Glucocorticoid Therapy and the Risk of Infection in Patients With Newly Diagnosed Autoimmune Disease

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Abstract: Glucocorticoid (GC) therapy is associated with the risk of life-threatening adverse events in patients with autoimmune disease. To determine accurately the incidence and predictors of GC-related adverse events during initial GC treatment, we conducted a cohort study. Patients with autoimmune disease who were initially treated with GCs in Japan National Hospital Organization (NHO) hospitals were enrolled. Cox proportional hazard regression was used to determine the independent risks for GC-related serious adverse events and mortality. Survival was analyzed according to the Kaplan-Meier method and was assessed with the log-rank test.

The 604 patients had a total follow-up of 1105.8 person-years (mean, 1.9 year per patient). One hundred thirty-six patients had at least 1 infection with objective confirmation, and 71 patients had serious infections. Twenty-two cardiovascular events, 55 cases of diabetes, 30 fractures, 23 steroid psychosis events, and 4 avascular bone necrosis events occurred during the follow-up period. The incidence of serious infections was 114.8 (95% confidence interval, 95.7–136.6) per 1000 person-years. After adjustment for covariates, the following independent risk factors for serious infection were found: elderly age (hazard ratio [HR], 1.25/10-yr age increment; $p = 0.016$), presence of interstitial lung disease (HR, 2.01; $p = 0.011$), high-dose GC use (≥29.9 mg/d) (HR, 1.71; $p = 0.047$), and low performance status (Karnofsky score, HR, 0.98/1-score increment; $p = 0.002$). During the follow-up period, 73 patients died, 35 of whom died of infection. Similarly, elderly age, the presence of interstitial lung disease, and high-dose GC use were found to be significant independent risk factors for mortality. The incidence of serious and life-threatening infection was higher in patients with autoimmune disease who were initially treated with GCs. Although the primary diseases are important confounding factors, elderly age, male sex, the presence of interstitial lung diseases, high-dose GCs, and low performance status were shown to be risk factors for serious infection and mortality.

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Abbreviations: AE = adverse event, CI = confidence interval, CMV = cytomegalovirus, CT = computed tomography, GC = glucocorticoid, GI = gastrointestinal, HR = hazard ratio, IR = incidence rate, NHO = National Hospital Organization, RR = relative risk, SLE = systemic lupus erythematous, SOC = System Organ Class.

INTRODUCTION

Glucocorticoids (GCs) are commonly used as antiinflammatory and immunosuppressive therapies in autoimmune diseases.[3,6] Despite the considerable benefits of GCs in controlling autoimmune diseases, serious adverse events (AEs) have been observed.[29] These AEs vary from mild and self limited to major or life threatening.[21] It is generally considered that GC-related AEs are dose related, thus, the higher the initial and cumulative doses, the longer the course, and the greater the likelihood of significant side effects.[8,12] However, there remains considerable debate regarding the true incidence of these AEs.[7,23] The inability to differentiate AEs that are attributable to GCs from those occurring due to underlying diseases or other comorbidities confounds the identification of potential associations. Although there is emerging evidence concerning the AEs of lower- to moderate-dose GCs,[8,10,16,17,26,27] clear guidelines on the use of GCs are lacking. Comorbid conditions and risk factors for serious AEs of GCs should be identified before initiating GC therapy. To better define the toxicity of GCs, we addressed the question of whether the dose of GCs can cause an increased incidence of serious GC-associated AEs in patients with autoimmune disease. We undertook a multicenter cohort study of GC treatments of patients with newly diagnosed autoimmune disease, and investigated the incidence of GC-related AEs in the Japan National Hospital Organization (NHO)-EBM study group.

METHODS

Patients and Study Design

We conducted a multicenter cohort study following patients with newly diagnosed autoimmune diseases in NHO hospitals (total 55 hospitals). Patients were eligible if they were initially treated with GCs against the following autoimmune diseases, which were newly diagnosed (within the 4 weeks prior to entry) by the established criteria. The cohort start date was defined as the time of initiation of the first GC prescription. The autoimmune diseases registered in this study were rheumatic disease, systemic lupus erythematous (SLE), mixed connective tissue disease, polymyositis, dermatomyositis, vasculitis, Behçet disease, systemic scleroderma, adult-onset Still disease, Sjögren syndrome, rheumatoid arthritis, autoimmune bullous diseases, and anaphylactoid purpura. Neurologic diseases included multiple sclerosis,

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myasthenia gravis, and chronic inflammatory demyelinating polyradiculoneuropathy. The following gastro-hepatobiliary diseases were included: ulcerative colitis, autoimmune hepatitis, autoimmune pancreatitis, and primary biliary cirrhosis. Interstitial lung diseases included idiopathic interstitial pneumonia and collagen vascular disease preceded by interstitial pneumonia. The primary glomerular diseases included were rapidly progressive glomerulonephritis, chronic glomerulonephritis, and nephrotic syndrome. Patients were excluded from the study if they fit any of the following criteria: 1) clinically unstable cardiovascular disease, 2) age <16 years at study entry, 3) previous use of steroids to treat other diseases <6 months before cohort entry, or 4) other pre-existing autoimmune diseases. A total of 604 patients with newly diagnosed autoimmune disease were enrolled. These patients were enrolled between April 1, 2007, and March 31, 2008, and were regularly followed for the observation period that ended on March 31, 2009. The study was approved by the ethical committees of the NHO central institutional review board.

Data Collection

Data from all participating physicians were entered into the J-NHOSAC database at the data center of International Medical Center of Japan (Shinjuku, Tokyo) via the Hospnet Internet system. Information was collected during the study follow-up period regarding the development of the following AEs: fracture, avascular bone necrosis, diabetes, hyperlipidemia, infections, cardiovascular events (myocardial infarction, pulmonary emboli, heart failure, arrhythmia, and cerebrovascular accidents], gastrointestinal (GI) bleeding, and death. Physicians assessed AEs and serious AEs according to accepted guidelines. Diagnosis of pulmonary emboli required that a contrast-enhanced computed tomography (CT) scan of the chest or ventilation/perfusion scintigraphy indicated the presence of an embolism. Diagnosis of avascular osteonecrosis was based on the 2011 revised criteria for classification of osteonecrosis from the Japanese Ministry of Health, Labor, and Welfare.[24] Osteonecrosis due to primary joint diseases, such as osteoarthritis or septic arthritis, was excluded. For quality assurance, the participating physicians were provided with the definitions of AEs and serious AEs. These definitions were included in the case report form at each visit.

Data on Study Entry

The past comorbid conditions of each of the patients were reviewed by each of the principal physicians. In addition, the incidences of specific conditions, including pre-existing pulmonary tuberculosis, hepatitis viral infection (hepatitis B virus, hepatitis C virus), diabetes, hyperlipidemia, arrhythmia, and performance status (Karnofsky score) were assessed. The physicians also provided information on smoking or drinking habits and history of tuberculosis. At entry, patients underwent chest X-ray and were screened for hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus antibodies.

Medications

Every day of steroid use in each patient was recorded in the J-NHOSAC database, and average and cumulative steroid doses were calculated. Information on concomitant medications was recorded and hospitalizations for any reason were documented. Details of GCs, immunosuppressive agents, and biological agents were recorded at each visit, including the route of administration and the dose. In addition, we recorded the use of other medications, including prophylaxis agents, antibiotics, cardiovascular drugs, immunomodulating drugs, disease-modifying antirheumatic drugs (DMARDs), anti-osteoporosis agents, and nonsteroidal antiinflammatory drugs (NSAIDs). We categorized GC exposure according to the average daily dose throughout the follow-up period for each patient. We calculated "dose equivalents" of prednisolone as follows: 1 mg of prednisolone = 5 mg of cortisone = 4 mg of hydrocortisone = 1 mg of prednisone = 0.8 mg of triamcinolone = 0.8 mg of methylprednisolone = 0.15 mg of dexamethasone = 0.15 mg of betamethasone.[5]

Outcome Variables

At the start of the study, standardized lists were used to document AEs, which were classified using the System Organ Class (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA, v. 11.1; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH], Geneva, Switzerland). All physicians documented episodes of infection requiring medical care and death certificates and the causes of deaths that occurred during the follow-up period. Serious infections occurring during the observation periods were counted. Serious infections (≥grade 3, defined by Common Terminology Criteria for Adverse Events v. 3.0; National Cancer Institute, National Institutes of Health, Bethesda, MD) were defined as life threatening, requiring hospitalization and/or intravenous antibiotic therapy, or leading to significant disability/incapacity.[2] Fungal infection was defined as a "proven" or "possible" invasive fungal infection according to the criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group.[1] Cytomegalovirus (CMV) infection was defined as CMV end-organ disease,[20] in which the signs and symptoms of affected organs (pneumonia, GI disease, hepatitis) plus CMV antigenemia were present. Diagnosis of CMV antigenemia was defined by a positive CMV PP65 antigenemia assay. If a serious infection was identified, verification was sought by the patient's physician. If not already provided, additional information about all serious infections was required, including causative organism, treatment, and outcomes. Telephone interviews concerning the health assessment and presence of GC-related AEs were conducted with a few patients who were moved or transferred to another hospital at the end of the cohort study. The overall outcome was not available for 17 patients (2.8%) at the end of the study. In statistical analyses, we excluded the participants without final outcome data.

Statistical Analysis

The chi-square test for categorical variables and the Mann-Whitney test for continuous variables were used to calculate statistical differences between the 2 groups. The incidence rate (IR) (per 1000 person-years) was calculated with 95% confidence interval (CI).[13] Cox proportional hazard models were used to estimate the risk of serious infections and mortality. In Cox proportional hazard models, we identified the best subset of explanatory variables by all combinations as variable selection in terms of score statistics. The variables included in the analysis were age, sex, types of primary autoimmune disease, comorbidities (diabetes, renal diseases, cardiovascular diseases, and interstitial lung diseases), medications (average dose of GC, use of immunosuppressive agents), and performance status or laboratory data on entry (Karnofsky score, serum albumin, serum IgG, lymphocyte counts). The analysis was conducted using SAS v. 9.1 software (SAS Institute, Cary, NC). Two-sided p values < 0.05 were considered statistically significant.

TABLE 1. Characteristics of 604 Patients With Autoimmune Diseases

Characteristic	No.	(%)
Demographics		
Age, yr (mean±SD)	59.5±16.9	
Sex, male/female	246/358	
Primary disease		
Rheumatic disease	313	(51.8)
Systemic lupus erythematous	38	(6.3)
Mixed connective tissue disease	10	(1.7)
Polymyositis	18	(3.0)
Dermatomyositis	16	(2.6)
Vasculitis	46	(7.6)
Behçet disease	5	(0.8)
Systemic sclerosis	12	(2.0)
Adult-onset Still disease	13	(2.2)
Sjögren syndrome	6	(1.0)
Rheumatoid arthritis	136	(22.5)
Autoimmune bullous diseases	7	(1.2)
Anaphylactoid purpura	6	(1.0)
Neurologic disease	25	(4.1)
Multiple sclerosis	4	(0.7)
Myasthenia gravis	20	(3.3)
Chronic inflammatory demyelinating polyneuropathy	1	(0.2)
Gastro-hepatobiliary disease	79	(13.1)
Ulcerative colitis	20	(3.3)
Autoimmune hepatitis	51	(8.4)
Autoimmune pancreatitis	4	(0.7)
Primary biliary cirrhosis	4	(0.7)
Interstitial lung disease	133	(22.0)
Primary glomerular disease	54	(8.9)
Rapidly progressive glomerulonephritis	7	(1.2)
Chronic glomerulonephritis	18	(3.0)
Nephrotic syndrome	29	(4.8)
Total	604	(100)
Antimicrobial prophylaxis		
Isoniazid	69	(11.4)
Trimethoprim-sulfamethoxazole	138	(22.8)
Treatment		
Dose of prednisolone (mean±SD) (First 1 mo)	50.4±63.1 mg/d	
Immunosuppressive treatments	283	(46.9)

*Data are expressed as mean ± standard deviation or number (%).

Propensity analysis was also performed regarding the probability of high-dose GC use (≥30 mg/d). The propensity for high-dose corticosteroid use was determined without regard to outcome. For each patient, a propensity score indicating the likelihood of having high-dose GCs prescribed was calculated by logistic regression analysis and included 25 covariates: age, sex and primary autoimmune diseases, previous cerebrovascular disease, ischemic heart disease, diabetes, hyperlipidemia, proteinuria, macrohematuria, previous autoimmune diseases, and performance status (Karnofsky score). The patients were stratified into 5 groups according to the propensity score, and the effect of high-dose GC (≥30 mg/d) on mortality was analyzed using the log-rank test.

RESULTS

Demographic Data

This cohort study comprised 604 patients, of whom 59.3% were female. The mean age at entry, which was within 4 weeks of the first diagnosis of autoimmune diseases, was 59.1 ± 16.9 years. The total follow-up time was 1105.8 person-years, and the mean follow-up was 22.4 months. The distribution of primary autoimmune diseases and general characteristics are shown in Table 1. All patients received GCs at entry, and the mean GC dose for the first month was 50.4 ± 63.1 mg/d. Table 2 lists variables examined at the time of cohort initiation, including performance status, laboratory data, and comorbidities. During the follow-up period, 46.9% (283) of patients had been treated with either an immunosuppressive or biological agent (see Table 1).

Types and Incidence of AEs

Overall, 434 AEs occurred (Table 3). Based on the AE categories classified using the SOC allocation, infections were the most common, followed by metabolic disease, fractures, steroid psychosis, and cardiovascular events.

TABLE 2. Clinical and Laboratory Findings on Entry

Feature	Value*
Height (cm)	157.8±8.8
BW (kg)	55.9±10.9
Karnofsky score	79.4±18.3
Laboratory data	
WBC (/μL)	7764.9±3871.9
Lymphocyte count (/μL)	1530.8±714.2
Serum albumin (mg/dL)	3.4±0.8
Serum IgG (mg/dL)	1851.3±855.8
Serum creatinine (mg/dL)	0.79±0.67
Cigarette smoking	
Never smoker	421 (69.7)
Past smoker	122 (20.2)
Current smoker	59 (9.8)
Previous TB	34 (5.6)
Comorbidity	
Interstitial lung disease	166 (27.5)
Cardiovascular disease	
Cerebrovascular accident	20 (3.3)
Ischemic heart disease	25 (4.1)
Hypertension	128 (21.2)
Arrhythmia	19 (3.1)
Other	12 (2.0)
Metabolic disease	
Hyperlipidemia	149 (24.7)
Hyperuricemia	44 (7.3)
Diabetes	65 (10.8)
Chronic kidney disease	32 (5.3)

Abbreviations: IgG = immunoglobulin G, WBC = white blood cells.
*Data are expressed number (%) or mean ± SD.

TABLE 3. Categories of Adverse Events (AE) by System Organ Class Allocation

System Organ Class Allocation	Total No. of Events	Incidence Rate (/1000 person–years)	95% CI
Infections	227	205.3	179.4–233.8
Bacterial infection	117	105.8	87.5–12.8
Fungal infection	36	32.6	22.8–45.1
TB	2	1.8	0.2–6.5
Nontuberculous mycobacterium	1	0.9	0.0–5.0
CMV infection	25	22.6	14.6–33.4
Pneumocystis jirovecii pneumonia	8	7.2	3.1–14.3
Other	38	34.4	24.3–47.2
(Serious infection)	(127)	114.8	95.7–136.6
Cardiac disorders	10	9.0	8.3–23.5
Heart failure	5	4.5	1.5–10.6
Arrhythmia	4	3.6	1.0–9.3
Myocardial infarction	1	0.9	0.0–5.0
Vascular disorders	12	10.9	2.0–11.8
Cerebral vascular disorder	6	5.4	2.0–11.8
Pulmonary emboli	3	2.7	0.6–7.9
Deep vein thrombosis	3	2.7	0.6–7.9
Musculoskeletal and connective tissue disorders	34	30.7	21.3–43.0
Fracture	30	27.1	18.3–38.7
Avascular osteonecrosis	4	3.6	1.0–9.3
Metabolism and nutrition disorders	79	71.4	56.6–89.0
Diabetes	55	49.7	37.5–64.7
Hyperlipidemia	24	21.7	13.9–32.3
Nervous system disorders	23	20.8	13.2–31.2
Steroid psychosis	23	20.8	13.2–31.2
GI disorders	7	6.3	2.5–13.0
Esophageal ulcer	1	0.9	0.0–5.0
Gastroduodenal ulcer	4	3.6	1.0–9.3
GI bleeding	2	1.8	0.2–6.5
Other	42	38.0	27.4–51.3
Total	434	392.5	

Predictors of Serious Infections

A total of 136 patients experienced at least 1 infectious AE, 43 of whom experienced 2 or more infections. A significant number of the infections were opportunistic infections, including *Pneumocystis jirovecii* pneumonia (IR, 7.2 events/1000 person-years), fungal infection (IR, 32.6 events/1000 person-years), and CMV infection (IR, 22.6 events/1000 person-years), in addition to bacterial infections. There were 2 cases of *Mycobacterium tuberculosis* and 1 case of nontuberculosis mycobacterium (see Table 3). The crude IR for tuberculosis was 1.8 events/1000 person-years, and for nontuberculosis mycobacterium it was 0.9 events/1000 person-years. A total of 71 patients had serious infections; the crude IR of serious infections was 114.8 events/1000 person-years. The cumulative incidence curve of infectious AEs increased steadily from the cohort start, and close to 30% of patients experienced their first AEs within 3 months after the start of GC treatment. Average daily doses of GCs were time-dependent categorical variables. Therefore, the average daily dose for the first 1 month was used for analysis.

Univariate analysis revealed several statistically significant predictors for increased risk of infection (Table 4). The factors that were independently associated with an increase in the risk of serious infections in multivariate models are shown in Table 5. Factors associated with serious infections included increasing age (hazard ratio [HR], 1.25/10-yr age increment; 95% CI, 1.04–1.50), male sex (HR, 1.72; 95% CI, 1.06–2.79), the presence of interstitial lung disease (HR, 2.01; 95% CI, 1.18–2.89), low performance status (Karnofsky score, HR, 0.98/1-score increment; 95% CI, 0.97–0.99; $p = 0.002$), and high-dose GCs (≥29.88 mg/d) (HR, 1.71; 95% CI, 1.01–2.89).

Fatal Outcome

During the follow-up period, 73 patients died. The most common cause of death was infection, followed by interstitial pneumonia, respiratory failure, and cardiovascular events (Table 6). Factors that were independently associated with risk for mortality in Cox multivariate regression analysis are shown in Table 7. Factors associated with mortality included increasing age (HR, 1.62/10-yr age increment; 95% CI, 1.31–3.41), male sex (HR, 2.12; 95% CI, 1.31–3.41), presence of interstitial lung disease (HR, 2.55; 95% CI, 1.53–4.27), low performance status (Karnofsky score, HR, 0.98/1-score increment; 95% CI, 0.97–0.99; $p = 0.001$), and high-dose GCs (HR, 2.19; 95% CI, 1.35–3.58).

In Kaplan-Meier survival curves stratified by the categorical ranges of the average prednisolone dose, a statistically significant difference was observed between patients receiving high-dose GCs (≥29.9 mg/d) and those receiving low-dose GCs (<12.7 mg/d) ($p < 0.0001$, log-rank test, Figure 1A). There was a significant difference in survival between patients receiving steroid pulse therapy (>500 mg of intravenous methylprednisolone) and those without steroid pulse therapy (Figure 1B). The overall survival was estimated for each category of autoimmune disease. The survival rate was comparable among patients with rheumatic disease and those with neurologic disease, primary glomerular disease, and gastro-hepatobiliary diseases. However, there was a significant difference in survival between patients with rheumatic disease and interstitial lung disease (Figure 2A). Similarly, the presence of interstitial lung disease significantly affected patient survival ($p < 0.0001$, log-rank test) (Figure 2B).

Propensity Score Analysis

Because high-dose GC treatment is reserved for severe autoimmune diseases, incomplete adjustment for underlying diseases or their disease activity would bias these results toward higher mortality rates, assuming that severe autoimmune diseases are associated with a higher mortality rate. Therefore, we used propensity score analysis[30] to address the effect of covariate imbalance between patients receiving high-dose GCs (≥30 mg/d) and those not receiving high-dose GCs (<30 mg/d). In the propensity analysis, variables that correlated strongly with prescription of high-dose GCs were underlying primary autoimmune diseases (rheumatoid arthritis, systemic sclerosis, SLE, vasculitis, primary Sjögren syndrome, dermatomyositis, polymyositis, ulcerative colitis, and myasthenia gravis), presence of comorbidities

TABLE 4. Risk Factors for Serious Infection in Patients Treated With GCs

Characteristic	Patients With Serious Infections (n=71)	Patients Without Serious Infections (n=516)	P†
Age, yr	66.5±16.3	58.7±16.6	<0.0001
Sex, male/female	41/30	196/320	0.001
Primary disease			
Rheumatic disease	28 (39.4)	274 (53.1)	0.031
Neurologic disease	2 (2.8)	23 (4.5)	0.398
Gastro-hepatobiliary disease	6 (8.5)	71 (13.8)	0.214
Interstitial pneumonia	34 (47.9)	98 (19.0)	<0.0001
Primary glomerular disease	1 (1.4)	50 (9.7)	0.020
Medication			
Mean dose of prednisolone (mg/d)	59.2±58.8	48.8±62.7	0.004
Immunosuppressive treatment	38 (53.5)	186 (36.0)	0.004
Clinical parameters on entry			
Karnofsky score	69.9±20.5	80.8±17.7	<0.0001
WBC (/μL)	7838.7±3303.6	7761.3±3980.3	0.417
Lymphocyte count (/μL)	1654.9±988.3	1517.1±669.7	0.794
Serum albumin (mg/dL)	3.40±0.69	3.45±0.77	0.470
Serum IgG (mg/dL)	2055.5±817.7	1828.7±864.2	0.024
Serum creatinine (mg/dL)	0.84±0.90	0.77±0.58	0.409

Abbreviations: See previous tables.Data are expressed as number (%) or mean ± SD. Patients (n=17) without final outcome data were excluded in this analysis.

†P values were calculated with chi-square test for qualitative data and Mann-Whitney test for quantitative data.

(interstitial lung disease, diabetes, hyperlipidemia, and ischemic heart disease), and presence of proteinuria and macrohematuria. The likelihood of receiving high-dose GCs for each patient was modeled using logistic regression conditioned on covariate values for each individual. Effect of high-dose GCs on survival in each of 5 strata of equal size was analyzed on the basis of the propensity score (Table 8). In the log-rank test, the difference in time to death was statistically significant (HR, 2.07; 95% CI, 1.07–4.00; p = 0.029) between patients receiving or not receiving high-dose GCs, suggesting that patients receiving high-dose GCs had a mortality risk even after adjustment for treatment selection bias. However, in the individual propensity score quintiles, the adjusted relative risk (RR) for mortality did not reach statistical significance except in the lowest propensity score group (quintile 1).

TABLE 5. Predictors of Serious Infection Identified in the Multivariate Model*

Predictor	Hazard Ratio	95% CI	P
Demographic variables			
Age/10-year increment	1.25	1.04–1.50	0.016
Male sex	1.72	1.06–2.79	0.028
Comorbidities			
Interstitial lung disease	2.01	1.18–3.43	0.011
Performance status			
Karnofsky score/1-score increment	0.98	0.97–0.99	0.002
Medications			
High-dose GCs (≧29.9 mg/d)	1.71	1.01–2.89	0.047
Use of immunosuppressant	1.35	0.79–2.32	0.270

*The hazard ratios for serious infection were estimated using the Cox proportional hazard model after adjusting for the confounding factors. Cox-proportional hazard models included 12 covariates: age, sex, types of primary autoimmune disease, comorbidities (diabetes, renal diseases, cardiovascular diseases and interstitial lung diseases), medications (average dose of GCs, the use of immunosuppressive agents) and performance status or laboratory data on entry (Karnofsky score, serum albumin, serum IgG, lymphocyte counts).

DISCUSSION

Glucocorticoids (GCs) are among the most indispensable therapeutic agents used against autoimmune diseases.[4] Despite the considerable benefits of GCs in controlling autoimmune diseases, various AEs are well established.[21] However, there is little evidence concerning their incidence, dose-dependence, and true impact on survival. Several large retrospective reviews have reported that long-term GC use was a significant predictor of potentially serious AEs.[15] Considering the diversity of their mechanisms and sites of action, GCs can cause a wide array of AEs.[18] One population-based study showed that patients who were exposed to dosages of GCs greater than the equivalent of 7.5 mg of prednisolone per day for 1–5 years had

TABLE 6. Causes of Death

Cause	No. (%) (n=73)
Infection	35 (47.9)
(Opportunistic infection)	10 (13.7)
Interstitial pneumonia	11 (15.1)
Respiratory failure	9 (12.3)
Cancer	5 (6.8)
Cardiovascular event	5 (6.8)
Renal failure	3 (4.1)
Hepatic failure	2 (2.7)
Other	3 (4.1)

TABLE 7. Predictors of Mortality Identified in the Multivariate Model*

Predictor	Hazard Ratio	95% CI	P
Demographic variables			
Age/10-year increment	1.62	1.32–2.01	<0.0001
Male sex	2.12	1.31–3.41	0.0021
Comorbidities			
Interstitial lung disease	2.55	1.53–4.27	0.0004
Performance status			
Karnofsky score/1-score increment	0.98	0.97–0.99	0.001
Medications			
High-dose GCs (≧29.9 mg/d)	2.19	1.35–3.58	0.0016
Use of immunosuppressant	1.58	0.94–2.57	0.0859

*The hazard ratios for mortality were estimated using the Cox proportional hazard model after adjusting for the confounding factors. Cox-proportional hazard models included 12 covariates: age, sex, types of primary autoimmune disease, comorbidities (diabetes, renal diseases, cardiovascular diseases and interstitial lung diseases), medications (average dose of GCs, use of immunosuppressive agents) and performance status or laboratory data on entry (Karnofsky score, serum albumin, serum IgG, lymphocyte counts).

substantially higher rates of all cardiovascular diseases.[35] The incidence of cardiovascular events was reported to be 23.9 per 1000 person-years in the group exposed to GCs.[35] In the current cohort study with a mean follow-up of 1.9 years, the incidence of cardiovascular events in patients with autoimmune disease treated with GCs was 19.9 per 1000 person-years, which is consistent with that previous study.[35] However, the overall incidence of infections was 205.3 per 1000 person-years, which was substantially higher compared with the overall incidence of cardiovascular events. Furthermore, some of these infections, including opportunistic infections, were serious enough to contribute to a fatal outcome. Opportunistic infections have been reported with corticosteroid use in conjunction with other risk factors, including immunosuppressive therapy.[14,19,31,32] Data from the current study indicated that the actual incidence of fungal infections was 32.6 persons/1000 person-years in patients treated initially with GCs; CMV was 22.6 persons; *Mycobacterium tuberculosis* was 1.8 persons; nontuberculosis mycobacterium was 0.9 persons; and *Pneumocystis jirovecii* pneumonia was 7.2 persons/1000 person-years in patients treated initially with GCs. The identified risk factors for serious infection included male sex, increasing age, interstitial lung disease, low performance status, and an initial high dose of GCs (≥29.9 mg/d). Some of these factors (sex, increasing age, and performance status) have already been demonstrated to be risks for infection or mortality in patients treated with GCs.[11,25,28]

Moderate- to high-dose GC therapy leads to an increased risk of infection.[9] The risk of infection increases with the dose and duration of treatment, and tends to remain low in patients exposed to low doses, even with a high cumulative dosage.[22,34] The strongest evidence for increased risk of infection from GCs is meta-analysis of 71 controlled clinical trials in which patients were treated with corticosteroid or placebo.[33] Stuck et al[33] found a significant risk of lethal and nonlethal infections in patients receiving systemic corticosteroid (RR, 1.6; 95% CI, 1.3–1.9). This association was dose-dependent with no increased risk observed in patients receiving ≤10 mg of prednisolone a day or a cumulative dosage ≤700 mg. The RR of infection increased with a mean daily dosage of steroid (RR, 1.3; 95% CI, 1.0–1.6) of <20 mg prednisolone, RR of 2.1 (95% CI, 1.3–3.6) with a daily dose of 20–40 mg prednisolone, and RR of 2.1 (95% CI, 1.6–2.9) with a daily dose >40 mg prednisolone.[33] Our results are in overall agreement with this previous meta-analysis in that risk of serious infections increased in a dose-dependent manner related to GC usage. When underlying disease was considered, Stuck et al[33] detected no significant increase in the incidence of infection in those patients with pulmonary diseases, which were mainly chronic obstructive pulmonary diseases. These results are in contrast with results from our study, in which the presence of interstitial lung disease was an independent risk factor for serious infections and mortality. It is likely that differences between the types of pulmonary disease may contribute to the differential outcome between our study and the previous meta-analysis.

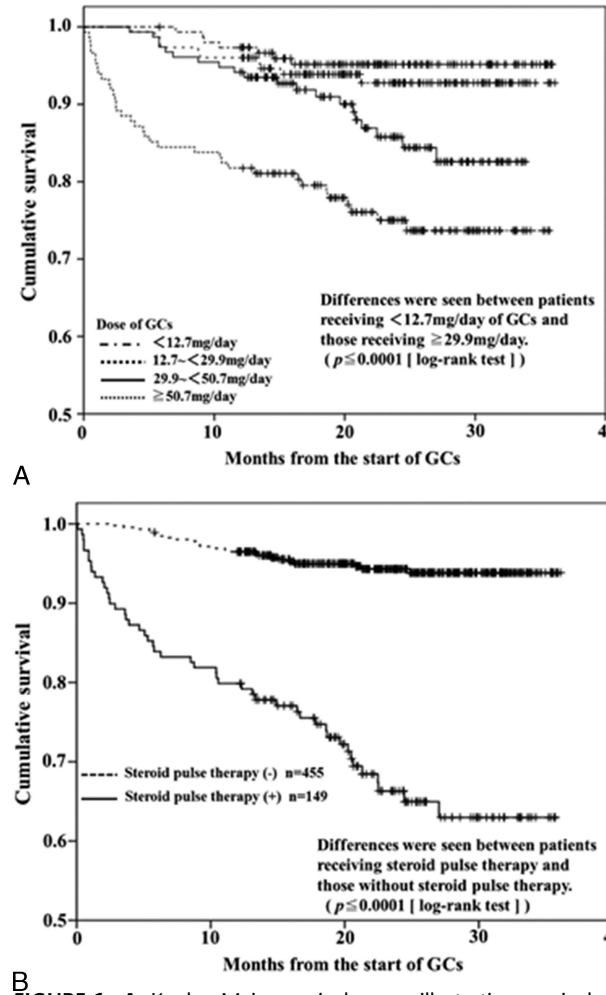
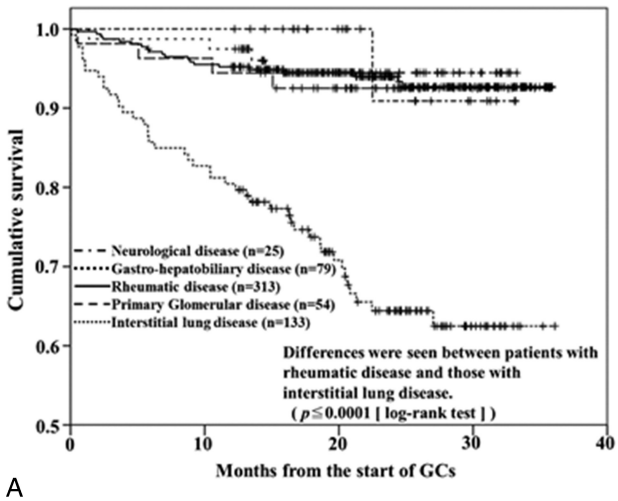


FIGURE 1. A, Kaplan-Meier survival curves illustrating survival distribution. Curves are stratified by average prednisolone dose (ranges shown in lower left corner). Statistically significant differences were observed between patients receiving high-dose GCs (≥29.88 mg/d) and those receiving low-dose GCs (<12.7 mg/d). **B,** Kaplan-Meier survival curves stratified by the presence or absence of steroid pulse therapy (>500 mg/d of intravenous methylprednisolone). There was a significant difference in survival between patients receiving and those not receiving steroid pulse therapy (p < 0.0001, log-rank test).



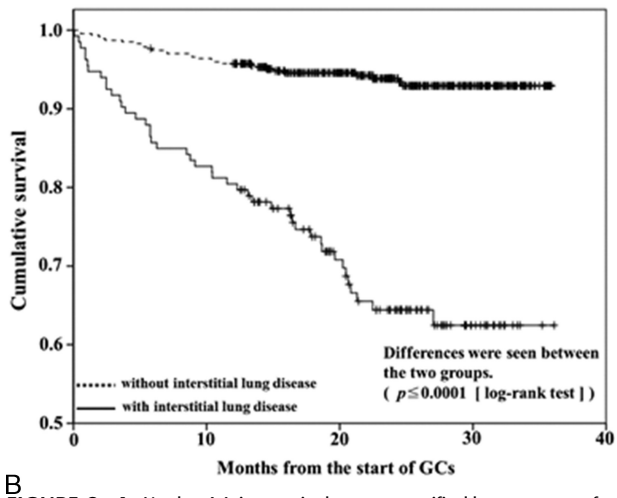


FIGURE 2. A, Kaplan-Meier survival curves stratified by category of autoimmune disease. The survival rate was comparable among patients with rheumatic disease and those with neurologic disease, renal disease, and gastro-hepatobiliary disease. However, there was a significant difference in survival between patients with rheumatic disease and those with interstitial lung disease ($p < 0.0001$, log-rank test). **B**, Kaplan-Meier survival curves stratified by the presence or absence of interstitial lung disease. Statistically significant differences were observed between patients with or without interstitial lung disease ($p < 0.0001$, log-rank test).

Although high-dose GCs have been demonstrated to be a causal risk factor for mortality, a key question of our cohort study was whether the association of high-dose GC use with mortality reflects the effects of GCs or an association with the underlying diseases for which high-dose GCs were prescribed. The difference in mortality by high-dose GC treatments needs to be analyzed by including all available confounding factors into the models. Statistical adjustment through propensity scoring, including types of diseases and activity, may partly resolve these problems.[30] We found an association between high-dose GCs and mortality in propensity score-based stratification groups. However, our results also indicated that the association between high-dose GC exposure and mortality tends to be weak in high propensity scoring groups. These data suggest that the association between high-dose GCs and mortality may not be prominent in patients with autoimmune disease for which high-dose GCs are necessary.

One major limitation of the present study is that nonrandom allocation of subjects would confound our results. Therefore, some degree of residual confounding was inevitable, bringing with it the possibility that we were not able to distinguish the effects of GCs versus disease specificity against the risk of infection or mortality. Second, our observational study had an important and inherent treatment bias for confounding by various autoimmune diseases, and the clinical assessment of disease activity was not complete. Patients receiving high-dose GCs were most likely to have the worst disease and high disease activity. Confounding factors were adjusted by multivariate Cox regression analysis, and the results were not contradictory to those obtained with propensity score analysis. However, it must be acknowledged that observational studies can only partially control for confounding factors. The strengths of the current study include the high follow-up rate. We focused on serious AEs that contribute to morbidity or mortality. Thus, we could completely survey detailed clinical data from participating doctors directly using the Internet throughout the follow-up period. Furthermore, the percentage of loss to follow-up (2.8%) was very low.

In conclusion, initial GC therapy against autoimmune disease was associated with an increased incidence of AEs, including infection. Predictors of serious infection or mortality include male sex, increasing age, comorbidities (interstitial lung disease), low performance status, and initial high dose of GCs (≥29.9 mg/d). These results advance our understanding of the relationship between GC therapy and serious AEs, and may help to prospectively identify high-risk patients.

TABLE 8. Effects of High-Dose Corticosteroid on Mortality, Stratification by Propensity Score*

	No. of Patients		Death No. (%)		Hazard Ratio (95% CI)	P
	Low Dose†	High Dose‡	Low Dose†	High Dose‡		
Propensity score Q1	146	4	4 (2.7)	2 (50.0)	29.246 (5.223–163.753)	<0.0001
Propensity score Q2	35	14	1 (2.9)	1 (7.1)	2.594 (0.162–41.497)	0.4841
Propensity score Q3	57	67	2 (3.5)	8 (11.9)	3.663 (0.778–17.257)	0.0785
Propensity score Q4	47	105	6 (12.8)	21 (20.0)	1.596 (0.644–3.957)	0.3080
Propensity score Q5	18	111	4 (22.2)	24 (21.6)	1.028 (0.356–2.963)	0.9593
Propensity score Q1–Q5	303	301	17 (5.6)	56 (18.6)	2.066 (1.067–4.000)	0.0287

*Propensity scores indicating the likelihood of prescribing high-dose GCs (≧30 mg/d) were calculated by logistic regression analysis including 25 covariates (see Methods section). The effect of high-dose GCs on mortality was analyzed using the log-rank test, and hazard ratios for mortality were estimated using the Cox proportional hazard model.

†Low dose <30 mg/d.

‡High dose ≧30 mg/d.

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