherwise, no significant differences were observed between the 2 groups in terms of other sociodemographic factors, clinical features, and organ damage (data not shown). Of the 610 patients enrolled in the study, 92% were women with a mean ($\pm$ SD) age of 44.6 ($\pm$ 13.1) years and a mean ($\pm$ SD) SLE disease duration of 9.76 ($\pm$ 7.46) years; 37% were African-American; 57%, Caucasian; 3%, Asian; 2%, Hispanic; and 1%, other ethnic groups.

Clinical features

The clinical features were cumulative manifestations from the onset of SLE until the first hsCRP measurement, which were updated regularly during the follow-up. The following clinical features were defined according to the ACR 1982 revised classification criteria for SLE (12): malar rash, discoid rash, photosensitivity, oral ulcer, arthritis, pleuritis, pericarditis, proteinuria, hemolytic anemia, leukopenia, lymphopenia, and thrombocytopenia.

Neuropsychiatric manifestations, which included seizure, psychosis, organic brain syndrome (acute confusional state), aseptic meningitis, stroke, depression, headache, mononeuritis multiplex, cognitive impairment, optic neuritis, cranial neuropathy, peripheral neuropathy, and transverse myelitis, were defined according to the ACR nomenclature and case definitions for neuropsychiatric lupus (13).

Other clinical manifestations were defined as follows: fever, temperature of $>38^{\circ}\text{C}$ or $>100.4^{\circ}\text{F}$ in the absence of suspected or proven infection; lymphadenopathy, enlarged nodes ($>0.5\text{ cm}$) of the cervical, axillary, or inguinal area in the absence of infection or malignancy; alopecia, increased hair loss due to SLE that is clearly visible to the physician; Raynaud's phenomenon, blanching of fingers and/or toes induced by exposure to cold, stress, or both with definite two-phase color change; subacute cutaneous LE, photosensitive, non-scarring dermatitis appearing in either papulosquamous or annular form; bullous LE, vesiculobullous lesions diagnosed by physical examination or skin biopsy; cutaneous vasculitis, urticarial lesions lasting more than 24 hours, palpable purpura, splinter hemorrhages of the tips of the fingers, toes, or cuticles of the nail folds, painful, tender erythematous indurated lesions on the palms and finger tips, or gangrene of the digits or extremities, as observed by the physician or reported by the patient; leg ulcer, painful sharply marginated ulcerative lesion in the pretibial area or ankle, as observed by the physician or reported by the patient; panniculitis, tender subcutaneous nodules diagnosed by physical examination or skin biopsy; livedo reticularis, reddish or cyanotic discoloration of the skin with a reticular pattern, as observed by the physician; arthralgia, symptoms of joint pain without signs of inflammation; erosions, erosive lesions documented on x-rays; myositis, muscle weakness accompanied by elevation of muscle enzymes and electromyographic and/or biopsy findings characteristic of myositis; myocarditis, inflammation of the myocardium for which viral, bacterial, and drug causes were excluded; Libman-Sacks endocarditis, valve vegetations detected by 2-dimensional echocardiography and negative blood culture; heart murmur, a murmur detected on physical examination, irrespective of characteristics, except if it is functional or limited to pregnancy; interstitial pulmonary fibrosis, diffuse interstitial infiltrates on chest x-ray with a restrictive pattern on pulmonary function studies or chest computed tomography (CT); pulmonary hypertension, mean pulmonary artery pressure $>25\text{ mmHg}$ at rest on right cardiac catheterization, or calculated pulmonary artery systolic pressure $>35\text{ mmHg}$ on Doppler echocardiography if right cardiac catheterization was not available; hepatomegaly, documented on physical examination or radiological imaging; abnormal liver function tests, >1.5 times the upper limit of normal for aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase, regardless of medications, and not counted if it occurred only during a known illness such as viral infection; splenomegaly, documented on physical examination or radiological imaging; gastrointestinal lupus, colitis, vasculitis, or serositis of the abdominal cavity, as documented by CT, colonoscopy, or arteriography; pancreatitis, confirmed by imaging and/or the presence of raised levels of lipase and/or amylase; nephrotic syndrome, nephrotic range proteinuria ($\geq 3\text{ g/day}$); hematuria, ≥ 5 red blood cells/high-power field and any urinary protein not caused by infection or menstrual causes; renal insufficiency, serum creatinine $\geq 1.5\text{ mg/dl}$ or $<75\%$ glomerular filtration rate due to SLE; renal failure, a state requiring dialysis or transplantation; anemia, hemoglobin concentration $<11.0\text{ gm/dl}$ in a woman and $<12.0\text{ gm/dl}$ in a man, or hematocrit of $<33\%$ in a woman and $<36\%$ in a man; dry eye, confirmed by abnormal Schirmer's test and not attributable to medications (e.g., antidepressants, diuretics); dry mouth, confirmed by

sialometry, salivary scintigraphy, or positive minor salivary gland biopsy; and Sjögren's syndrome, dry eyes confirmed by Schirmer's test or dry mouth confirmed by positive minor salivary gland biopsy, or dry eyes and mouth with the presence of anti-Ro and/or anti-La antibodies.

Organ Damage

Cumulative SLE damage was assessed by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index at the time of the first hsCRP measurement (14). The Damage Index includes 41 non-reversible items, encompassing 12 organ systems. The item must be present for at least 6 months, unless stated otherwise. Repeat lesions have to occur at least 6 months apart to obtain a score of 2. The standard definitions for each item, as outlined in the SLICC/ACR Damage Index glossary (14), were used in the present study.

Other covariates

Known or suspected predictors for changes in hsCRP level, such as age, gender, ethnicity, disease duration, body mass index (BMI), years of education, the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) version of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), current prednisone dose, and use of statins or oral estrogen, were included as potential confounders, and these variables were recorded at the time of the first hsCRP measurement.

Laboratory data

The level of hsCRP was measured by a latex-enhanced immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN) using the Roche/Hitachi Modular P analyzer. The range of detection for the hsCRP assay in this study was 0.1–20 mg/L. When the hsCRP concentration of the sample is above 20 mg/L, the Roche/Hitachi Modular P analyzer automatically reruns the assay and extends the measuring range up to 300 mg/L. In a study comparing the performance of nine hsCRP methods, samples with very high CRP concentrations were analyzed to test each method for susceptibility to falsely low results with very high CRP concentrations caused by a prozone effect (15). In that study, the Roche method used in our study showed no evidence of a prozone effect at CRP concentrations up to 480 mg/L. The intra-assay coefficient of variation (CV) was 0.3–1.3%, and the interassay CV was 2.5–5.7%.

Anti-dsDNA antibodies (anti-dsDNA) were measured at the time of hsCRP measurements, using a *Crithidia lucillae* assay. The tests for anti-Ro, anti-La, anti-Sm, and anti-RNP antibodies, as well as for IgG/IgM anti-cardiolipin antibodies (aCL), were performed as described in our previous studies (16,17). Lupus anticoagulant (LA) was assessed by the dilute Russell's viper venom time and confirmatory tests (18). The tests for these autoantibodies were performed at the first cohort visit, and in the case of aCL, tests were repeated during follow-up.

Statistical analysis

As the distribution of hsCRP was skewed rightward, median hsCRP values were reported with interquartile ranges (IQR). When we analyzed our data by dividing the patients into three groups according to hsCRP levels of less than 5, 5 to 10, and greater than 10 mg/L, there were similar trends, but weaker associations, of hsCRP levels with clinical features, autoantibodies, and organ damage compared to the continuous variable analyses of hsCRP. Thus, we chose to present the continuous variable data rather than the categorical data. The Mann–Whitney *U* test was used to compare the distribution of hsCRP levels with clinical features, laboratory tests, and the SLICC/ACR Damage Index. The association of the first hsCRP measurement with the second and third hsCRP measurements was evaluated by Spearman's correlation

coefficient. Linear regression analysis was used to test the association of hsCRP with clinical features, laboratory tests, and the SLICC/ACR Damage Index. Log-transformed hsCRP values were used as the dependent variable to improve its skewed distribution in the regression models. Three models were fitted. The first model was adjusted for sociodemographic factors, which included age, gender, ethnicity, disease duration, BMI, and education. The second model was adjusted for sociodemographic factors and disease activity, and the third model was adjusted for sociodemographic factors, disease activity, and treatment factors, including current prednisone dose, statin use, and estrogen use. All p values were two-tailed, and values less than 0.05 were considered as statistically significant. Data processing and statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL).

RESULTS

The baseline characteristics of patients with SLE are shown in Table 1. All 610 SLE patients had at least 1 hsCRP measurement; 253 patients had 2 measurements, and 43 patients had three measurements. The mean ($\pm$ SD) interval between the first and second measurements was 3.34 ($\pm$ 3.74) months, and the mean ($\pm$ SD) interval between the second and third measurements was 2.03 ($\pm$ 2.25) months. The correlation coefficients of the first hsCRP measurement with the second and third hsCRP measurements were 0.791 and 0.790, respectively ($p < 0.001$ for each comparison). The correlation coefficient for the second and third hsCRP measurements was 0.855 ($p < 0.001$). When there were 2 or more serial measurements, the average value was used to evaluate the associations between the hsCRP level and the variables according to a recommendation made by the Centers for Disease Control and Prevention and the American Heart Association (19). The median value of the averaged hsCRP levels was 2.12 mg/L (IQR, 0.90–6.20). When we performed the statistical analyses using both the first hsCRP value alone and the average hsCRP value, the results using the first hsCRP measures were not different from those using the average value (data not shown).

The comparison between the clinical features and hsCRP levels is presented in Table 2. The median hsCRP levels were significantly higher in patients with a history of fever ($p < 0.05$), discoid rash ($p < 0.05$), pericarditis ($p < 0.05$), myocarditis ($p < 0.05$), cardiac murmur ($p < 0.001$), pleuritis ($p < 0.05$), interstitial pulmonary fibrosis ($p < 0.01$), pulmonary hypertension ($p < 0.01$), gastrointestinal lupus manifestations ($p < 0.05$), seizure ($p < 0.05$), and anemia ($p < 0.01$) than in those without. Patients with a history of Raynaud's phenomenon ($p < 0.05$) and livedo reticularis ($p < 0.05$) had significantly lower hsCRP levels. The hsCRP levels were marginally higher in patients who had a history of alopecia ($p = 0.080$) and depression ($p = 0.095$) and were marginally lower in those who had a history of transverse myelitis ($p = 0.061$). Linear regression models were fitted with log-transformed hsCRP levels as the dependent variable and the 13 clinical features as the independent variables, which were chosen depending on the results of the above association studies (Table 3). In the univariate linear regression analysis, the log-transformed hsCRP levels were significantly associated with discoid rash, livedo reticularis, pericarditis, myocarditis, cardiac murmur, pleuritis, interstitial pulmonary fibrosis, pulmonary hypertension, gastrointestinal lupus manifestations, seizure, and anemia. After adjustment for age, gender, ethnicity, disease duration, BMI, and education (Model 1), the regression coefficients ranged from -7% to 80% , and the associations with myocarditis, cardiac murmur, pleuritis, interstitial pulmonary fibrosis, gastrointestinal lupus manifestations, and seizure remained statistically significant. When SELENA-SLEDAI was added to the first model (Model 2), the regression coefficients ranged from -9% to 91% , and there was a statistically significant association between log-transformed hsCRP and myocarditis, cardiac murmur, pleuritis, gastrointestinal lupus manifestations, and seizure, after adjustment. The log-transformed hsCRP was marginally associated with interstitial pulmonary fibrosis, pulmonary hypertension, and anemia. When treatment variables, which included current prednisone dose, estrogen use, and statin use, were added to the second model to give Model 3, the regression

coefficients ranged from –39% to 75%, and the associations with myocarditis, cardiac murmur, interstitial pulmonary fibrosis, pulmonary hypertension, gastrointestinal lupus manifestations, and anemia remained statistically significant. The log-transformed hsCRP levels were marginally associated with pleuritis and seizure.

The association of hsCRP levels with autoantibody status is shown in Table 4. Patients who were positive for anti-dsDNA at the time of the first hsCRP measurement had a significantly higher hsCRP level than those who were negative for anti-dsDNA ($p<0.001$). The hsCRP levels were significantly higher in patients with positive for LA ($p<0.001$). However, no differences were observed in the hsCRP levels in relation to a history of anti-Ro, anti-La, anti-Sm, anti-RNP, and IgG/IgM aCL. The hsCRP levels were significantly correlated with anti-dsDNA titers ($p=0.165$, $p<0.001$) and SELENA-SLEDAI scores ($p=0.148$, $p=0.001$). In an unadjusted regression analysis, the log-transformed hsCRP levels were significantly associated with anti-dsDNA antibodies, and there was no reduction in the regression coefficient after adjustment (Table 3). The association between the log-transformed hsCRP levels and LA was reduced by 28% after adjustment for sociodemographic factors, by 23% after disease activity was added to the first model, and by 26% after treatment factors were added to the second model, but the associations retained statistical significance.

Table 5 shows the association between the hsCRP levels and the SLICC/ACR Damage Index. The median hsCRP levels were significantly higher in patients with pulmonary ($p<0.01$), musculoskeletal ($p<0.01$), and endocrine (diabetes mellitus) ($p<0.01$) damage. Patients with a total damage score ≥ 1 had a significantly higher hsCRP levels ($p<0.001$). With regard to the pulmonary system, the hsCRP levels were significantly higher in patients with pulmonary fibrosis ($p<0.01$) and pleural fibrosis ($p<0.01$), and marginally higher in patients with pulmonary hypertension ($p=0.059$). With regard to the musculoskeletal system, the hsCRP levels were significantly higher in patients with muscle atrophy or weakness ($p<0.01$), deforming or erosive arthritis ($p<0.001$), and avascular necrosis ($p<0.05$). In addition, seizures that required therapy for 6 months ($p<0.05$) and end-stage renal disease ($p=0.05$) were significantly associated with higher hsCRP levels. Cerebrovascular accident ever or resection not for malignancy ($p=0.066$) and claudication ($p=0.084$) were marginally associated with higher hsCRP levels. However, no associations were noted between the hsCRP levels and the cardiovascular system. To investigate the relationship among the hsCRP level, LA, and cardiovascular and peripheral vascular damage, we compared the hsCRP levels with the damage in these organ systems only in LA-positive patients; no association was revealed between hsCRP levels and cardiovascular and peripheral vascular damage (data not shown).

In the unadjusted and adjusted models, the log-transformed hsCRP levels were significantly associated with the pulmonary, musculoskeletal, and total SLICC/ACR damage scores (Table 6). Although still statistically significant, the regression coefficients between the log-transformed hsCRP levels and the pulmonary, musculoskeletal, and total damage scores were reduced by 27% to 45% after adjustment for sociodemographic factors, by 27% to 45% after adjustment for sociodemographic factors and disease activity, and by 26% to 36% after adjustment for sociodemographic, disease activity, and treatment factors. The regression coefficient between the log-transformed hsCRP level and the endocrine damage score decreased by 61% after adjustment for sociodemographic factors, and the association was no longer statistically significant; this lack of statistical significance persisted after further adjustment for disease activity and treatment factors. In the pulmonary system, the log-transformed hsCRP levels were significantly associated with pulmonary fibrosis and pleural fibrosis after adjustment for sociodemographic, disease activity, and treatment factors, with a reduction of ~20% in the regression coefficient. However, the association between the log-transformed hsCRP levels and pulmonary hypertension was no longer significant after adjustment for sociodemographic factors, and this lack of statistical significance persisted after

further adjustment for disease activity and treatment factors. In the musculoskeletal system, the log-transformed hsCRP levels were consistently associated with deforming or erosive arthritis after adjusting for confounders, whereas muscle atrophy or weakness and avascular necrosis were no longer associated with the log-transformed hsCRP levels after adjustment. In addition, seizure was significantly associated with the log-transformed hsCRP levels in the unadjusted and adjusted models. Cerebrovascular accident and end-stage renal failure were marginally associated with the log-transformed hsCRP levels in the unadjusted and adjusted models.

DISCUSSION

In this study, we found that the hsCRP levels in a group of SLE patients were associated with a broad range of clinical features such as myocarditis, cardiac murmur, interstitial pulmonary fibrosis, pulmonary hypertension, gastrointestinal lupus manifestations, and anemia. The hsCRP levels were associated with both anti-dsDNA and LA. We showed a linear association of the hsCRP levels with pulmonary, musculoskeletal, and total damage scores in terms of organ damage. These findings are meaningful, as we have adjusted for the effects of confounders through detailed statistical analyses. Marked differences in the hsCRP levels have been reported among various ethnic groups and between men and women (20,21), and BMI has been associated with elevated CRP levels (22). Medication such as statins may reduce the hsCRP levels independent of their effect on the low-density lipoprotein cholesterol level (23). The use of oral contraceptives and hormone replacement therapy is associated with higher hsCRP levels (24,25). In SLE, the hsCRP levels are potentially influenced by both disease activity and corticosteroid use (2,26). Therefore, we considered the above-mentioned confounders in linear regression models. Additional strengths of the present study lie in the inclusion of a well-organized prospective lupus cohort, the enrollment of a large number of patients, and the use of a high-sensitivity assay for CRP.

Initially, we found a strong association between the hsCRP levels and pulmonary involvement in SLE patients. Of the pulmonary manifestations, interstitial pulmonary fibrosis and pulmonary hypertension were significantly associated with the hsCRP levels, and there was a marginal association between the hsCRP levels and pleuritis. In the pulmonary component of the SLICC/ACR Damage Index, pulmonary fibrosis and pleural fibrosis were significantly associated with the hsCRP levels. The association between CRP and pleural involvement has been well-defined in several prospective follow-up studies of SLE patients (27–29). In these studies, the median CRP levels were reported to be higher during exacerbations with pleuritis than during exacerbations without pleuritis. A study of 23 SLE patients with various pulmonary involvements showed that the CRP level was elevated at the time of pleuritis, and that the elevation was greater in patients with pleuritis than in patients with interstitial lung disease (9). These findings are in accordance with our results describing an association between hsCRP levels and pleural involvement. Although the large inflammatory cell mass and vasculitic components of the pleural lesion have been put forward to explain this association, the evidence to support this assumption is circumstantial.

The association of hsCRP with interstitial lung disease and pulmonary hypertension in SLE in the present study is noteworthy. In both interstitial lung disease and pulmonary hypertension, chronic inflammation is known to play a role in the disease development and progression. In animal studies, the overexpression of proinflammatory cytokines, such as tumor necrosis factor (TNF)- α and interleukin (IL)-1 β , in the lower respiratory tract lead to acute/subacute and chronic inflammation, and chronic inflammation with repeated or persistent episodes of injury evolve into pulmonary fibrosis (30,31). Similarly, in the monocrotaline-induced pulmonary hypertension model, TNF- α , IL-1, and IL-6 produced by alveolar macrophages were involved in the development of pulmonary hypertension (32). In the same model, chronic treatment with

a human IL-1 receptor antagonist inhibited the development of pulmonary hypertension (33). Interestingly, in human aortic endothelial cells, CRP reduced endothelial nitric oxide synthase expression and bioactivity (34), and in saphenous vein endothelial cells, CRP increased endothelin-1 release (35), which suggests that CRP contributes to endothelial dysfunction and may promote vascular remodeling and increased vascular resistance. Clinically, CRP levels are elevated in patients with idiopathic pulmonary fibrosis (36) and acute exacerbation of idiopathic pulmonary fibrosis (37). In addition, elevated CRP has been identified as a predictor of pulmonary hypertension in patients with chronic obstructive pulmonary disease (38) and Gaucher's disease (39), suggesting a role for CRP in the development of pulmonary hypertension in these patients. Extrapolating these findings to SLE patients, the association of hsCRP with interstitial lung disease and pulmonary hypertension in our patients appears to be substantiated. However, further studies are needed to clarify the causal relationship between CRP and the development or progression of interstitial lung disease and pulmonary hypertension in SLE patients.

We found no association between hsCRP and arthralgia or arthritis in the musculoskeletal manifestations; however, hsCRP was significantly associated with deforming or erosive arthritis in musculoskeletal damage. Spronk *et al.* (8) observed elevated CRP levels in SLE patients with Jaccoud's arthropathy, as compared to SLE patients without Jaccoud's arthropathy, even during periods of no clinical disease activity. They hypothesized that patients with both SLE and Jaccoud's arthropathy may have persistent inflammation of the joints and surrounding tissues, resulting in the production of proinflammatory cytokines, including IL-6, which stimulate the production of CRP in the liver. In this context, it is assumed that the CRP responses of SLE patients who have arthralgia or transient arthritis may be different from those of patients with deforming or erosive arthritis. Therefore, the lack of an association between hsCRP and arthralgia/arthritis in musculoskeletal manifestations in the present study can be attributed to differences in the chronicity and severity of the inflammatory reaction.

With regard to cardiac manifestations, we showed that an elevated hsCRP level was associated with cardiac murmurs and myocarditis in the unadjusted and adjusted linear regression models. We also showed an association between the hsCRP level and pericarditis in the unadjusted model. However, the inclusion of disease activity and treatment factors resulted in the greatest reduction of the regression coefficient for pericarditis, and the hsCRP level was no longer associated with pericarditis after adjustment. Although we do not specify the causes of cardiac murmur in this study, structural valvular diseases, most often mitral regurgitation, are the most frequent cause of murmur in SLE patients (40,41). Other causes of cardiac murmur in these patients, albeit unusual, are Libman-Sacks endocarditis, infective endocarditis, mitral valve prolapse, and myocarditis (42). Regardless of the source of cardiac murmur, inflammation is presumed to play a pivotal role in the pathogenesis of cardiac involvement in SLE (43). In a study of lupus-prone MRL-lpr/lpr mice (44), ventricular homogenates and cardiomyocytes constitutively overexpressed genes that encode the proinflammatory cytokines IL-1 β , IL-6, IL-10, and interferon- γ , which suggests the possibility that proinflammatory cytokines emanating from the heart may contribute to high serum levels of CRP. Histopathological studies of pericarditis, myocarditis, and endocarditis in SLE patients have shown that active or previous inflammation is far more frequent than clinical evidence of these diseases and that immune complex components can be found throughout the tissues, even in areas where histology is normal by light microscopy (45). In several studies, patients with pericarditis, myocarditis, and endocarditis have been reported to have elevated CRP levels (46,47). Considering cardiac murmur as a sign of cardiac involvement in SLE, the association of hsCRP with cardiac murmur in the current study is plausible. Our findings also confirm previous observations that describe an association between CRP and cardiac involvement in SLE. However, the lack of association between hsCRP and Libman-Sacks endocarditis in this study should be noted. Recently, with the use of corticosteroids to treat many aspects of SLE, fewer

cases of Libman–Sacks endocarditis have been detected (48). In the present study, we identified only five cases of Libman–Sacks endocarditis in our 610 SLE patients, raising the possibility of type II error.

The finding in our lupus cohort that the hsCRP levels are associated with seizures, particularly seizures requiring therapy for more than 6 months, is noteworthy. A considerable body of experimental and clinical evidence suggests that IL-1 β , IL-6, and TNF- α are induced by seizure activity and that these cytokines contribute to the formation of structural changes, such as neuronal damage and gliosis, after sustained seizure activity (49–51). Interestingly, in patients with recent generalized tonic-clonic seizures, the IL-6 level was selectively elevated in cerebrospinal fluid (CSF) and plasma without any change in IL-1 β and TNF- α levels (52), and the elevated plasma IL-6 level was correlated with peripheral blood leukocyte counts and CRP (53). Several studies have shown that the IL-6 level in the CSF is elevated in neuropsychiatric SLE (NPSLE) patients (54–56). Increased levels of other cytokines, including IL-1, IL-8, and interferon- γ , have also been reported in the CSF of SLE patients with central nervous system involvement (57). Furthermore, in NPSLE patients, these cytokines, particularly IL-6, were shown to lead to neuronal destruction, which was manifested as increased levels of neuronal and astrocytic degradation products (58). Trysberg *et al.* (59) have compared the changes in the CSF and serum IL-6 levels in NPSLE patients before and after treatment with immunosuppressive drugs. Interestingly, the treatment significantly decreased the CSF IL-6 level, whereas the serum IL-6 level in the same patients was not significantly decreased. Therefore, it can be postulated that a persistently elevated serum IL-6 level induces CRP elevation in NPSLE patients. Combining the results for the seizure patients and NPSLE patients, it appears that hsCRP is associated with seizures in SLE patients.

We found an association between hsCRP and colitis, vasculitis, and serositis as gastrointestinal manifestations. As colitis, vasculitis, and serositis were uncommon in our lupus cohort, we combined these clinical features into one group to analyze the association between the hsCRP level and clinical presentation of gastrointestinal lupus. Although studies regarding gastrointestinal lupus have not directly addressed the association between CRP and colitis, vasculitis, and serositis, there is a small case series that describe these associations (60). Given the inflammatory nature of these conditions, an association of hsCRP with colitis, vasculitis, and serositis, among many gastrointestinal manifestations, might be expected.

The link between inflammation and anemia has long been known. However, until recently, little was known about the pathogenesis of anemia of inflammation, also known as anemia of chronic disease. The discovery of hepcidin, which is now considered as a central regulator of iron metabolism, made it possible to explain the mechanism of anemia of inflammation (61). Like CRP, hepcidin is produced in hepatocytes by proinflammatory cytokines, particularly IL-6 (62). Increased hepcidin expression inhibits intestinal iron absorption, placental iron transport, and release of recycled iron from macrophages, effectively decreasing the delivery of iron to maturing erythrocytes in the bone marrow (63,64). Thus, persistent stimulation of the IL-6 and hepcidin axis by chronic inflammatory disorders is responsible for the resulting anemia commonly seen in these conditions. In the current study, we found that hsCRP was associated with anemia but not with hemolytic anemia. Given that IL-6 stimulates the production of CRP in the liver, it seems logical to predict an association of CRP with anemia of inflammation.

We showed that the hsCRP level was marginally associated with end-stage renal disease in renal damage. Similar findings have been reported by Williams *et al.* (5) They reported that the serum CRP level tended to be higher in SLE patients with renal failure than in those with active or inactive nephritis, although this association was not statistically significant. Clinical support for this association is provided by the observation that an elevated CRP level is

relatively common in patients with chronic renal failure before and after dialysis (65,66). Further support for this linkage is found in the observation that CRP is deposited in the glomeruli of kidney biopsy specimens from patients with lupus nephritis, and CRP may amplify kidney damage by binding to Fcγ receptor IIa-R131, which has low affinity for IgG2 but high affinity for CRP (10). Arguably, the serum hsCRP levels are elevated in patients with lupus nephritis, particularly in those with end-stage renal disease and decreased renal clearance of CRP and/or proinflammatory cytokines may play a role in the elevation of serum CRP.

The most striking finding in this study is that hsCRP was independently associated with total SLICC/ACR damage. The prevalence of damage in at least one organ system was 63% in our SLE patients, after a mean follow-up of 9.8 years. As several studies have shown that accrued damage in SLE is predicted by disease activity over the follow-up period (67,68), the association between hsCRP and organ damage is explained by the finding that hsCRP reflects lupus activity. In the current study, we have shown that hsCRP is associated with anti-dsDNA antibodies, SELENA-SLEDAI scores, and a broad range of clinical manifestations, many of which are components of disease activity measures. Therefore, we believe that lupus activity occurring over a decade of disease processes also mediates the association of hsCRP with organ damage.

Sailer *et al.* (69) found that the hsCRP level was significantly higher in patients with LA, with or without thrombosis, compared with controls. Using linear regression analysis, the presence of LA was significantly associated with hsCRP after adjusting for confounding factors in that study. The hsCRP level did not differ between LA-positive patients with or without thrombosis and was not associated with thrombosis in multivariate logistic regression analyses. The same findings were reproduced in the present study. We found a significantly higher hsCRP level in patients with LA than in those without LA and a significant association between hsCRP and LA in unadjusted and adjusted regression models. Similarly, the hsCRP level was not associated with angina or myocardial infarction in terms of cardiovascular damage, or with venous thrombosis in terms of peripheral vascular damage, both in the total number of SLE patients and in LA-positive patients. It is thus hypothesized that, although an inflammatory state might be associated with LA, this state is not sufficient to cause the development of cardiovascular events in LA-positive patients. A prospective study is needed to elucidate the role of inflammation in cardiovascular events in LA-positive patients.

This study has several limitations. Owing to its cross-sectional design, this study does not allow causal relationships to be inferred. We were unable to measure the hsCRP level at the time of occurrence of clinical features and organ damage in our patient cohort, which may have caused bias in accurately determining the inflammatory state. As an acute phase reactant, hsCRP increases with acute infection or trauma. Although patients with manifest infections were excluded from this study, it is always possible that occult infection or trauma contributed to cause an elevation of the hsCRP level.

In conclusion, hsCRP is associated with damage to various organs, particularly those of the pulmonary and musculoskeletal systems, in SLE patients. These findings highlight hsCRP as a strong marker for increased disease activity and organ damage accrued over the course of SLE. Serial measurement, in addition, may be useful for assessing disease activity and damage in the individual patient of SLE who have an elevated hsCRP level during the course of the disease.

ACKNOWLEDGEMENT

We are indebted to Daniel Goldman, PhD for assisting with analyzing the data from the cohort database.

This study was supported by the Hopkins Lupus Cohort AR43727 and the General Clinical Research Center MO1-RR-00052

REFERENCES

1. Marnell L, Mold C, Du Clos TW. C-reactive protein: ligands, receptors and role in inflammation. *Clin Immunol* 2005;117:104–111. [PubMed: 16214080]
2. Pereira Da Silva JA, Elkon KB, Hughes GR, Dyck RF, Pepys MB. C-reactive protein levels in systemic lupus erythematosus: a classification criterion? *Arthritis Rheum* 1980;23:770–771. [PubMed: 7387742]
3. Becker GJ, Waldburger M, Hughes GR, Pepys MB. Value of serum C-reactive protein measurement in the investigation of fever in systemic lupus erythematosus. *Ann Rheum Dis* 1980;39:50–52. [PubMed: 7377859]
4. Honig S, Gorevic P, Weissmann G. C-reactive protein in systemic lupus erythematosus. *Arthritis Rheum* 1977;20:1065–1070. [PubMed: 869953]
5. Williams RC Jr, Harmon ME, Burlingame R, Du Clos TW. Studies of serum C-reactive protein in systemic lupus erythematosus. *J Rheumatol* 2005;32:454–461. [PubMed: 15742436]
6. al-Mekaimi A, Malaviya AN, Serebour F, Umamaheswaran I, Kumar R, al-Saeid K, et al. Serological characteristics of systemic lupus erythematosus from a hospital-based rheumatology clinic in Kuwait. *Lupus* 1997;6:668–674. [PubMed: 9364426]
7. Morrow WJ, Isenberg DA, Parry HF, Snaith ML. C-reactive protein in sera from patients with systemic lupus erythematosus. *J Rheumatol* 1981;8:599–604. [PubMed: 7299761]
8. Spronk PE, ter Borg EJ, Kallenberg CG. Patients with systemic lupus erythematosus and Jaccoud's arthropathy: a clinical subset with an increased C reactive protein response? *Ann Rheum Dis* 1992;51:358–361. [PubMed: 1575582]
9. Mochizuki T, Aotsuka S, Satoh T. Clinical and laboratory features of lupus patients with complicating pulmonary disease. *Respir Med* 1999;93:95–101. [PubMed: 10464859]
10. Zuniga R, Markowitz GS, Arkachaisri T, Imperatore EA, D'Agati VD, Salmon JE. Identification of IgG subclasses and C-reactive protein in lupus nephritis: the relationship between the composition of immune deposits and FCgamma receptor type IIA alleles. *Arthritis Rheum* 2003;48:460–470. [PubMed: 12571856]
11. Petri M. Hopkins Lupus Cohort. 1999 update. *Rheum Dis Clin North Am* 2000;26:199–213. [PubMed: 10768209]v.
12. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25:1271–1277. [PubMed: 7138600]
13. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42:599–608. [PubMed: 10211873]
14. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996;39:363–369. [PubMed: 8607884]
15. Roberts WL, Moulton L, Law TC, Farrow G, Cooper-Anderson M, Savory J, et al. Evaluation of nine automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Part 2. *Clin Chem* 2001;47:418–425. [PubMed: 11238291]
16. To CH, Petri M. Is antibody clustering predictive of clinical subsets and damage in systemic lupus erythematosus? *Arthritis Rheum* 2005;52:4003–4010. [PubMed: 16320348]
17. Petri M, Rheinschmidt M, Whiting-O'Keefe Q, Hellmann D, Corash L. The frequency of lupus anticoagulant in systemic lupus erythematosus. A study of sixty consecutive patients by activated partial thromboplastin time, Russell viper venom time, and anticardiolipin antibody level. *Ann Intern Med* 1987;106:524–531. [PubMed: 3103510]
18. Brandt JT, Barna LK, Triplett DA. Laboratory identification of lupus anticoagulants: results of the Second International Workshop for Identification of Lupus Anticoagulants. On behalf of the

Subcommittee on Lupus Anticoagulants/Antiphospholipid Antibodies of the ISTH. *Thromb Haemost* 1995;74:1597–1603. [PubMed: 8772243]

19. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511. [PubMed: 12551878]
20. Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, et al. Race and gender differences in C-reactive protein levels. *J Am Coll Cardiol* 2005;46:464–469. [PubMed: 16053959]
21. Albert MA, Glynn RJ, Buring J, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). *Am J Cardiol* 2004;93:1238–1242. [PubMed: 15135696]
22. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *Jama* 1999;282:2131–2135. [PubMed: 10591334]
23. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20–28. [PubMed: 15635109]
24. van Rooijen M, Hansson LO, Frostegard J, Silveira A, Hamsten A, Bremme K. Treatment with combined oral contraceptives induces a rise in serum C-reactive protein in the absence of a general inflammatory response. *J Thromb Haemost* 2006;4:77–82. [PubMed: 16409455]
25. Cushman M, Legault C, Barrett-Connor E, Stefanick ML, Kessler C, Judd HL, et al. Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study. *Circulation* 1999;100:717–722. [PubMed: 10449693]
26. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000;43:1801–1808. [PubMed: 10943870]
27. ter Borg EJ, Horst G, Limburg PC, van Rijswijk MH, Kallenberg CG. C-reactive protein levels during disease exacerbations and infections in systemic lupus erythematosus: a prospective longitudinal study. *J Rheumatol* 1990;17:1642–1648. [PubMed: 2084238]
28. Jonsson H, Nived O, Sturfelt G. Outcome in systemic lupus erythematosus: a prospective study of patients from a defined population. *Medicine (Baltimore)* 1989;68:141–150. [PubMed: 2785628]
29. Sturfelt G, Sjöholm AG. Complement components, complement activation, and acute phase response in systemic lupus erythematosus. *Int Arch Allergy Appl Immunol* 1984;75:75–83. [PubMed: 6086533]
30. Kolb M, Margetts PJ, Anthony DC, Pitossi F, Gauldie J. Transient expression of IL-1 β induces acute lung injury and chronic repair leading to pulmonary fibrosis. *J Clin Invest* 2001;107:1529–1536. [PubMed: 11413160]
31. Sime PJ, Marr RA, Gauldie D, Xing Z, Hewlett BR, Graham FL, et al. Transfer of tumor necrosis factor- α to rat lung induces severe pulmonary inflammation and patchy interstitial fibrogenesis with induction of transforming growth factor- β 1 and myofibroblasts. *Am J Pathol* 1998;153:825–832. [PubMed: 9736031]
32. Miyata M, Sakuma F, Yoshimura A, Ishikawa H, Nishimaki T, Kasukawa R. Pulmonary hypertension in rats. I. Role of bromodeoxyuridine-positive mononuclear cells and alveolar macrophages. *Int Arch Allergy Immunol* 1995;108:281–286. [PubMed: 7580294]
33. Voelkel NF, Tuder RM, Bridges J, Arend WP. Interleukin-1 receptor antagonist treatment reduces pulmonary hypertension generated in rats by monocrotaline. *Am J Respir Cell Mol Biol* 1994;11:664–675. [PubMed: 7946395]
34. Venugopal SK, Devaraj S, Yuhanna I, Shaul P, Jialal I. Demonstration that C-reactive protein decreases eNOS expression and bioactivity in human aortic endothelial cells. *Circulation* 2002;106:1439–1441. [PubMed: 12234944]
35. Verma S, Li SH, Badiwala MV, Weisel RD, Fedak PW, Li RK, et al. Endothelin antagonism and interleukin-6 inhibition attenuate the proatherogenic effects of C-reactive protein. *Circulation* 2002;105:1890–1896. [PubMed: 11997273]
36. Magro CM, Waldman WJ, Knight DA, Allen JN, Nadasdy T, Frambach GE, et al. Idiopathic pulmonary fibrosis related to endothelial injury and antiendothelial cell antibodies. *Hum Immunol* 2006;67:284–297. [PubMed: 16720208]

37. Kondoh Y, Taniguchi H, Kawabata Y, Yokoi T, Suzuki K, Takagi K. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. *Chest* 1993;103:1808–1812. [PubMed: 8404104]
38. Joppa P, Petrasova D, Stancak B, Tkacova R. Systemic inflammation in patients with COPD and pulmonary hypertension. *Chest* 2006;130:326–333. [PubMed: 16899829]
39. Elstein D, Nir A, Klutstein M, Rudensky B, Zimran A. C-reactive protein and NT-proBNP as surrogate markers for pulmonary hypertension in Gaucher disease. *Blood Cells Mol Dis* 2005;34:201–205. [PubMed: 15885602]
40. Roldan CA, Shively BK, Crawford MH. An echocardiographic study of valvular heart disease associated with systemic lupus erythematosus. *N Engl J Med* 1996;335:1424–1430. [PubMed: 8875919]
41. Galve E, Candell-Riera J, Pigrau C, Permanyer-Miralda G, Garcia-Del-Castillo H, Soler-Soler J. Prevalence, morphologic types, and evolution of cardiac valvular disease in systemic lupus erythematosus. *N Engl J Med* 1988;319:817–823. [PubMed: 3412413]
42. Doria A, Iaccarino L, Sarzi-Puttini P, Atzeni F, Turriel M, Petri M. Cardiac involvement in systemic lupus erythematosus. *Lupus* 2005;14:683–686. [PubMed: 16218467]
43. Kao AH, Sabatine JM, Manzi S. Update on vascular disease in systemic lupus erythematosus. *Curr Opin Rheumatol* 2003;15:519–527. [PubMed: 12960475]
44. Tomita M, Dragoman M, Worcester H, Conran P, Santoro TJ. Proinflammatory cytokine genes are constitutively overexpressed in the heart in experimental systemic lupus erythematosus: a brief communication. *Exp Biol Med (Maywood)* 2004;229:971–976. [PubMed: 15388894]
45. Mandell BF. Cardiovascular involvement in systemic lupus erythematosus. *Semin Arthritis Rheum* 1987;17:126–141. [PubMed: 3334284]
46. Weich HS, Burgess LJ, Reuter H, Brice EA, Doubell AF. Large pericardial effusions due to systemic lupus erythematosus: a report of eight cases. *Lupus* 2005;14:450–457. [PubMed: 16038109]
47. Kaneko K, Kanda T, Hasegawa A, Suzuki T, Kobayashi I, Nagai R. C-reactive protein as a prognostic marker in lymphocytic myocarditis. *Jpn Heart J* 2000;41:41–47. [PubMed: 10807528]
48. Maksimowicz-McKinnon K, Mandell BF. Understanding valvular heart disease in patients with systemic autoimmune diseases. *Cleve Clin J Med* 2004;71:881–885. [PubMed: 15570736]
49. Sallmann S, Juttler E, Prinz S, Petersen N, Knopf U, Weiser T, et al. Induction of interleukin-6 by depolarization of neurons. *J Neurosci* 2000;20:8637–8642. [PubMed: 11102468]
50. Jankowsky JL, Derrick BE, Patterson PH. Cytokine responses to LTP induction in the rat hippocampus: a comparison of in vitro and in vivo techniques. *Learn Mem* 2000;7:400–412. [PubMed: 11112799]
51. Vezzani A, Conti M, De Luigi A, Ravizza T, Moneta D, Marchesi F, et al. Interleukin-1beta immunoreactivity and microglia are enhanced in the rat hippocampus by focal kainate application: functional evidence for enhancement of electrographic seizures. *J Neurosci* 1999;19:5054–5065. [PubMed: 10366638]
52. Peltola J, Hurme M, Miettinen A, Keranen T. Elevated levels of interleukin-6 may occur in cerebrospinal fluid from patients with recent epileptic seizures. *Epilepsy Res* 1998;31:129–133. [PubMed: 9714504]
53. Peltola J, Laaksonen J, Haapala AM, Hurme M, Rainesalo S, Keranen T. Indicators of inflammation after recent tonic-clonic epileptic seizures correlate with plasma interleukin-6 levels. *Seizure* 2002;11:44–46. [PubMed: 11888259]
54. Tsai CY, Wu TH, Tsai ST, Chen KH, Thajeb P, Lin WM, et al. Cerebrospinal fluid interleukin-6, prostaglandin E2 and autoantibodies in patients with neuropsychiatric systemic lupus erythematosus and central nervous system infections. *Scand J Rheumatol* 1994;23:57–63. [PubMed: 8165438]
55. Hirohata S, Tanimoto K, Ito K. Elevation of cerebrospinal fluid interleukin-6 activity in patients with vasculitides and central nervous system involvement. *Clin Immunol Immunopathol* 1993;66:225–229. [PubMed: 8432047]
56. Alcocer-Varela J, Aleman-Hoey D, Alarcon-Segovia D. Interleukin-1 and interleukin-6 activities are increased in the cerebrospinal fluid of patients with CNS lupus erythematosus and correlate with local late T-cell activation markers. *Lupus* 1992;1:111–117. [PubMed: 1301962]

57. Svenungsson E, Andersson M, Brundin L, van Vollenhoven R, Khademi M, Tarkowski A, et al. Increased levels of proinflammatory cytokines and nitric oxide metabolites in neuropsychiatric lupus erythematosus. *Ann Rheum Dis* 2001;60:372–379. [PubMed: 11247868]
58. Trysberg E, Nylen K, Rosengren LE, Tarkowski A. Neuronal and astrocytic damage in systemic lupus erythematosus patients with central nervous system involvement. *Arthritis Rheum* 2003;48:2881–2887. [PubMed: 14558094]
59. Trysberg E, Carlsten H, Tarkowski A. Intrathecal cytokines in systemic lupus erythematosus with central nervous system involvement. *Lupus* 2000;9:498–503. [PubMed: 11035414]
60. Houtman PM, Hofstra SS. Lupus peritonitis presented as vague abdominal complaints in a SLE patient. *Neth J Med* 1992;40:232–235. [PubMed: 1436259]
61. Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. *J Biol Chem* 2001;276:7806–7810. [PubMed: 11113131]
62. Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. *Blood* 2003;101:2461–2463. [PubMed: 12433676]
63. Nicolas G, Bennoun M, Porteu A, Mativet S, Beaumont C, Grandchamp B, et al. Severe iron deficiency anemia in transgenic mice expressing liver hepcidin. *Proc Natl Acad Sci U S A* 2002;99:4596–4601. [PubMed: 11930010]
64. Nicolas G, Bennoun M, Devaux I, Beaumont C, Grandchamp B, Kahn A, et al. Lack of hepcidin gene expression and severe tissue iron overload in upstream stimulatory factor 2 (USF2) knockout mice. *Proc Natl Acad Sci U S A* 2001;98:8780–8785. [PubMed: 11447267]
65. Ortega O, Rodriguez I, Gallar P, Carreno A, Ortiz M, Espejo B, et al. Significance of high C-reactive protein levels in pre-dialysis patients. *Nephrol Dial Transplant* 2002;17:1105–1109. [PubMed: 12032204]
66. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 1999;55:648–658. [PubMed: 9987089]
67. Becker-Merok A, Nossent HC. Damage accumulation in systemic lupus erythematosus and its relation to disease activity and mortality. *J Rheumatol* 2006;33:1570–1577. [PubMed: 16845708]
68. Stoll T, Sutcliffe N, Mach J, Klaghofer R, Isenberg DA. Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus--a 5-yr prospective study. *Rheumatology (Oxford)* 2004;43:1039–1044. [PubMed: 15161983]
69. Sailer T, Vormittag R, Pabinger I, Vukovich T, Lehr S, Quehenberger P, et al. Inflammation in patients with lupus anticoagulant and implications for thrombosis. *J Rheumatol* 2005;32:462–468. [PubMed: 15742437]

Table 1

Baseline characteristics of the 610 patients with systemic lupus erythematosus*

Variables	Total
Age (years)	44.6 ± 13.1
Women (%)	563/610 (92)
Ethnicity (%)	
Caucasian	346/610 (57)
African-American	223/610 (37)
Asian	18/610 (3)
Hispanic	15/610 (3)
Others	8/610 (1)
Body mass index (kg/m ²)	28.4 ± 7.4
Education (years)	14.1 ± 2.8
Disease duration of SLE (years)	9.76 ± 7.5
SELENA-SLEDAI [†]	2.36 ± 3.0
Current prednisone dose (mg)	4.75 ± 9.0
Statin use (%)	67/600 (11)
Estrogen use (%)	19/556 (5)

* Except where indicated otherwise, values are the mean ± SD.

[†] SELENA-SLEDAI denotes Safety of Estrogen in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index.

Table 2
Differences between hsCRP level and clinical features

Clinical features	Number (%) [*]	Presence ^{**}	Absence ^{**}	P value [†]
Systemic				
Fever	217/610 (36)	2.50 (1.23, 6.33)	2.00 (0.80, 6.00)	0.048
Lymphadenopathy	169/608 (28)	2.00 (0.83, 7.25)	2.20 (0.90, 6.00)	NS
Skin				
Malar rash	311/610 (51)	2.13 (0.95, 6.00)	2.10 (0.90, 6.30)	NS
Discoid rash	117/610 (19)	2.50 (1.20, 7.70)	2.00 (0.85, 5.74)	0.017
Photosensitivity	329/609 (54)	2.10 (0.90, 5.70)	2.20 (0.90, 6.30)	NS
Mouth ulcers	330/610 (54)	2.00 (0.96, 5.13)	2.35 (0.80, 7.05)	NS
Alopecia	317/610 (52)	2.40 (1.00, 6.24)	1.90 (0.80, 6.10)	0.08
Raynaud phenomenon	298/609 (49)	1.90 (0.80, 4.90)	2.40 (1.00, 6.90)	0.032
Subacute cutaneous LE	38/610 (6)	1.82 (1.00, 7.80)	2.20 (0.90, 6.18)	NS
Bullous LE	5/603 (1)	2.74 (1.38, 6.28)	2.10 (0.90, 6.00)	NS
Vasculitis	80/610 (13)	2.05 (1.20, 5.21)	2.18 (0.85, 6.28)	NS
Leg ulcer	9/610 (2)	2.20 (1.15, 4.12)	2.10 (0.90, 6.20)	NS
Panniculitis	23/610 (4)	2.95 (1.30, 9.50)	2.10 (0.90, 6.10)	NS
Livedo reticularis	147/609 (24)	1.75 (0.90, 3.40)	2.30 (0.90, 6.53)	0.019
Musculoskeletal				
Arthralgia	570/610 (93)	2.20 (0.90, 6.28)	1.58 (0.75, 3.16)	NS
Arthritis	460/610 (75)	2.26 (0.90, 6.59)	1.98 (0.90, 4.25)	NS
Erosions	7/511 (1)	1.85 (1.75, 23.40)	2.14 (0.90, 6.10)	NS
Myositis	31/609 (5)	3.40 (1.30, 7.04)	2.10 (0.90, 6.13)	NS
Cardiovascular				
Pericarditis	139/609 (23)	2.74 (1.20, 8.75)	2.00 (0.85, 5.53)	0.02
Myocarditis	12/610 (2)	4.55 (2.41, 22.53)	2.10 (0.90, 6.03)	0.02
Libman-Sacks endocarditis	5/609 (1)	3.40 (1.08, 11.00)	2.12 (0.90, 6.20)	NS
Murmur	297/610 (49)	2.74 (1.20, 7.68)	1.70 (0.73, 4.80)	<0.001
Pulmonary				
Pleuritis	267/609 (44)	2.40 (1.00, 7.50)	2.00 (0.80, 5.71)	0.037
Interstitial pulmonary fibrosis	50/610 (8)	2.85 (1.70, 11.29)	2.05 (0.90, 5.94)	0.009
Pulmonary hypertension	51/607 (8)	3.00 (1.60, 11.20)	2.00 (0.85, 5.75)	0.004
Gastrointestinal				
Hepatomegaly	18/609 (3)	3.15 (1.18, 11.49)	2.10 (0.90, 6.00)	NS
Abnormal liver function tests	205/609 (34)	2.40 (1.03, 6.60)	2.00 (0.85, 5.94)	NS
Splenomegaly	27/610 (4)	1.50 (0.80, 7.10)	2.15 (0.90, 6.20)	NS
Colitis, vasculitis, and serositis	35/610 (6)	3.00 (1.80, 10.05)	2.10 (0.90, 6.00)	0.014
Pancreatitis	19/610 (3)	4.03 (1.20, 10.45)	2.10 (0.90, 6.00)	NS
Renal				
Proteinuria	224/610 (37)	2.40 (1.00, 7.05)	2.00 (0.90, 5.70)	NS
Nephrotic syndrome	107/607 (18)	2.30 (0.97, 5.50)	2.10 (0.90, 6.25)	NS
Hematuria	179/610 (29)	2.30 (1.00, 6.50)	2.00 (0.85, 6.00)	NS
Renal insufficiency	87/610 (14)	2.50 (1.20, 6.20)	2.00 (0.90, 6.20)	NS

Clinical features	Number (%) *	Presence **	Absence **	P value †
Renal failure	28/609 (5)	2.53 (1.63, 6.85)	2.10 (0.90, 6.20)	NS
Neuropsychiatric				
Seizure	42/610 (7)	4.00 (1.55, 8.80)	2.00 (0.90, 6.00)	0.018
Psychosis	19/609 (3)	2.65 (1.40, 9.70)	2.10 (0.90, 6.00)	NS
Organic brain syndrome	33/610 (5)	2.00 (0.93, 5.68)	2.15 (0.90, 6.20)	NS
Aseptic meningitis	10/610 (2)	1.40 (0.50, 2.48)	2.18 (0.90, 6.20)	NS
Stroke	18/610 (3)	2.23 (1.51, 13.69)	2.12 (0.90, 6.10)	NS
Depression	217/610 (36)	2.50 (1.10, 6.33)	2.00 (0.80, 6.00)	0.095
Headache	45/610 (7)	2.20 (1.15, 6.35)	2.10 (0.90, 6.15)	NS
Mononeuritis multiplex	12/610 (2)	2.15 (1.64, 8.15)	2.12 (0.90, 6.20)	NS
Cognitive impairment	33/604 (6)	2.20 (0.85, 5.00)	2.10 (0.90, 6.20)	NS
Optic neuritis	5/604 (1)	2.50 (1.55, 3.35)	2.10 (0.90, 6.10)	NS
Cranial neuropathy	7/604 (1)	2.40 (1.60, 3.60)	2.10 (0.90, 6.10)	NS
Peripheral neuropathy	38/604 (6)	3.00 (0.86, 6.28)	2.10 (0.90, 6.00)	NS
Transverse myelitis	3/602 (1)	0.50 (0.40, 1.05)	2.13 (0.90, 6.10)	0.061
Hematological				
Anemia	334/609 (55)	2.68 (1.00, 7.35)	1.85 (0.85, 4.47)	0.002
Hemolytic anemia	47/608 (8)	2.30 (0.90, 7.10)	2.10 (0.90, 6.05)	NS
Leukopenia	282/610 (46)	2.00 (0.80, 6.23)	2.20 (1.00, 6.18)	NS
Lymphopenia	253/608 (42)	2.00 (0.91, 5.70)	2.20 (0.90, 6.45)	NS
Thrombocytopenia	128/609 (21)	2.30 (0.95, 5.88)	2.10 (0.90, 6.20)	NS
Miscellaneous				
Dry eye	133/609 (22)	1.83 (0.90, 6.00)	2.30 (0.90, 6.29)	NS
Dry mouth	90/609 (15)	2.17 (0.98, 7.80)	2.10 (0.90, 6.00)	NS
Sjogren's syndrome	92/606 (15)	1.82 (1.00, 6.15)	2.23 (0.90, 6.20)	NS

Abbreviation: NS, not significant.

* Number of patients who had pertinent clinical feature.

** hsCRP levels are presented as median values (interquartile ranges).

† The P values were calculated using the Mann–Whitney U test.

Table 3
Regression coefficients for log-transformed hsCRP levels* by clinical features and autoantibodies

Unadjusted				Adjusted										
Model 1 [†]				Model 2 [‡]				Model 3 [§]						
β	95% CI	P	B	95% CI	P	% Red [¶]	β	95% CI	P	% Red [¶]	β	95% CI	P	% Red [¶]
0.08	-0.01, 0.18	0.094	0.03	-0.06, 0.12	NS	61	0.05	-0.04, 0.14	NS	36.3	0.04	-0.06, 0.14	NS	46
0.14	0.03, 0.26	0.015	0.03	-0.08, 0.14	NS	80	0.01	-0.10, 0.13	NS	90.8	0.04	-0.08, 0.15	NS	75
-0.09	-0.18, 0.00	0.053	-0.02	-0.11, 0.06	NS	73	-0.04	-0.13, 0.06	NS	60.7	-0.04	-0.13, 0.06	NS	61
-0.13	-0.24, -0.03	0.013	-0.05	-0.15, 0.06	NS	65	-0.08	-0.19, 0.04	NS	43.6	-0.07	-0.19, 0.04	NS	44
0.13	0.02, 0.23	0.023	0.09	-0.01, 0.19	0.071	27	0.04	-0.06, 0.15	NS	64.8	0.05	-0.06, 0.16	NS	60
0.41	0.08, 0.73	0.014	0.39	0.10, 0.68	0.009	3	0.44	0.13, 0.76	0.006	-9.1	0.57	0.22, 0.92	0.002	-39
0.21	0.02, 0.29	<0.001	0.11	0.02, 0.20	0.019	47	0.15	0.05, 0.25	0.003	27.3	0.16	0.06, 0.26	0.002	22
0.10	0.01, 0.19	0.036	0.09	0.01, 0.18	0.032	6	0.10	0.01, 0.19	0.031	-2.1	0.08	-0.01, 0.18	0.094	17
0.25	0.08, 0.41	0.003	0.18	0.03, 0.33	0.019	27	0.16	-0.00, 0.32	0.051	35.9	0.17	0.01, 0.33	0.043	31
0.24	0.08, 0.41	0.003	0.10	-0.05, 0.25	NS	59	0.15	-0.01, 0.31	0.066	38.7	0.18	0.01, 0.34	0.036	27
0.24	0.05, 0.44	0.013	0.21	0.03, 0.38	0.021	16	0.26	0.06, 0.46	0.012	-5.3	0.28	0.07, 0.49	0.008	-15
0.21	0.04, 0.39	0.019	0.23	0.07, 0.39	0.006	-7	0.19	0.02, 0.36	0.027	9.9	0.17	-0.01, 0.35	0.069	22
0.14	0.05, 0.23	0.003	0.07	-0.02, 0.16	NS	48	0.09	-0.00, 0.19	0.055	32.8	0.12	0.02, 0.22	0.021	14
0.00	0.00, 0.00	<0.001	0.00	0.00, 0.00	<0.001	0	0.00	0.00, 0.00	<0.001	0	0.00	0.00, 0.00	<0.001	0
0.18	0.08, 0.28	<0.001	0.13	0.04, 0.22	0.007	28	0.14	0.04, 0.24	0.006	22.8	0.13	0.03, 0.24	0.013	26

CI, confidence interval; NS, not significant.

*hsCRP ranged from -1.00 to 1.93.

†Age, ethnicity, disease duration, body mass index, and education

‡Age, ethnicity, disease duration, body mass index, education, and SELENA-SLEDAI.

§Age, ethnicity, disease duration, body mass index, education, SELENA-SLEDAI, current prednisone dose, statin use, and estrogen use.

¶Regression coefficients from the unadjusted model, calculated as: (regression coefficientunadjusted - regression coefficientmodel 1 or 2 or 3)/(regression

Table 4

Differences between hsCRP level and autoantibodies

Autoantibodies	Number (%) [*]	Presence	Absence	<i>P</i> value [†]
Anti-dsDNA	135/577 (23)	2.95 (1.30, 8.90)	2.00 (0.85, 5.06)	<0.001
Anti-Ro	178/602 (30)	2.10 (1.00, 6.03)	2.20 (0.90, 6.29)	NS
Anti-La	83/602 (14)	2.00 (1.00, 6.35)	2.20 (0.90, 6.20)	NS
Anti-Sm	105/598 (18)	2.27 (0.80, 7.00)	2.10 (0.93, 6.00)	NS
Anti-RNP	152/597 (26)	2.00 (0.80, 7.01)	2.20 (0.90, 6.00)	NS
Lupus anticoagulant	168/608 (28)	2.85 (1.36, 7.93)	1.90 (0.80, 5.48)	<0.001
IgG/IgM anti-cardiolipin	318/607 (52)	2.30 (1.00, 6.24)	2.00 (0.80, 6.05)	NS

Abbreviation: NS, not significant.

The hsCRP levels are presented as median values with interquartile ranges. The anti-dsDNA antibodies were measured at the time of the first hsCRP measurements. Other autoantibodies were measured at the first cohort visit and in the case of anti-cardiolipin, tests were repeated during follow-up.

^{*} Number of patients who had pertinent autoantibody.

[†] The *P* values were calculated using the Mann–Whitney *U* test.

Table 5
Differences between hsCRP level and SLICC/ACR damage index

Damage Index	Number (%) [*]	Presence	Absence	P value [†]
Ocular	92/606 (15)	2.20 (1.20, 5.20)	2.10 (0.90, 6.20)	NS
Any cataract ever	76/606 (13)	2.30 (1.05, 5.20)	2.10 (0.90, 6.20)	NS
Retinal change or optic atrophy	32/606 (5)	1.78 (0.98, 3.55)	2.20 (0.90, 6.22)	NS
Neuropsychiatric	117/604 (19)	2.00 (0.88, 5.60)	2.15 (0.90, 6.24)	NS
Cognitive impairment OR major psychosis	40/606 (7)	2.30 (1.15, 4.63)	2.10 (0.90, 6.24)	NS
Seizures requiring therapy for 6 months	21/604 (4)	3.60 (1.90, 14.81)	2.10 (0.90, 6.00)	0.018
Cerebral vascular accident ever OR resection not for malignancy	42/606 (7)	2.80 (1.40, 13.10)	2.10 (0.90, 6.00)	0.066
Cranial OR peripheral neuropathy	46/606 (8)	2.10 (0.89, 5.55)	2.14 (0.90, 6.25)	NS
Transverse myelitis	4/606 (1)	1.05 (0.35, 7.53)	2.18 (0.90, 6.20)	NS
Renal	56/606 (9)	2.60 (1.16, 7.54)	2.05 (0.90, 6.10)	NS
Estimated or measured GFR < 50%	13/606 (2)	2.95 (2.07, 9.85)	2.10 (0.90, 6.10)	NS
Proteinuria 24h ≥ 3.5 g OR	40/606 (7)	2.45 (0.73, 5.51)	2.10 (0.90, 6.22)	NS
End-stage renal disease	14/606 (2)	3.08 (1.95, 13.08)	2.10 (0.90, 6.10)	0.05
Pulmonary	70/603 (12)	2.95 (1.53, 11.38)	2.00 (0.84, 5.74)	0.002
Pulmonary hypertension	22/606 (4)	3.10 (1.59, 12.39)	2.10 (0.90, 6.03)	0.059
Pulmonary fibrosis	40/607 (7)	2.95 (1.70, 11.70)	2.05 (0.90, 6.00)	0.006
Shrinking lung	3/604 (1)	4.13 (2.67, 25.84)	2.15 (0.90, 6.20)	NS
Pleural fibrosis	17/606 (3)	6.08 (2.13, 18.14)	2.10 (0.90, 6.00)	0.002
Pulmonary infarction OR resection not for malignancy	6/605 (1)	1.65 (1.24, 2.68)	2.15 (0.90, 6.20)	NS
Cardiovascular	61/606 (10)	2.30 (1.25, 5.00)	2.13 (0.90, 6.24)	NS
Angina OR coronary artery bypass	12/606 (2)	2.00 (1.15, 2.95)	2.20 (0.90, 6.29)	NS
Myocardial infarction ever	14/606 (2)	1.85 (1.20, 4.70)	2.15 (0.90, 6.20)	NS
Cardiomyopathy	20/606 (3)	2.15 (1.31, 4.50)	2.14 (0.90, 6.20)	NS
Valvular disease	13/606 (2)	2.80 (1.55, 7.20)	2.13 (0.90, 6.20)	NS
Pericarditis OR pericardiectomy	15/606 (3)	2.70 (0.80, 9.90)	2.13 (0.90, 6.10)	NS
Peripheral vascular	29/606 (5)	2.85 (1.44, 7.86)	2.10 (0.90, 6.18)	NS
Claudication	4/606 (1)	3.80 (2.78, 13.95)	2.10 (0.90, 6.18)	0.084
Minor tissue loss	5/606 (1)	1.47 (0.43, 10.48)	2.15 (0.90, 6.20)	NS
Significant tissue loss ever	4/606 (1)	4.05 (1.64, 10.09)	2.12 (0.90, 6.18)	NS
Venous thrombosis with swelling, ulceration, OR venous stasis	17/606 (3)	2.58 (1.28, 7.29)	2.12 (0.90, 6.20)	NS
Gastrointestinal	91/604 (15)	2.74 (1.20, 7.60)	2.10 (0.90, 6.00)	NS
Infarction or resection of bowel below duodenum, spleen, liver, or gallbladder ever	86/606 (14)	2.80 (1.13, 7.56)	2.10 (0.90, 6.00)	NS
Mesenteric insufficiency	3/605 (1)	8.00 (4.15, 13.73)	2.12 (0.90, 6.10)	NS
Chronic peritonitis	3/604 (1)	2.50 (1.85, 11.36)	2.12 (0.90, 6.18)	NS
Stricture OR upper gastrointestinal tract surgery ever	3/605 (1)	1.40 (0.85, 1.58)	2.18 (0.90, 6.20)	NS
Pancreatic insufficiency requiring enzyme replacement or with pseudocyst	1/605 (0)	15.50	2.12 (0.90, 6.18)	NS

Damage Index	Number (%) [*]	Presence	Absence	<i>P</i> value [†]
Musculoskeletal	137/604 (23)	3.40 (1.55, 8.05)	1.90 (0.80, 5.25)	<0.001
Muscle atrophy or weakness	15/605 (3)	6.45 (2.50, 21.40)	2.10 (0.90, 6.00)	0.007
Deforming or erosive arthritis	31/605 (5)	5.30 (2.99, 14.35)	2.00 (0.90, 5.88)	<0.001
Osteoporosis with fracture or vertebral collapse	63/605 (10)	2.60 (1.25, 7.48)	2.10 (0.90, 6.00)	NS
Avascular necrosis	47/605 (8)	3.70 (1.48, 7.88)	2.00 (0.90, 6.00)	0.017
Osteomyelitis	1/605 (0)	4.60 (1.60, 7.60)	2.13 (0.90, 6.15)	NS
Ruptured tendon	13/605 (2)	2.77 (0.88, 13.53)	2.10 (0.90, 6.10)	NS
Skin	37/604 (6)	3.25 (1.17, 5.74)	2.10 (0.90, 6.20)	NS
Scarring chronic alopecia	15/604 (3)	3.08 (1.21, 8.26)	2.10 (0.90, 6.20)	NS
Extensive scarring or panniculum other than scalp and pulp space	18/605 (3)	3.33 (1.51, 10.55)	2.10 (0.90, 6.20)	NS
Skin ulceration for more than 6 months	9/605 (2)	1.40 (0.90, 6.12)	2.14 (0.90, 6.20)	NS
Premature gonadal failure	46/605 (8)	1.90 (0.68, 5.50)	2.14 (0.90, 6.28)	NS
Diabetes	34/605 (6)	4.08 (1.74, 10.48)	2.10 (0.85, 6.00)	0.005
Malignancy	44/605 (7)	1.70 (0.86, 6.65)	2.20 (0.90, 6.20)	NS
Total damage score ≥ 1	384/598 (64)	2.55 (1.20, 7.25)	1.50 (0.70, 4.65)	<0.001

Abbreviation: NS, not significant.

The hsCRP levels are presented as median values with interquartile ranges.

^{*} Number of patients who had pertinent SLICC/ACR damage.

[†] The *P* values were calculated using the Mann–Whitney *U* test.

Table 6
Regression coefficients of log-transformed hsCRP level by SLICC/ACR damage index

Unadjusted			Adjusted											
			Model 1				Model 2				Model 3			
β	95% CI	P	β	95% CI	P	% Red	β	95% CI	P	% Red	β	95% CI	P	% Red
-0.03	-0.19, 0.13	NS	-0.06	-0.21, 0.08	NS	-100.0	-0.09	-0.24, 0.07	NS	-175.0	-0.09	-0.25, 0.08	NS	-172
0.33	0.08, 0.57	0.010	0.37	0.14, 0.59	0.001	-12.3	0.31	0.09, 0.54	0.006	3.7	0.35	0.12, 0.59	0.003	-8
0.17	-0.01, 0.35	0.060	0.14	-0.02, 0.30	0.091	18.3	0.11	-0.05, 0.28	NS	33.1	0.16	-0.01, 0.33	0.070	8
0.08	-0.08, 0.23	NS	0.03	-0.11, 0.17	NS	58.7	-0.01	-0.16, 0.15	NS	109.3	0.06	-0.11, 0.23	NS	20
0.10	-0.00, 0.20	0.056	0.06	-0.03, 0.15	NS	41.8	0.06	-0.04, 0.16	NS	37.8	0.11	-0.00, 0.22	0.054	-12
0.24	0.10, 0.37	0.001	0.17	0.05, 0.30	0.007	27.4	0.17	0.04, 0.31	0.012	27.4	0.18	0.04, 0.31	0.012	26
0.23	0.00, 0.46	0.050	0.10	-0.11, 0.31	NS	56.5	0.10	-0.11, 0.32	NS	55.2	0.12	-0.11, 0.34	NS	50
0.27	0.09, 0.44	0.003	0.21	0.05, 0.37	0.010	22.0	0.21	0.04, 0.38	0.018	22.4	0.20	0.03, 0.37	0.024	26
0.43	0.16, 0.69	0.002	0.41	0.17, 0.65	0.001	4.9	0.32	0.07, 0.57	0.013	25.1	0.37	0.11, 0.63	0.005	13
0.23	0.13, 0.34	<0.001	0.16	0.06, 0.26	0.002	31.0	0.16	0.05, 0.27	0.005	32.3	0.15	0.04, 0.26	0.010	36
0.41	0.12, 0.70	0.006	0.23	-0.04, 0.49	NS	45.0	0.23	-0.03, 0.50	NS	43.1	0.21	-0.06, 0.47	NS	50
0.42	0.22, 0.62	<0.001	0.31	0.12, 0.50	0.001	25.0	0.31	0.12, 0.51	0.002	24.5	0.29	0.09, 0.49	0.005	32
0.20	0.03, 0.36	0.021	0.05	-0.10, 0.21	NS	72.4	0.15	-0.02, 0.32	NS	24.0	0.15	-0.03, 0.34	NS	21
0.26	0.07, 0.46	0.008	0.10	-0.08, 0.29	NS	61.0	0.09	-0.10, 0.29	NS	64.8	0.13	-0.07, 0.34	NS	49
0.05	0.03, 0.07	<0.001	0.03	0.00, 0.05	0.031	44.9	0.03	0.00, 0.05	0.049	44.9	0.03	0.01, 0.06	0.020	33

Semin Arthritis Rheum. Author manuscript; available in PMC 2009 A

Semin Arthritis Rheum. Author manuscript; available in PMC 2009 August 1.

ression coefficient; CI, confidence interval; NS, not significant.
itions of the models.