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Risk factors for infection and role of C-reactive protein in Korean patients with systemic lupus erythematosus

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ABSTRACT

To evaluate risk factors for infection and the role of C-reactive protein (CRP) in the diagnosis of infection, a retrospective case control study was performed among Korean systemic lupus erythematosus patients. Of 120 proven infections, 31 episodes (25.8%) occurred in patients taking no corticosteroids (CS). The risk of infection was lower in patients taking low-dose CS (< 300 mg prednisolone/month) than no CS (odds ratio (OR) 0.36). In patients receiving high-dose CS (> 1000 mg prednisolone/month), however, the risk increased (OR 2.9). In patients taking no CS, disease activity manifested as increased SLEDAI, anemia and active urinary sediment, was associated with infection. The CRP was higher in the patients with infection than controls and the CRP levels over 50 mg/l were observed only in infection. These results suggest that CS have a bimodal influence on infection depending on dose. Disease activity is an important risk factor for infection in patients taking no CS. Finally, CRP levels greater than 50 mg/l suggest the presence of infection.

Introduction

A high incidence of infection among patients with systemic lupus erythematosus (SLE) has been well described (1, 2). The increased rate of infection presumably reflects the global dysregulation of the immune system that is the hallmark of SLE. Clinical studies have provided conflicting data regarding risk factors that predispose SLE patients to infection (1-7). The diagnosis of SLE itself, the presence of active nephritis and the degree of overall disease activity have all been linked to the increased risk of infection (1-5) but not confirmed by others (6, 7). In addition,immunosuppressive drugs such as corticosteroids (CS) are known to increase the risk of infection. Several reports, however, showed that the infection rate did not correlate significantly with prednisolone dose (1, 2, 5).

Fever in SLE always poses the problem of differential diagnosis between disease flare and superimposed infection. The value of C-reactive protein (CRP) levels in distinguishing between disease activity and infection has been a controversial matter (8-11). In one study, in the absence of serositis, CRP levels exceeding 60 mg/l were always associated with infection in SLE (9).

The aim of this study was to ascertain risk factors that predispose SLE to infection and the role of CRP in the diagnosis of infection.

Patients and methods

173 SLE patients being followed in the Rheumatology Clinic of Yonsei University Medical Center from January 1992 to December 1996 were included. All fulfilled at least 4 of the American College of Rheumatology 1982 Revised Criteria for SLE.

Infections were confirmed both by clinical findings and by positive culture. Herpes zoster was considered when the patient was found to have the characteristic vesicular rash in a dermatomal distribution. Controls were age- and sex-matched SLE patients with no evidence of infection.

The following information present at diagnosis and at infection were recorded:demographic data, CS dose and laboratory parameters including complete blood count, erythrocyte sedimentation rate (ESR), creatinine, complement, anti-ds DNA antibody and urinalysis. C-reactive protein was determined by nephelometry. Disease activity was assessed by the SLE disease activity index (SLEDAI), the presence of cytopenia, complements level, anti-ds DNA antibody and active urinary sediment (hematuria or urinary cast). To clarify the contribution of CS to the risk of infection, we divided patients into 4 subsets based on the cumulative prednisolone equivalent dose per month; none, 1-300 mg, 301-1000 mg, and > 1000 mg. The presence of these potential risk factors was determined at the time of infection and over a similar time period for controls. The ^{2} test, t-test, Mann-Whitney U test, or multiple logistic regression analysis was used where appropriate.

Results

Seventy-three SLE patients had at least one documented infection during 5

Table I. Comparison of SLE patients with infection and controls.

Variable	Patients with infection n = 73	Controls n = 100	P value
Diagnosis age, years#	26.5 ± 11.1	29.7 ± 10.5	0.148
Female sex, %	93.0	89.2	0.355
Disease duration, months#	54.6 ± 36.3	45.4 ± 33.9	0.237
Initial corticosteroid dose, mg prednisolone/day*	448.5 (0 - 1250)	290.5 (0 - 1000)	0.026

#Values are the means ± SD, *Value represents the mean (range) because of skewed distribution.

Table II. Influence of corticosteroid dose on the infection.

Corticosteroid Dose (mg)#	Infection n = 120	Control n = 100	Odds Ratio	95% Confidence Interval
0	31 (25.8%)	20 (20%)		
1-300	26 (21.7%)	46 (46%)	0.36	0.17 - 0.76
301-1000	36 (30.0%)	28 (28%)	0.83	0.39 - 1.75
1001-	27 (22.5%)	6 (6%)	2.90	1.02 - 8.28

#Cumulative prednisolone equivalent dose of one month.

Table III. Influence of disease activity on the infection.

Variable	Infection (n = 120)	Control (n = 100)	p value
SLEDAI	8.72	6.64	0.005
Leukopenia (%)	24.0	30.0	0.333
Lymphopenia (%)	54.0	45.0	0.177
Anemia (%)	38.0	21.0	0.007
Thrombocytopenia (%)	17.0	11.0	0.238
Decreased C3 (%)	58.1	50.0	0.294
Decreased C4 (%)	25.8	32.5	0.343
Anti-ds DNA (%)	59.5	54.9	0.553
Active urinary sediment (%)	61.1	46.4	0.033

Table IV. Influence of disease activity on the infection according to corticosteroid dose.

Corticosteroid dose (mg)#	SLEDAI		Anemia (%)		Active urinary sediment (%)	
	Infection	Control	Infection	Control	Infection	Control
0	11.12*	5.10*	48.4*	20.0*	63.3*	31.6*
1 - 300	7.21	5.50	15.4	11.1	51.2	50.3
301- 1000	8.67	7.21	30.1	25.0	60.0	60.9
1001-	12.14	11.67	51.9	50.0	76.9	100.0

#Cumulative prednisolone equivalent dose of one month; *p < 0.05.

years. The demographic characteristics are summarized in Table I. There were no demographic differences between patients with infection and controls, but the mean prednisolone dose per day at diagnosis was higher in infected patients than in controls (448.5 vs. 290.5 mg, p = 0.026). The distribution of fulfilled ACR criteria was comparable in the two groups.

One hundred and twenty infections were diagnosed in 73 patients with an overall infection rate of 16.9 infections per 100 patient-years of follow-up. Twenty-four patients had more than one infection (range; 2-5). Seventy-eight bacterial infections, 11 infections per 100 patient-years, were observed among 49 patients. *Escherichia coli*, *Staphylococcus aureus* and Salmonella species were common bacterial pathogens. The most common bacterial infection site was the urinary tract. Septicemia and pneumonia were also commonly observed. Opportunistic infections were diagnosed 42 times among 39 patients with a frequency of 5.9 infections per 100 patient-years. Opportunistic infections were common on the skin and mucous membrane, principally herpes zoster and oral thrush.

The mean cumulative prednisolone dose per month in patients with infection was higher than in controls (832.3 mg vs. 335.4 mg, p < 0.001). Among those with infection, 31 episodes (25.8 %) occurred in patients taking no CS for a month before the infection. By dividing patients based on the monthly prednisolone dose, it was possible to assess the influence of the CS dose. The odds ratio (OR) in patients receiving low-dose CS (1-300 mg/month) was 0.36 (95% confidence interval [95% CI] 0.17 - 0.76) compared to patients taking no CS (Table II). In patients receiving high-dose CS (> 1000 mg/month),the OR was increased to 2.9 (95% CI 1.02 - 8.28).

Disease activity was compared at the time of infection and over a similar time period for controls (Table III). The patients with infection showed higher SLEDAI score than controls (8.72 vs. 6.64, p = 0.005). At the time of infection, anemia (38% vs.21%, p = 0.007) and active urinary sediment (61.1% vs. 46.4%, p = 0.033) were more frequently observed. Disease activity was increased according to the CS dose (Table IV). In infection, patients taking no CS showed increased disease activity comparable to high-dose CS probably due to the patients initially diagnosed with infection. In patients receiving no CS, clinical risk factors such as a high SLEDAI score, anemia and acute nephritis were commonly associated with infection. However, risk factors were not different between infection and controls among patients taking CS. The ESR and CRP were measured at infection to assess their role in the diagnosis of infection. The ESR was not

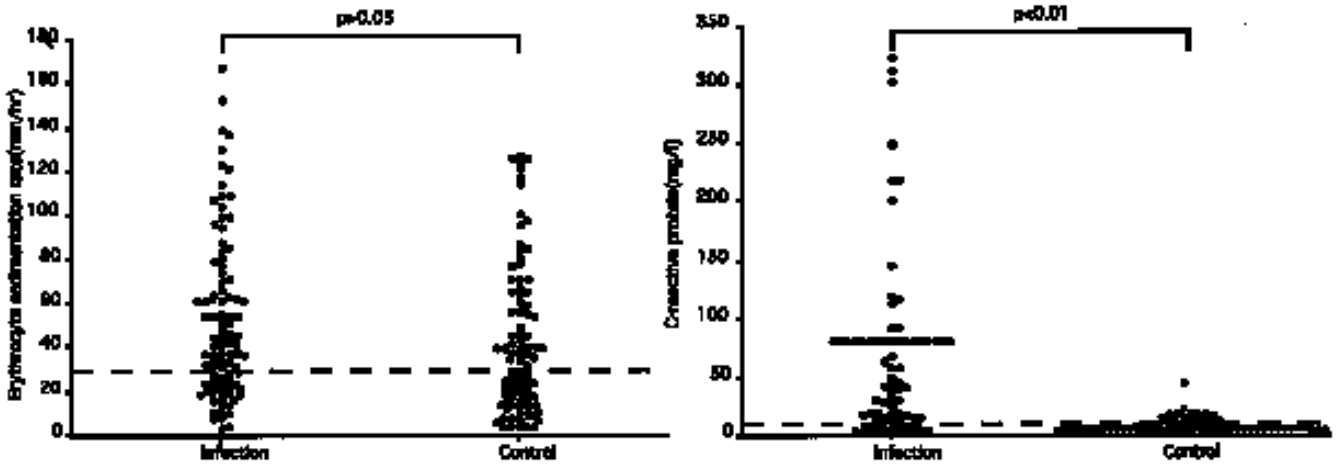

Fig. 1. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in SLE. The horizontal interrupt lines indicate cutoff level of normal value. There was no difference in ESR between patients with infection and controls. The patients with infection showed higher CRP than controls (66 mg/l vs 5.4 mg/l, $p < 0.001$). None of controls showed CRP level greater than 50 mg/l.

different between patients with infection and controls. The CRP, however, was higher in infection than controls (66 mg/l vs. 5.4 mg/l, $p < 0.001$). Nearly all patients with infection showed CRP positivity. In controls, some patients showed CRP positivity, but none was higher than 50 mg/l (Figure 1).

Discussion

It is generally believed that both CS and disease activity are associated with an increased incidence of infection in SLE. The results of this study are consistent with this hypothesis: high dose CS treatment and disease activity, as reflected by a high SLEDAI score, anemia and acute nephritis, increase the risk of infection.

Interestingly, in our study patients taking low-dose CS showed a lower incidence of infection than those not taking CS. CS have a dual influence on the immune system in SLE (3). Suppression of abnormally functioning cells may normalize other aspects of the immune system. In untreated SLE patients neutrophil migration is significantly depressed, but it is usually normal in the treated group (12). It has been reported that patients treated with low-dose CS have increased infection (4). A meta-analysis of controlled clinical trials showed that the infection rate was not increased in patients given low-dose CS (13), and as pharmacological data show, this dose is inadequate to impair host resistance against infection (14). Lupus patients treated with low-dose CS reveal no significant phagocyte dysfunction (15). Probably, the observed infections in SLE treated with low-dose CS are attributable to disease activity. With intermediate-doses of CS, the incidence of infection was not much different from that in patients taking no CS. However, it was increased by about 3 times in patients taking high-dose CS. CS thus showed a bimodal pattern in the risk of infection in SLE; it decreased risk at low-dose and increased at high-dose.

Even without CS, infections are common in SLE. These infections are usually associated with disease exacerbation. Ginzler *et al*. (4) reported that exacerbation was associated with increased infection, and that active urinary sediment was a predictor of infection. Similar results were observed; patients with high SLEDAI, anemia and active urinary sediment had an elevated infection risk. However, decreased complement and anti-ds DNA were not. If we stratified patients according to the cumulative monthly CS dose, disease activity was not different between infection and controls in patients taking CS. In patients taking no CS, however, infection was associated with a high SLEDAI, anemia and active urinary sediment. These results support the view that the increased incidence of infection in patients taking no CS is related to elevated disease activity.

It is well established that the incidence of infection is increased in SLE. Two studies (2, 4) reported an overall infection rate of 59-142 per 100 patient-years, of which bacterial infection was approximately 40%. The incidence of infection in Korean was 16.9 per 100 patient-years and it was quite lower than Caucasians. About 65% of the infections were of bacterial origin. These results suggest that there are racial differences in the susceptibility to infection. The lower infection rate and higher incidence of bacterial infection are partially due to the fact that we did not register clinically suspected viral infection. Another difference from previous reports is that Salmonella infection and herpes zoster were more common in Korean SLE.

Early diagnosis of infection in SLE is very important because the timing of therapeutic intervention is critical in SLE with infection. Honig *et al*. (8) reported that significant CRP positivity in SLE might suggest the presence of superimposed infection. Becker *et al*. (9) suggested that CRP levels greater than 60 mg/l indicated the presence of intercurrent infection and served as a valuable aid to differentiate pyrexia in SLE. Two other studies (10, 11), however, showed that CRP elevation did not differentiate between lupus activity and infection. In Korean SLE, CRP was significantly elevated in patients with infection. Some controls showed elevated CRP but not higher than 50

mg/l. Therefore, CRP was useful in differentiating infection from disease activity, especially CRP levels greater than 50 mg/l.

In conclusion, high-dose CS and disease activity predispose to infection in Korean SLE. Low-dose CS, however, is associated with a lower risk of infection. Disease activity is an important risk factor in patients not taking CS. CRP levels greater than 50 mg/l suggest the presence of infection.

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References

1. STAPLES PJ, GERDING DN, DECKER JL, GORDON RS JR: Incidence of Infection in systemic lupus erythematosus. *Arthritis Rheum* 1974; 17: 1-10.
2. NIVED O, STURFELT G, WOLLHEIM F: Systemic lupus erythematosus and infection: A controlled and prospective study including an epidemiological group. *Q J Med* 1985; 55: 271-87.
3. ILIOPOULOS AG, TSOKOS GC: Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. *Semin Arthritis Rheum* 1996; 25: 318-36.
4. GINZLER E, DIAMOND H, KAPLAN D, WEINER M, SCHLESINGER M, SELEZNICK M: Computer analysis of factors influencing frequency of infection in systemic lupus erthematosus. *Arthritis Rheum* 1978; 21: 37-44.
5. DUFFY KN, DUFFY CM, GLADMAN DD: Infection and disease activity in systemic lupus erythematosus: A review of hospitalized patients. *J Rheumatol* 1991; 18: 1180-4.
6. RUBIN LA, UROWITZ MB, GLADMAN DD: Mortality in systemic lupus erythematosus: The bimodal pattern revisited. *Q J Med* 1985; 55: 87-98.
7. HELLMANN DB, PETRI M, WHITING-O'KEEFE Q: Fatal infections in systemic lupus erythematosus: The role of opportunistic organisms. *Medicine* 1987; 66: 341-8.
8. HONIG S, GOREVIC P, WEISSMANN G: C-reactive protein in systemic lupus erythematosus. *Arthritis Rheum* 1977; 20: 1065-70.
9. BECKER GJ, WALDBURGER M, HUGHES GRV, PEPYS MB: Value of serum C-reactive protein measurement in the investigation of fever in systemic lupus erythematosus. *Ann Rheum Dis* 1980; 39: 50-2.
10. ZEIN N, GANUZA C,KUSHNER I: Significance of serum C-reactive protein elevation in patients with systemic lupus erythematosus. *Arthritis Rheum* 1979; 22: 7-12.
11. STAHL NI,KLIPPEL JH, DECKER JL: Fever in systemic lupus erythematosus. *Am J Med* 1979; 67: 935-40.
12. AL-HADITHY H,ISENBERG DA,ADDISON IE, GOLDSTONE AH, SNAITH ML: Neutrophil function in systemic lupus erythematosus and other collagen diseases. *Ann Rheum Dis* 1982; 41: 33-8.
13. STUCK AE, MINDER CE, FREY FJ: Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis* 1989; 11: 954-63.
14. CALDWELL JR, FURST DE: The efficacy and safety of low-dose corticosteroids for rheumatoid arthritis. *Semin Arthritis Rheum* 1991; 21: 1-11.
15. BOGHOSSIAN SH, ISENBERG DA, WRIGHT G, SNAITH ML, SEGAL AW: Effect of high-dose methylprednisolone therapy on phagocyte function in systemic lupus erythematosus. *Ann Rheum Dis* 1984; 43: 541-50.