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Original Article

Risk Factors for Infection in Patients with Remitted Rheumatic Diseases Treated with Glucocorticoids

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It is well known that infection is one of the major causes of morbidity and mortality in rheumatic disease patients treated with high-dose glucocorticoids, especially in the early phase after achievement of disease remission. The aim of this study was to identify the risk factors for infection, with a focus on the dose of glucocorticoids administered, following the achievement of disease remission in rheumatic diseases patients. We retrospectively analyzed the medical records of rheumatic disease patients who had been treated with glucocorticoids. The primary endpoint was the incidence rate of infection during a period from 1 to 2 months after the commencement of treatment. From April 2006 to March 2010, 19 of 92 patients suffered from infection during the observation period. Age ≧ 65 yrs, presence of interstitial pneumonia, diagnosis of systemic vasculitis and serum creatinine level ≧ 2.0 mg/dl were found to be univariate predictors for infection. However, only the presence of interstitial pneumonia was an independent risk factor for infection (HR = 4.50, 95% CI = 1.65 to 14.44) by the Cox proportional hazard model. Even after achievement of clinical remission, careful observation is needed for patients with interstitial pneumonia, more so than for those receiving high-dose glucocorticoids.

Key words: infection, rheumatic disease, glucocorticoids, interstitial pneumonia, risk factors

The overall survival of patients with rheumatic diseases has improved, but infection is still one of the major causes of morbidity and mortality in these patients [1–4]. Previous studies have shown that infection-induced complications occurred in 14–45% of patients with systemic lupus erythematosus (SLE) [5, 6], and a review of 30 studies showed that the median rate of mortality due to infection was 5.2% (range, 1.2–36%) [7]. It has also been reported that the infection-related mortality rate in patients with rheumatoid arthritis (RA) was significantly higher than that in an age- and sex-matched healthy population [7–9].

The high rate of infectious complications in patients with rheumatic diseases is generally attributed to the activity of primary diseases and impairment of immune function due to the influence of immunosuppressive therapy [10]. The use of high-dose glucocorticoids and/or other immunosupressants increases the risk of infectious complications in patients with rheumatic diseases [5, 11–17]. Yuhara *et al.* reported that the average duration between the

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commencement of treatment with glucocorticoids and the occurrence of infections was 52 ± 44 (mean $\pm$ SD) days [18]. Therefore, careful observation and appropriate examinations for early detection of infection-related complications in patients with rheumatic diseases in the early phase after achievement of disease remission are clinically important.

The aim of the present study was to identify the risk factors for infection-induced complications, with a focus on the dose of glucocorticoids administered, following achievement of disease remission in patients with rheumatic diseases.

Patients and Methods

Patients. We retrospectively reviewed the medical records of adult patients with rheumatic disease who were admitted to Okayama University Hospital during the period from April 2006 to March 2010. The diagnostic criteria used for the patients included the 1997 revised criteria of the American College of Rheumatology (ACR) for SLE, the criteria of the ACR and Chapel Hill Consensus Conference (CHCC) for systemic vasculitis, the criteria of the ACR for RA, and the criteria of Bohan and Peter for polymyositis/dermatomyositis. Patients who had been treated with glucocorticoids at doses over 30 mg/day and/or other immunosupressants and who had achieved remission were enrolled in this study. Remission was defined as the state of absence of disease activity, including physical examination, radiologic study and biomarker levels from a blood or urine test at one month after the commencement of treatment. Since the purpose of our study was to investigate predictors for infection-related complications in the early phase after achievement of disease remission, patients who did not achieve remission and patients who received treatment with glucocorticoids in other hospitals before being transferred to our hospital were excluded from the study.

Risk factors for infection. Clinical variables for analysis included age, sex, body weight, smoking habit, Charlson score [19], vital organ involvement (heart, kidney and central nervous system) at baseline, presence of interstitial pneumonia at baseline, presence of diabetes mellitus at baseline, serum albumin level, serum creatinine level, serum IgG level, use of methylprednisolone pulse, doses of glucocorticoids, use of immunosupressants, and prophylactic use of sulfamethoxazole-trimethoprim. Data were extracted from the hospital charts of patients and recorded on study forms.

Study endpoint and definition of infection. The primary endpoint of the present study was the incidence rate of infection during a period of one month after achievement of disease remission (1 to 2 months after treatment began). Infection was confirmed by the existence of supportive clinical features, laboratory findings, positive cultures and radiographic evidence [12, 18]. When causal organisms were not identified, the diagnosis of infection was made on the basis of clinical findings in combination with improvement following antimicrobial therapy. Cytomegalovirus (CMV) infection was defined in the study as either detection of CMV pp65 antigenaemia in blood samples or compatible tissue biopsy findings. We defined an antigenaemia count of 10 per 1×10^5 PMNs as a cut-off to start prophylactic anti-viral therapy before the infection became too severe [20].

Statistical analysis. Statistical analysis was performed with JMP® 7 (SAS Institute Inc, Cary, NC, USA). Potential predictors of infection including variables with a possible relation to infection were studied by life table analysis using the Kaplan-Meier method. Survival (cumulative probability without infection) curves with the presence or absence of variables with a possible relation to infection were compared using the non-parametric log-rank test (univariate model). In order to identify independent predictors of infection, all variables with $p < 0.20$ in the univariate analysis were entered into multivariate analysis using the Cox proportional hazard model. The hazard ratio (HR) and 95% confidence intervals (CI) were calculated for each of the factors studied. Statistical significance was defined as a two-tailed p-value of less than 0.05.

Results

Study population. In the period from April 2006 to March 2010, 944 patients were admitted to Okayama University Hospital for treatment of active rheumatic diseases. Among them, 144 patients were treated with glucocorticoids at initial doses of over 30 mg/day. Of those patients, 92 were included in the cohort at the time of this study (Table 1). The 92

patients were comprised of 28 men (30.5%) and 64 women (69.5%). The mean (SD) age at diagnosis was 57.5 (19.4) years. The mean (SD) dose of glucocorticoids at the commencement of treatment was 41.5 (10.7) mg/dl. The mean (SD) dose of glucocorticoids at the time of achievement of disease remission (the starting point of our study) was 34.1 (9.2) mg/dl. The percentage of patients with each type of rheumatic disease is shown in Table 2. Systemic vasculitis was the most frequent rheumatic disease in our study.

Infectious complications in the study population. Nineteen patients (20.7%) suffered from at least one infection and were admitted to the hospital during a one-month period after achievement of disease remission. The localizations of infection are shown in Table 3. CMV infection was the most frequent infection in patients with rheumatic diseases in our study (10 of 19 patients), and ganciclovir was administered to these 10 patients. No patients died due to infections during the study period.

Univariate correlates of infection. The baseline of infected (or non-infected) patients with rheumatic diseases is shown in Table 4. Risk factors for infection were studied by univariate (log-rank test) analysis. Age $\geqq$ 65 yrs, a diagnosis of systemic vasculitis, the presence of interstitial pneumonia, and serum creatinine level $\geqq$ 2.0 mg/dl were found to be univariate predictors for infection. Use of glucocorticoids and immunosupressants was not associated with infection during the study period.

Multivariate correlation of infection. All variables with $p < 0.20$ in the univariate analysis were entered into the multivariate Cox proportional hazard model, and only the presence of interstitial pneumonia was an independent risk factor for predicting infection (HR = 4.50, 95%CI = 1.65 to 14.44) (Table 5). The remaining variables, including daily dose of glucocorticoids, were not associated with infection.

Discussion

Previous studies have shown that early mortality in patients with rheumatic diseases is predominantly related to the individual activity of disease progression, vital organ involvement and infectious complication [21]. Noel *et al.* reported that 35 (40%) of 87

Table 1 Patient profile regarding rheumatic diseases in our study

Subjects	n (%)
Sex (male/female)	28/64
Age, median (SD), yrs	57.5 (19.4)
Body height, median (SD), cm	155.9 (9.0)
Body weight, median (SD), kg	54.0 (12.3)
Mean dose of prednisolone at the commencement of treatment, median (SD), mg/day	41.7 (10.7)
Mean dose of prednisolone at the time of achievement of disease remission, median (SD), mg/day	34.1 (9.2)

Data are expressed as number and mean ± SD.

Table 2 Disease profile of the rheumatic diseases in our study

Diagnosed disease	n (%)
Systemic vasculitis	35 (38.0%)
Systemic lupus erythematosus	29 (31.5%)
Polymyositis/Dermatomyositis	11 (12.0%)
Rheumatoid arthritis	4 (4.3%)
Sjogren's syndrome	2 (2.2%)
Henoch-Schonlein purpura	1 (1.1%)
Relapsing polychondritis	1 (1.1%)
Systemic sclerosis	1 (1.1%)
Adult-onset Still's disease	1 (1.1%)
Others	7 (7.6%)

Data are expressed as number of patients (%).

Table 3 Characteristics of infectious complications in patients with rheumatic diseases

Infection site	n (%)
CMV viraemia	8 (42.1%)
Pulmonary	4 (21.1%)
Urinary tract	3 (15.8%)
CMV colitis	2 (10.5%)
Facial herpes zoster	1 (5.3%)
Herpesvirus ulceration of the cornea	1 (5.3%)

CMV, cytomegalovirus.
Data are expressed as number of infectious episodes (%).

Table 4 Univariate analysis of potential risk factors for infection in our cohort of 92 patients with rheumatic diseases

	Infected	Non-infected		
Variables	n = 19 (%)	n = 73 (%)	HR (95%CI)	*P*-value
Age ≧ 65 yrs	15 (78.9)	30 (41.1)	4.52 (1.64–15.86)	0.0027※
Sex (woman)	15 (78.9)	49 (67.1)	1.74 (0.63–6.11)	0.30
Smoking (yes)	5 (26.3)	19 (26.0)	1.12 (0.35–3.08)	0.84
Charlson score ≧ 1	8 (42.1)	22 (30.1)	1.64 (0.63–4.04)	0.30
Diagnosis of systemic vasculitis (yes)	11 (57.1)	24 (32.9)	2.56 (1.04–6.61)	0.042※
Diagnosis of systemic lupus erythematosus (yes)	3 (15.8)	26 (35.6)	0.37 (0.085–1.10)	0.077
Presence of interstitial pneumonia (yes)	14 (73.7)	21 (28.8)	5.35 (2.04–16.55)	0.00050※
Presence of diabetes mellitus (yes)	9 (47.4)	21 (28.8)	2.05 (0.81–5.08)	0.13
Serum creatinine level ≧ 2.0 mg/dl	7 (36.8)	9 (12.3)	3.10 (1.15–7.71)	0.027※
Serum albumin level < 3.0 mg/dl	11 (57.1)	25 (34.2)	2.32 (0.94–5.99)	0.068
Serum IgG level < 870 mg/dl	9 (47.4)	39 (53.4)	0.58 (0.031–3.07)	0.58
Use of methylprednisolone pulse (yes)	10 (52.6)	32 (43.8)	1.44 (0.58–3.63)	0.43
Dose of prednisolone ≧ 1 mg/kg/day at the commencement of treatment	11 (57.1)	53 (72.6)	0.76 (0.18–2.29)	0.65
Dose of prednisolone ≧ 1 mg/kg/day at the point of the achievement of disease remission	3 (15.8)	29 (39.7)	1.26 (0.070–6.12)	0.83
Use of immunosupressants (yes)	11 (57.1)	34 (46.6)	1.46 (0.59–3.78)	0.41
Prophylactic use of sulfamethoxazole-trimethoprim (yes)	8 (42.1)	41 (56.2)	0.61 (0.15–4.04)	0.55

HR, hazard ratio; CI, confidence interval.
Data are expressed as variables followed by number of patients, hazard ratio, 95% confidence interval and *p*-value.
※ $p < 0.05$

Table 5 Multivariate analysis (Cox proportional hazard model) for variables predicting infection in our cohort of 92 patients with rheumatic diseases

Variables	HR (95%CI)	*P*-value
Age ≧ 65 yrs	2.35 (0.77–8.73)	0.14
Presence of interstitial pneumonia	4.50 (1.65–14.44)	0.0028※
With heart involvement	1.24 (0.25–4.71)	0.77
Diagnosis of systemic vasculitis	1.41 (0.39–5.68)	0.61
Diagnosis of systemic lupus erythematosus	0.90 (0.17–4.10)	0.89
Presence of diabetes mellitus	1.09 (0.37–3.17)	0.88
Serum creatinine level ≧ 2.0 mg/dl	1.58 (0.50–4.65)	0.42
Serum albumin level < 3.0 mg/dl	1.75 (0.67–4.83)	0.25

HR, hazard ratio; CI, confidence interval.
Data are expressed as variables followed by hazard ratio, 95% confidence interval and *p*-value.
※ $p < 0.05$

patients with SLE had at least one infectious episode during a mean period of 9.4 years [5, 6]. Although our observation period was short, the rate of infectious complications in the present study was 20.7% (19 out of 92 patients). This high frequency of infection might be associated with the presence of CMV viraemia diagnosed on the basis of positive CMV antigenaemia, which is the most frequent infection in patients with rheumatic diseases.

CMV infection is a major cause of morbidity and mortality in immunocompromised hosts [20]. Prophylactic administration of ganciclovir for CMV antigenaemia-positive patients is an effective therapeutic strategy [22–25]. In addition, Takizawa *et al.* suggested that the threshold of the antigenaemia count is 5.6 per 1×10^5 PMNs, which predicts that patients are at a higher risk of being symptomatic, leading to a lethal condition [20]. Therefore, we continuously investigated CMV pp65 antigenaemia in blood samples for all of the patients enrolled in our study. In the present study, we diagnosed CMV infection by a threshold (or cut-off value) of an antigenaemia count of

over 10 per 1×10^5 PMNs. Our results indicated that patients with rheumatic diseases are at high risk for occult CMV infection even without any symptoms. The high frequency of positive CMV antigenaemia also leads to high susceptibility to various infections.

Various risk factors for infection, including decreasing renal function [26–29], hypoalbuminemia [30–33] and diabetes mellitus [34–37], have been reported. High-dose glucocorticoids have been reported to be the most critical risk factor for progression of infections [5, 38]. However, unlike in previous studies, infectious complications in the early phase after achievement of disease remission were not statistically associated with decreasing renal function, hypoalbuminemia, presence of diabetes mellitus or even the daily dose of glucocorticoids in the present study.

In Japan, considering the infectious complications of glucocorticoids after discharge, even patients who have achieved remission often remain in hospital until the daily dose of prednisolone is reduced to less than 30 mg. This traditional practice is generally accepted without clear evidence in Japan, but there is controversy over this practice [39]. However, our results indicated that the daily dose of glucocorticoids should not be the only factor for deciding when to discharge patients who have been treated with glucocorticoids and have achieved clinical remission.

Our multivariate analysis also showed that the presence of interstitial pneumonia is an approximately five-fold higher risk factor for infectious complications during the early period after achievement of disease remission. There has been no previous report regarding the association between the presence of interstitial pneumonia and infection in patients with rheumatic diseases. Our results also suggest that careful observation of patients with interstitial pneumonia is needed to reduce infection-related mortality, even after achievement of clinical remission.

This is the first report regarding clinical predictors of infection during the early phase after achievement of disease remission in patients with rheumatic diseases. Our findings indicate that careful observation and/or examination are needed, particularly for patients with interstitial pneumonia; such patients need more monitoring than those receiving high-dose glucocorticoids. Therefore, the daily dose of glucocorticoids does not appear to be a reliable factor for determining when to discharge patients. This study had several limitations. First, it was a retrospective study with selection bias and incomplete medical records. Second, the daily dose of glucocorticoids was set to 30 mg, and this dose could be changed. A future prospective study with a larger number of rheumatic disease patients is needed to confirm our findings and to determine the ideal and cost-beneficial duration for the hospitalization of patients with rheumatic diseases who are receiving high-dose glucocorticoids.

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