

## Original Article

# The incidence of infectious complications during admission and within 2 months after discharge in patients with systemic lupus erythematosus treated with high dose glucocorticoids

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## Abstract

**Objective** Prednisolone has traditionally been tapered below 30 mg daily before patients are discharged from hospitals in Japan because of concerns regarding the development of infectious complications. We undertook this study to compare the incidence of infectious complications in patients taking more than 30 mg of prednisolone daily with those taking less than 30 mg.

**Patients and Methods** The medical records of fifty-seven patients with systemic lupus erythematosus (SLE) were reviewed retrospectively, and divided into three groups based on the dose of glucocorticoids at the time of discharge: group A (n=13), newly-diagnosed SLE patients taking more than 30 mg of prednisolone daily; group B (n=22), newly-diagnosed SLE patients taking less than 30 mg; and group C (n=22), patients with an established diagnosis taking more than 30 mg daily for the treatment of an exacerbation of symptoms. The development of infectious complications within two months after discharge was identified from a review of the medical records to determine the effect of glucocorticoid dose at the time of discharge on the subsequent development of infectious complications.

**Results** Two patients in group A and three in group C developed infectious complications within two months following discharge, while no patients in group B contracted an infection. These included herpes zoster in group A (n=2) and herpes zoster, urinary tract infection and *Pneumocystis jirovecii* pneumonia in group C (n=3, one each). However, the incidence of infectious complications comparing groups A and B, and groups A and C was not statistically significantly different ( $p>0.05$ ). There was no correlation between the incidence of infection and the total dose of glucocorticoids given during admission.

**Conclusion** Although this study was retrospective and involved only a small number of patients with SLE, there is no increased risk of developing infectious complications in pa-

tients receiving more than 30 mg of prednisolone daily at the time of hospital discharge, compared to those taking less than 30 mg. Based on these results, prolonging hospitalization only to reduce the dose of prednisolone to less than 30 mg daily lacks justifiable grounds, even if it has been a tacit consensus in Japan.

(Key words : SLE, infection, dose, glucocorticoid, prednisolone)

## Introduction

Glucocorticoids are indispensable and the mainstay for the treatment of collagen-vascular diseases (CVD) such as systemic lupus erythematosus (SLE). However, they have strong immunosuppressive effects as well as anti-inflammatory activity, which sometimes causes serious and/or opportunistic infectious complications<sup>(1)</sup>. Because there has been significant progress in the diagnosis and treatment of CVD, the most important factor affecting mortality in patients with CVD is not the disease *per se*, but the development of infections<sup>(2)</sup>. Therefore, patients in Japan have traditionally been hospitalized until the daily dose of prednisolone is less than 30 mg for fear of contracting infectious complications following discharge.

There are several reports on the incidence of infection and predictive factors for the development of infectious complications after the initiation of steroid therapy. However, the relationship between the daily dose of glucocorticoids at the time of hospital-discharge and the incidence of infections following discharge has not been studied to date. Thus, the prolongation of the hospital stay until the daily dose of prednisolone is under 30 mg is a widespread practice without substantiating evidence. We investigated this issue retrospectively.

## Patients and Methods

Fifty-seven patients with SLE who had been admitted to the Jichi Medical University hospital between 1994 and 2004 were studied retrospectively for the development of infectious complications during admission and within two months after discharge in order to examine the effect of glucocorticoid dose at the time of discharge. Infections treated with parenteral antibiotics and/or opportunistic infection such as herpes zoster, cytomegalovirus, *Pneumocystis jirovecii*, *Candida*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* were included in this study. Mild infections cured by a short course of oral antibiotics or the common cold were excluded.

Patients were divided into three groups. Group A consisted of 13 newly-diagnosed patients with SLE taking more than 30 mg of prednisolone daily at the time of discharge from the hospital. Group B consisted of 22 newly-diagnosed patients taking less than 30 mg of prednisolone daily at the time of discharge. Group C consisted of 22 patients with recurrent SLE whose prednisolone dose was more than 30 mg daily at the time of discharge. Our hospital does not impose conditions now, on prednisolone dose for the discharge, which allowed the selection of 13 patients in group A in this study.

Fisher's exact test was employed to examine categorical variables, including the difference in the incidence of infection among the three groups. Continuous variables in the patients' profiles, and clinical and laboratory tests among the three groups were evaluated using the Mann-Whitney *U* test. Multiple regression analysis was used to determine if the abnormalities demonstrated by clinical and laboratory tests had a causal relationship to the development of an infection. A *p*-value of less than 0.05 was consid-

Table 1. Patients' clinical and laboratory profiles among three groups

	A (n=13)	B (n=22)	C (n=22)	p-value	
sex (women/men)	10/3	17/5	22/0	ns*	<0.05**
median age (range)	28.0 (15~50)	37.5 (13~70)	34.5 (18~54)	ns*	ns**
anti-dsDNA on admission (IU/ml)	40 (5~1501)	58 (5~472)	17 (5~2524)	ns*	ns**
albumin at discharge (g/dl)	3.3 (2.5~4.2)	3.6 (2.3~4.2)	3.4 (2.3~4.3)	ns*	ns**
IgG at discharge (mg/dl)	1264 (7.2~1976)	1671 (842~4100)	1345 (452~1893)	<0.05*	ns**
white blood cell count at discharge (/ $\mu$ l)	10400 (5300~15400)	6450 (2400~12800)	8750 (3900~12100)	<0.01*	ns**
number with infection during admission (case)	4	6	5	ns*	ns**
total prednisolone dose (mg)	2420 (750~7750)	345 (80~6230)	1745 (400~13956)	<0.01*	ns**
number with prednisolone-pulse (case)					
1 g for 3 days (%)	3 (23)	2 (9.1)	6 (27.3)	ns*	ns**
0.5 g for 3 days (%)	0 (0)	1 (4.5)	3 (13.6)	ns*	ns**
number with immunosuppressive drug*** (%)	0	0	15.4	ns*	ns**
number with preventive drugs (case)					
sulfamethoxazole-trimethoprim	5	1	6	<0.05	ns**
amphotericin-B syrup	0	1	5	ns*	ns**
body weight at discharge (kg)	53 (41~99)	51 (35~75)	50 (42~63)	ns*	ns**
duration of admission (day)	50 (12~86)	42 (3~97)	38 (11~124)	ns*	ns**

Numbers not otherwise specified represent median (range).

\*, group A v.s. group B; \*\*, group A v.s. group C; \*\*\*, cyclosporine-A; ns, not significant.

ered significant for all statistical analyses.

## Results

Table 1 depicts the patients' clinical and laboratory profiles, total dose of glucocorticoid used for the treatment during admission, and the number of cases for which an intravenous glucocorticoid-pulse, immunosuppressive drugs, and preventive treatment for opportunistic infections were employed. Although a statistically significant difference was observed in the gender ratio comparing groups A and C ( $p=0.05$ ), there was no significant difference in patient age among the three groups. There was no difference in the serum level of anti-dsDNA antibody and the serum complement level on admission among the groups. Patients in group A received a higher total dose of glucocorticoids during admission than those in group B ( $p<0.01$ ). The median level of serum IgG in group A was lower than that in group B ( $p=0.05$ ). Because this study is designed retrospectively, the number of CD4 T cell could not be measured. The white blood cell count at discharge in group B was significantly lower than that in group A ( $p<0.01$ ).

The target organ for which glucocorticoids were used for treatment is summarized in Table 2. The frequency of autoimmune thrombocytopenia was higher in group A than in group B ( $p=0.05$ ). Although skin and joint inflammation occurred at a higher frequency in group B than in group A, this difference did not reach statistical significance. As described in Table 1, no significant differences were observed among the three groups in serum albumin level and lymphocyte count at the time of discharge, the number of patients in which intravenous glucocorticoid-pulse and immunosuppressive drugs were introduced, the number of infectious events during admission, median body weight at discharge, or duration of admission.

Table 2. Organ Involvement and Conditions for Which Glucocorticoid Was Started to Treat.

conditions	group A (n=13)	group B (n=22)	group C (n=22)
mucocutaneous lesion	0 (0)	4 (18.2)	1 (4.5)
polyarthritis	0 (0)	5 (22.7)	0 (0)
serositis	1 (7.7)	4 (18.2)	2 (9.0)
nephritis	6 (46.2)	7 (31.8)	6 (27.3)
blood cell			
hemolytic anemia	1 (7.7)	0 (0)	2 (9.0)
thrombocytopenia*	3 (23.0)	0 (0)	2 (9)
pancytopenia	0 (0)	1 (4.5)	0 (0)
central nervous system	0 (0)	3 (13.6)	3 (13.6)
alveolar hemorrhage	1 (7.7)	1 (4.5)	1 (4.5)
interstitial pneumonia	1 (7.7)	1 (4.5)	1 (4.5)
lupus enteritis/cystitis	0 (0)	0 (0)	2 (9.0)
hemophagocytic syndrome	1 (7.7)	0 (0)	1 (4.5)
infection ( <i>P. jirovecii</i> )	0 (0)	0 (0)	1 (4.5)

Numbers represent case number with percentage in parentheses.

\*,  $p < 0.05$ , when group A is compared with group B.

A total of five, one and six patients received sulfamethoxazole-trimethoprim in groups A, B and C, respectively, to prevent *Pneumocystis jirovecii* pneumonia. One patient in group B and 5 in group C received amphotericin-B syrup to prevent fungal infection.

Two patients in group A were infected with herpes zoster and 3 in group C contracted herpes zoster, urinary tract infection and *Pneumocystis jirovecii* pneumonia (one each). No infections occurred in patients in group B. However, there were no statistically significant differences in the incidence comparing groups A and B ( $p > 0.05$ ), and groups A and C ( $p > 0.05$ ). There was no correlation between the incidence of infection and the dose of glucocorticoids at the time of discharge or the total dose of glucocorticoids used during admission. Multiple regression analysis revealed no cause and effect relationship between any infections and clinical and laboratory parameters examined in this study. There was no infection in patients receiving immunosuppressive drugs along with glucocorticoids in group C. The patient (Group C) who developed *Pneumocystis jirovecii* pneumonia did not receive sulfamethoxazole-trimethoprim for prophylaxis. The infectious diseases which occurred during admission were quite similar to those observed within two months after discharge, and herpes zoster and candidiasis were most frequent (Table 3).

## Discussion

According to current practice in Japan, the daily dose of glucocorticoids is tapered below 30 mg of prednisolone or its equivalent before discharge for fear that patients might contract serious infections at home if they receive more than 30 mg of prednisolone daily at the time of discharge. The situation is quite different in most other developed countries where the amount of glucocorticoids *per se* is not an indicator for hospital-discharge. We, therefore, examined, retrospectively, whether the amount of glucocorticoids at discharge has a relationship to the occurrence of infections shortly after discharge. A time frame of two

Table 3. Number and Types of Infection Occurred during Admission or after Discharge

infection	group A (n=13)	group B (n=22)	group C (n=22)
number during admission (%)	2 (15.4)	6 (27.3)	5 (22.7)
types (n)	oral candidiasis (1) herpes zoster (1)	oral candidiasis (1) esophageal candidiasis (1) urinary tract infection (3) acute gastroenteritis (1) bacterial meningitis (1) atypical pneumonia (1)	oral candidiasis (4) esophageal candidiasis (1) herpes zoster (1)
number after discharge (%)	2 (15.4)	0 (0)	3 (13.6)
types (n)	herpes zoster (2)		herpes zoster (1) urinary tract infection (1) pneumocystis pneumonia (1)

Numbers represent case number with percentage in parentheses.

months after discharge was arbitrarily used because we wanted to examine the direct and immediate effects of glucocorticoid dose *per se* on the development of subsequent infections.

Sakuma et al. reported that the incidence of infection is significantly higher in patients who are 52.9 years or older<sup>(3)</sup>. The average age of the patients who contracted infection was 28.6 in the present study, and the incidence of infection was not associated strongly with age.

There are several reports which correlate disease activity of SLE with the incidence of infections. Kim et al. showed that patients who died of infection had a higher serum level of anti-dsDNA antibody and lower serum level of complement than those who died of other causes<sup>(4)</sup>. Duffy et al. reported that patients with SLE disease activity index (SLEDAI) of 8 or more had a 2.7 times higher risk of developing infection than those with an SLEDAI less than 8<sup>(5)</sup>. Paton et al. reported a six to 10 times higher risk of developing infection during one month after recurrence of SLE<sup>(6)</sup>. Increased disease activity of SLE in the previous year is one of the risk factors for hospital-admission due to infection during the following year according to Petri et al<sup>(7)</sup>. In the present study, there was no significant difference in the serum level of anti-dsDNA antibody among the three groups studied. Because the level of anti-dsDNA antibody does not necessarily reflect disease activity of SLE, it remains to be determined whether SLEDAI and the total dose of glucocorticoids are independent risk factors for the development of infectious complications.

Serum albumin level fluctuates depending upon the inflammation in patients with SLE. Badsha et al. reported that, although not statistically significant, the risk of developing infection increases when the serum albumin level decreases below 2.0 g/dl<sup>(8)</sup>. In the present study, all the patients had serum albumin of higher than 2.0 g/dl and there was no inverse correlation between serum albumin level and the incidence of infection.

Serum concentration of IgG is an indicator of humoral immunity and it often decreases after glucocorticoids are introduced. Although the serum level of IgG at the time of discharge was lower in group A than that in group B, patients who developed infection after discharge had a comparable amount of IgG (804~1841 mg/dl). An inverse correlation was not found between serum IgG level and the incidence of infection in the present study.

Table 4. Initial Dosage of Glucocorticoid

	group A (n=13)	group B (n=22)	group C (n=22)
prednisolone or its equivalent in mg daily (range)	50 (40~80)	30 (15~60)	50 (35~120)

Numbers represent median with range in parentheses.

In group C, number represents dosage to which glucocorticoid was increased after admission.

There have been many debates about the influence of glucocorticoids on the development of infections. Moc et al. reported that, in two third of SLE patients who died of infection, daily prednisolone of more than 1mg/kg body weight at the start of treatment and the administration of intravenous glucocorticoid-pulse therapy are the most important risk factors of subsequent death<sup>(9)</sup>. On the other hand, there are several lines of evidence showing that the initial glucocorticoid amount or total glucocorticoid amount up to infection has no direct causal relationship with the development of infections<sup>(3)</sup>. According to Oh et al, the risk of infection increases after glucocorticoid therapy, but it is not dose-dependent<sup>(10)</sup>. It is also controversial whether intravenous glucocorticoid-pulse therapy has an impact on the occurrence of infectious complications. Paton et al. reported that the major infection-rate is increased up to 20 times by receiving an intravenous glucocorticoid-pulse within a month of therapy<sup>(6)</sup>, while Sakuma et al did not find such an infection-inducing effect of a glucocorticoid-pulse<sup>(3)</sup>. In the present study, there was no significant difference in the number of patients who received intravenous glucocorticoid-pulse therapy between groups A and B. The total dose of glucocorticoids given during admission was higher in group A than in group B, which might have made the serum level of IgG lower and white blood cell count higher in group A at discharge. However, there was no difference in the incidence of infections between the two groups. This might be due to the small number of the patients included in this study. Because patients in group C had a similar rate of infections compared to group A, the total dose of glucocorticoids administered did not have a strong correlation with the subsequent development of infections. This result is in accordance with the results reported by Sakuma et al<sup>(3)</sup>. Immunosuppressive drugs generally increase the risk of developing an infection. In the present study, however, cyclosporine-A was used in only 2 patients in group C, both of whom were infection-free.

Patients in group A had a higher incidence of autoimmune thrombocytopenia, while mucocutaneous and joint lesions occurred more frequently in group B. Group B had a case in which the initial prednisolone dose was less than 30 mg daily (Table 4). Less severe symptoms and organ involvement in group B were the reason for having tapered the prednisolone dose successfully to less than 30 mg daily before hospital-discharge; there was no difference in the duration of admission among the 3 groups.

Of those patients who develop an infection after therapy, more than 70% develop infections within a month after glucocorticoid-pulse according to Badsha et al<sup>(8)</sup>. Yuhara et al. reported that the average duration between glucocorticoid introduction and the development of infections was  $52 \pm 44$  days<sup>(1)</sup>. Immunosuppression induced by glucocorticoids becomes apparent one to two months after their administration. Thus, we searched for clinical data from medical records up to two months after hospital-discharge to examine the direct effects on infections of the glucocorticoid dose at hospital-discharge.

Infections observed after discharge were quite similar to those observed during admission, and there was no significant difference in the incidence of infection among the three groups; types of infection which occurred during admission were in agreement with those reported by Oh et al<sup>(10)</sup>.

In summary, the incidence of infectious complications in this study did not increase in patients with SLE taking more than 30 mg of prednisolone daily at the time of hospital-discharge compared to those taking less than 30 mg. The current practice in Japan of tapering the dose of prednisolone below 30 mg daily before hospital-discharge lacks rationale, and is not supported by the results of this study. The major limitations of this study are that this was a retrospective study and that it included a very small number of patients, which may not have statistical power to reveal any difference of the incidence among the three groups. Further studies are needed to make definitive conclusions. We must continue to be vigilant to identify infections in SLE patients taking prednisolone of any dose.

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