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Original Article

The efficacy and safety of reduced-dose sulfamethoxazole-trimethoprim for chemoprophylaxis of *Pneumocystis* pneumonia in patients with rheumatic diseases

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Abstract

Objectives: *Pneumocystis* pneumonia (PCP) is a life-threatening opportunistic infection. Sulfamethoxazole-trimethoprim (SMX/TMP) is the first-line drug for PCP prophylaxis. However, adverse events (AEs) force clinicians to alter or reduce the drug dosage.

Methods: We retrospectively reviewed all patients with rheumatic diseases who received SMX/TMP for prophylaxis and glucocorticoid therapy between April 2004 and March 2018. The rates of AEs, SMX/TMP discontinuation, and incidence of PCP were analyzed. Patients were divided into the conventional group and the dose-reduction group.

Results: One hundred forty-five patients and 75 patients were included in the conventional group and the dose-reduction group, respectively. Compared to the dose-reduction group, the conventional group had a significantly high frequency of AEs (10.7% vs. 24.1%; *P*=0.017); however, the rate of discontinuing SMX/TMP was not significantly different (8.0% vs. 14.5%; *P*=0.165). Thirteen conventional group patients required a reduced SMX/TMP dose because of AEs; no patient developed PCP. The conventional SMX/TMP dose and renal dysfunction were associated with AEs in multivariate analysis.

Conclusions: Patients who received a reduced SMX/TMP dose did not have PCP and had a lower frequency of AEs. A reduction in SMX/TMP for PCP prophylaxis is effective and safe in patients with rheumatic disease.

Introduction

Pneumocystis pneumonia (PCP) is a potentially life-threatening opportunistic infection caused by *Pneumocystis jirovecii* in compromised patients such as individuals with human immunodeficiency virus (HIV) infection and patients under immunosuppressive therapy [1-3]. An infectious disease is an important prognostic factor in rheumatic disease. *Pneumocystis* pneumonia occurs in HIV-positive patients, and it is one of the most common opportunistic infections in the absence of prophylaxis [4]. Its incidence is 5%–15% in patients with solid organ transplantation [5] and 2%–4% in patients with rheumatic diseases [6,7]. The mortality rate of PCP associated with rheumatic disease is higher than the rate associated with HIV-positive patients [7-10]; therefore, preventing PCP in patients with rheumatic disease is important.

The first-line prophylactic agent against PCP is the oral administration of low-dose sulfamethoxazole-trimethoprim (SMX/TMP) [11,12]. The prevention rate in HIV-positive patients is 89%–100% [13-15]. In patients with rheumatic disease, the SMX/TMP prophylactic method has high efficacy, and the prevention rate is

85%–100% when the treatment is adequately adhered to and tolerated [11,16,17]. Despite the high efficacy of SMX/TMP, the administration of SMX/TMP to patients with rheumatic diseases often induces adverse events (AEs) such as rash, electrolyte abnormalities, renal dysfunction, and elevated liver enzymes. Clinicians often have to discontinue or reduce the dose of SMX/TMP because of AEs. Patients who discontinue SMX/TMP are administered alternate second-line prophylactic agents such as inhaled pentamidine isethionate and atovaquone [18]. Atovaquone is less effective than SMX/TMP in patients with acquired immunodeficiency syndrome [19], and it is more expensive than SMX/TMP. The prophylactic effect of inhaled pentamidine isethionate is inferior to that of SMX/TMP [20]. Therefore, increasing the retention rate of SMX/TMP for preventing PCP is important.

Takenaka et al. [21] conducted a retrospective study to compare the conventional regimen and the dose escalation regimen. The dose escalation regimen is initiated with a 10% dose of one single-strength tablet; the dose is increased by 10% per week. No significant difference exists in the prophylactic effect of PCP; however, the SMX/TMP retention rate is higher with the dose escalation regimen than with the conventional regimen. Utsunomiya et al. [22] conducted a trial and compared the single-strength group (SMX/TMP at 400/80 mg daily), the half-strength group, and the escalation group. They reported that no significant differences existed in the prophylactic effect among the three groups and that the safety of treatment in the half-strength group and escalation group was superior to that of the single-strength group. These results indicate that a lower dose of SMX/TMP is a better regimen for the prophylaxis of PCP in patients with rheumatic diseases. However, these previous studies excluded patients with organ insufficiency such as deteriorated renal function. In addition, some studies used a small number of participants. The patients with rheumatic diseases often have organ insufficiency in the real world. The suitable regimen of SMX/TMP for the prophylaxis of PCP in the real world remains unclear. In the present study, we aimed to evaluate reduced-dose SMX/TMP for the prophylaxis of PCP in patients with rheumatic diseases in the real world.

Materials and methods

Patients

We conducted a retrospective review of the medical records of all patients who were admitted to our hospital during a 15-year period from April 1, 2004 to March 31, 2018 for the treatment of new-onset or relapsed rheumatic diseases, and were administered corticosteroids with or without immunosuppressive drugs, as well as SMX/TMP for the prophylaxis of PCP. Because short term administration of SMX/TMP cannot adequately assess the safety and efficacy of one, we excluded from this study patients who had complete SMX/TMP prophylaxis within 180

days because of tapering prednisolone (PSL) to a low dose or until the discontinuation of immunosuppressive therapy, and patients who could not be tracked because they changed hospitals. Patients who had a history of SMX/TMP use were also excluded by being unlikely to occur adverse events.

The prophylactic regimen was as follows. In the conventional group, patients were treated with SMX/TMP at the dose of a single-strength tablet (400 mg/80 mg) daily or a double-strength tablet three times weekly. In the dose-reduction group, patients were treated with SMX/TMP at the dose of a single tablet three times weekly or on alternate days. Another prophylactic regimen, such as a double tablet daily, was excluded. The choice of prophylactic regimen was determined by each clinician, based on the patients' characteristics such as their disease, sex, age, and renal and liver function. If AEs occurred, the clinician decided whether to discontinue or reduce the dose of SMX/TMP.

This observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the ethical review board of the Tottori University Hospital (Tottori, Japan; registration number, 18A176). The board waived the requirement for patients' informed consent by showing the information on the homepage of the institute and because of the anonymous nature of the data.

Clinical evaluation and outcome

The primary outcome was the retention rates of SMX/TMP and the percentage of patients who continued SMX/TMP treatment for 180 days. The secondary objectives were to compare the incidence rates of AEs of SMX/TMP between the conventional group and the dose-reduction group, the type of AEs, the rate of dose reduction of SMX/TMP due to AEs, and the incidence rates of PCP at 180 days and during long-term observation (until October 2018). We retrospectively analyzed the factors that contributed to the onset of AEs.

Statistical analysis

Descriptive statistics included the median (range) as appropriate for continuous variables and the frequency (percentage) for categorical variables. Parameters were analyzed by using Fisher's exact test for the comparison of categorical variables. To compare continuous variables between the two prophylaxis groups, the Mann-Whitney *U* test was used for parameters with a non-normal distribution. Multivariate analysis was performed by using multiple logistic regression analysis. Forced entry method was used for variable selection. All *P* values were two-tailed. A value of $P<0.05$ was statistically significant. SPSS software version 24 (SPSS Japan, Tokyo, Japan) was used for analyzing the data.

Results

Clinical and laboratory characteristics of patients with rheumatic diseases

One patient was excluded by using the regimen of double-strength tablet daily. Two hundred twenty patients met the entry criteria for the study. A comparison of the patients' characteristics and clinical data between two groups at baseline are presented in Table 1. One hundred forty-five patients were included in the conventional group and 75 patients were included in the dose-reduction group. The baseline serum creatinine levels were significantly lower in the conventional group than in the dose-reduction group, and the estimated glomerular filtration rate (eGFR) levels were significantly higher in the conventional group ($P<0.05$, for both comparisons). We defined renal dysfunction as an eGFR lower than 60 mL/min/1.73 m^2. Renal dysfunction was more frequent in the dose-reduction group than in the conventional group (28% vs. 9%, $P<0.001$). The frequency of diabetes mellitus was significantly lower in the conventional group than in the dose-reduction group ($P=0.012$). The frequency of Polymyositis/Dermatomyositis was significantly higher in the conventional group, and that of vasculitis syndrome was significantly lower in the conventional group ($P<0.001$ and $P=0.004$). No significant differences existed between the conventional group and the dose-reduction group for age, sex, body mass index, prednisolone dose, usage rate of immunosuppressant and pulse methylprednisolone, frequency of interstitial lung disease, systemic lupus erythematosus, adult onset still's disease, rheumatoid arthritis and other diseases, history of malignancy, white blood cell count, lymphocyte count, and immunoglobulin G level.

Discontinuation rate and adverse event rate of SMX/TMP

Figure 1(a) presents the cumulative discontinuation rate of SMX/TMP due to AEs, using Kaplan-Meier curves. Twenty-one (14.5%) patients in the conventional group and 6 (8.0%) patients in the dose-reduction group discontinued SMX/TMP. The cumulative discontinuation rate in the dose-reduction group was lower than that of the conventional group. However, the difference was not statistically significant.

Figure 1(b) shows the cumulative AEs rate of SMX/TMP. Thirty-five (24.1%) patients in the conventional group and 8 (10.7%) patients in the dose-reduction group experienced AEs. A statistically significant difference was observed between the conventional group and the dose-reduction group ($P=0.024$).

Adverse events

Forty-three AEs were documented among all patients. A comparison of the patients' characteristics with and without AEs is presented in Table 2. Patients with AEs were significantly older, had a lower renal function, and had a greater frequency of diabetes mellitus. Multivariate analysis of age, diabetes mellitus, eGFR, and prophylactic regimen demonstrated that low renal function (odds ratio, 0.986; 95% confidence interval, 1.002-1.026; *P*=0.025), conventional regimen (odds ratio, 4.367; 95% confidence interval, 0.090-0.581; *P*=0.002) were significant risk factors for AEs (Table 3). These results suggested that the conventional regimen independently influences the occurrence of AEs.

The AEs that occurred with SMX/TMP are summarized in Table 4. The AEs of interest—myelosuppression and liver dysfunction—occurred only in the conventional group. A dose reduction in SMX/TMP was required in the conventional group because of the following AEs: 10 events of electrolyte abnormalities, three events of myelosuppression, and three events of renal dysfunction. Discontinuation of SMX/TMP was required in the conventional group for the following AEs: one event of electrolyte abnormality, 10 events of drug eruption, six events of myelosuppression, two events of renal dysfunction, five events of liver dysfunction, and one event of fever. These results suggested that the conventional prophylactic regimen results in more AEs; however, some patients were able to continue SMX/TMP by decreasing the dose.

Incidence of Pneumocystis pneumonia

At 180 days, no patient in either group had developed PCP. We also investigated the incidence of PCP beyond the 180 days, until October 2018 (the observation period, expressed as the median [quartile], was 2728 [734–2791] days); in this period, two patients developed PCP. One patient developed PCP after the discontinuation of SMX/TMP because of a reduction in corticosteroid therapy. One patient, who was intolerant to SMT/TMP, developed PCP after changing to inhaled pentamidine isethionate.

Discussion

In this retrospective single-center analysis, the major findings were (1) reducing the dose of SMX/TMP reduced the rate of adverse events, whereas discontinuing SMX/TMP did not reduce this rate and (2) no patient in the conventional group or dose-reduction group developed PCP during the continuation of SMX/TMP in the long-term observation period.

The incidence of AEs with SMX/TMP was lower in the dose-reduction group than in the conventional group, although the discontinuation rate of SMX/TMP was not statistically significantly different between the two

groups in the present study. Several reports have shown risk factors for AEs with SMX/TMP use. Kitazawa et al. [18] reported that renal dysfunction and a low level of platelets were risk factors for AEs with SMX/TMP use in patients with rheumatic diseases. Utsunomiya et al. [22] reported that AEs were more frequent with the single-strength SMX/TMP dose. However, in their study, 40% of patients in the conventional group who experienced AEs did not discontinue SMX/TMP and decreased the dose of SMX/TMP, and 75% of patients in the dose-reduction group discontinued SMX/TMP.

AEs of SMX/TMP are classified dose-dependent AEs or dose-independent, allergic AEs. Electrolyte abnormality, bone marrow suppression, and elevation of serum creatinine are considered as dose-dependent AEs. Drug eruption, liver dysfunction, and fever are considered as allergic AEs [23]. In this study, the frequency of allergic AEs in conventional group tended to be lower than that in dose-reduction group. We presumed that these differences were linked to high discontinuation rate of SMX/TMP in dose-reduction group.

In this study, the discontinuation rate of SMX/TMP was 14.5% in the conventional group and 8.0% in the dose-reduction group. The incidence of AEs due to SMX/TMP was 24.1% in the conventional group and 10.7% in the dose-reduction group. In patients with solid organ transplantation, the incidence of AEs due to SMX/TMP is 40%–47% [24,25]. In patients with rheumatic disease, the incidence of AEs due to SMX/TMP is 12.2%–22.2% [17,26]. The discontinuation rate of SMX/TMP is reportedly 6.1%–43% [11,18]. The discontinuation rate and incidence of AEs in this study were similar to those in previous research.

The clinical characteristics of the dose-reduction group were a higher frequency of diabetes mellitus and a lower level of eGFR. Renal dysfunction has been reported as a risk factor for AEs with SMX/TMP use [18]. In this study, the frequency of renal dysfunction was greater in the dose-reduction group than in the conventional group. These data indicated that the dose-reduction group had more risk factors for AEs than did the conventional group, and that AEs were less frequent with a reduced dose of SMX/TMP for prophylaxis, even in groups with greater risk factors.

No cases of PCP had occurred in either group in this study by week 24. This finding was similar in long-term observation (i.e., until October 2018). Two patients developed PCP during long-term observation; however, these patients had discontinued SMX/TMP. One patient discontinued prophylaxis because of a reduced dose of corticosteroids, and one patient changed the prophylactic agent to inhaled pentamidine isethionate because of an intolerance to SMT/TMP. These results demonstrated that the prophylactic effect of inhaled pentamidine isethionate may be inferior to that of SMX/TMP. In the conventional group, the patients who reduced the dose of SMX/TMP continued chemoprophylaxis thereafter. Prasad et al. [24] reported that kidney transplantation

recipients who needed to reduce the dose of SMX/TMP to three times weekly at single strength because of AEs did not affect incidence of PCP during first transplantation year. These data indicated that the dose-reduction regimen is effective, even during long-term therapy.

This study has some limitations. First, our study was a retrospective study and was conducted in a single center. Thus, selection bias may exist. Second, there were small number of patients in this study. That might limit the evaluation of efficacy. Third, the decision of treatment group was determined by each physician. The characteristics of the dose-reduction group were a high frequency of diabetes mellitus and patients with a low eGFR. These background characteristics may have influenced the decision of treatment regimen. Fourth, the decision of dose reduction or discontinuation of SMX/TMP was determined by each physician. For some patients, SMX/TMP was reduced or discontinued, even for patients with mild AEs. This factor may have influenced the discontinuation rate. Regardless of these limitations, this study had the strength compared to previous similar study. The main point was to include patients who had organ insufficiency, such as renal dysfunction. Rheumatic diseases are often complicated with renal dysfunction, and 15.5% of patients complicated with renal dysfunction in this study. Therefore, present study is reflected the safety and efficacy of reduced-dose SMX/TMP in real world.

In conclusion, even in patients who have renal dysfunction, the dose-reduction regimen of SMX/TMP may be safer and more efficacious for the prophylaxis of PCP than the conventional SMX/TMP regimen. No cases of PCP occurred, even in the dose-reduction group, during long-term observation. These data indicated that a single tablet of SMX/TMP administered three times weekly or on alternate days is an adequate regimen for the chemoprophylaxis of PCP in patients with rheumatic diseases in the real world.

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Conflict of interest: None.

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diseases receiving prolonged, non-high-dose steroids-clinical implication of primary prophylaxis using trimethoprim-sulfamethoxazole. Arthritis Res Ther 2019;21(1):207.

Legends

Figure 1

(a) Discontinuation rate of treatment due to adverse events. (b) Rate of treatment-related adverse events. Cumulative discontinuation rate or rate of treatment-related adverse events were compared using log-rank test between the groups.

Table 1

Baseline clinical and laboratory characteristics of patients in the conventional group and in the dose-reduction group

Renal dysfunction is defined as <60 mL/min/1.73 m^2. Data are presented as the median (range) or as the number (%). The *P* values were determined by using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables.

SLE, systemic lupus erythematosus; *PM,* polymyositis; *DM,* dermatomyositis; *AOSD,* adult onset still's disease; *RA,* rheumatoid arthritis; *ILD*, interstitial lung disease; *IVCY,* intravenous cyclophosphamide; *CNI,* calcineurin inhibitor; *TAC,* tacrolimus; *CyA,* cyclosporin A; *DMARDs,* disease modifying anti-rheumatic drugs; *PSL*, prednisolone; *WBC*, white blood cell; *IgG*, immunoglobulin G; *eGFR*, estimated glomerular filtration rate

Table 2

Baseline clinical and laboratory characteristics of patients with and without adverse events

Renal dysfunction is defined as <60 mL/min/1.73 m^2. Data are presented as the median (range) or as the number (%). The *P* values were determined by using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables.

SLE, systemic lupus erythematosus; *PM,* polymyositis; *DM,* dermatomyositis; *AOSD,* adult onset still's disease; *RA,* rheumatoid arthritis; *ILD*, interstitial lung disease; *IVCY,* intravenous cyclophosphamide; *CNI,* calcineurin

inhibitor; *TAC,* tacrolimus; *CyA,* cyclosporin A; *DMARDs,* disease modifying anti-rheumatic drugs; *PSL*, prednisolone; *WBC*, white blood cell; *IgG*, immunoglobulin G; *eGFR*, estimated glomerular filtration rate

Table 3

Predictors for adverse events, based on multivariate logistic regression analysis

CI, confidence interval; *eGFR*, estimated glomerular filtration rate

Table 4

Comparison of adverse events between the conventional group and the dose-reduction group

Data are presented as the number (%). There is some overlapping in the contents of adverse events. The *P* values were determined by using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables.

AE, adverse event; *BM*, bone marrow

Figure 1

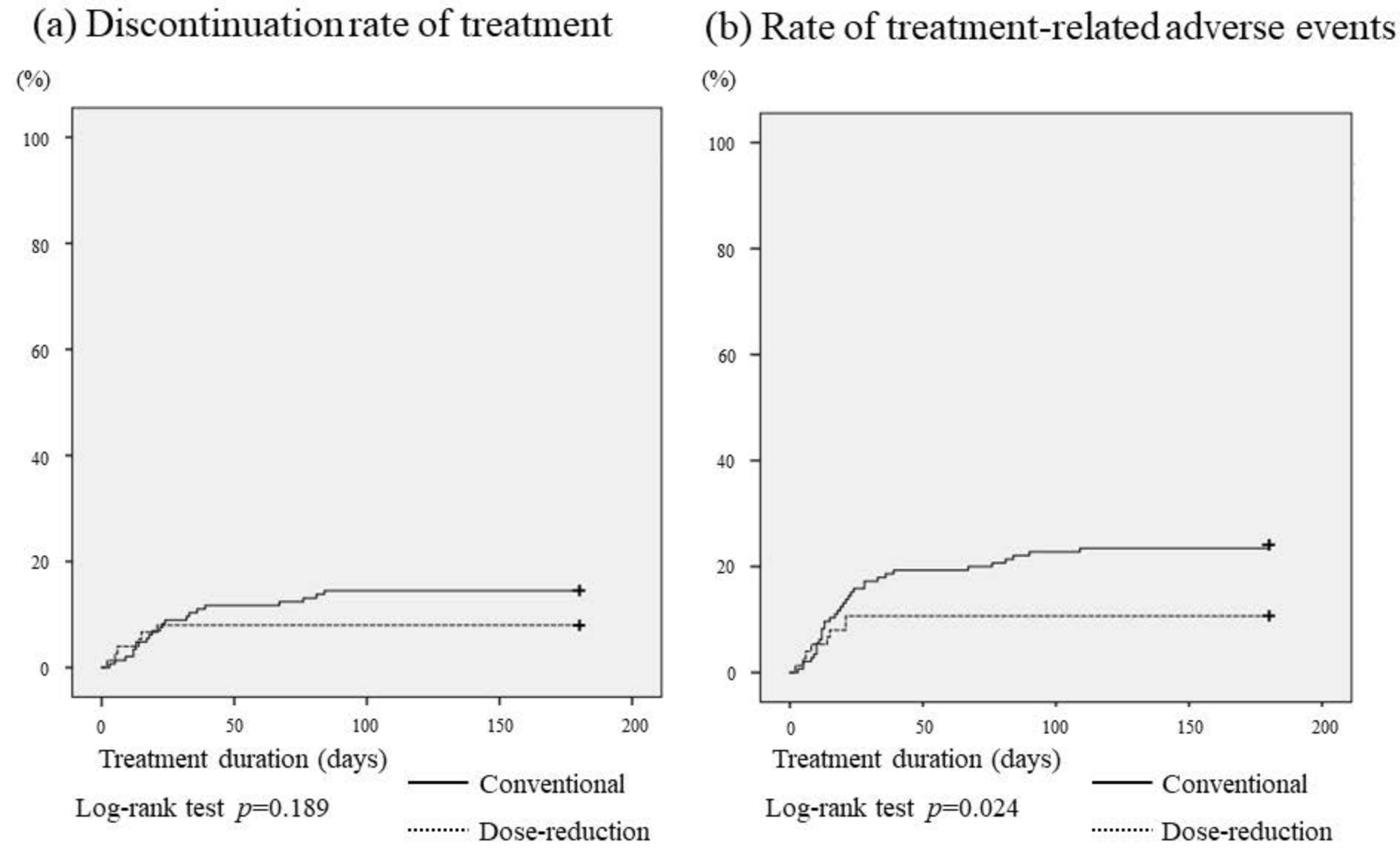
(a) Discontinuation rate of treatment
(%)
100
80
60
40
20
0
0
50
100
150
200
Treatment duration (days)
Conventional
Dose-reduction
Log-rank test p=0.189
(b) Rate of treatment-related adverse events
(%)
100
80
60
40
20
0
0
50
100
150
200
Treatment duration (days)
Conventional
Dose-reduction
Log-rank test p=0.024

Table 1 (final version)

Table 1 Baseline clinical and laboratory characteristics of patients in the conventional group and in the dose-reduction group

	Conventional group (n=145)	Dose-reduction group (n=75)	*P* value
Age, y	58 (16–85)	64 (16–87)	0.167
Female	95 (65.5%)	49 (63.3%)	0.547
Body mass index	21.0 (15.1–34.2)	21.3 (14.9–33.8)	0.928
Diseases			
SLE	32 (22.0%)	23 (30.7%)	0.110
PM/DM	42 (29.0%)	7 (9.3%)	<0.001
Vasculitis syndrome	32 (22.1%)	30 (40.0%)	0.004
AOSD	14 (9.7%)	5 (6.7%)	0.317
RA	9 (6.2%)	5 (6.7%)	0.552
Others	16 (11.0%)	5 (6.7%)	0.214
Comorbidities	80 (55.2%)	43 (57.3%)	0.436
ILD	53 (36.6%)	26 (34.7%)	0.451
Other lung disease	16 (11.0%)	10 (13.3%)	0.383
Diabetes	42 (29.0%)	34 (45.3%)	0.012
Malignancies	10 (7.6%)	1 (1.3%)	0.063
Methylprednisolone pulse	96 (66.2%)	42 (56.0%)	0.091
Immunosuppressive drugs	113 (77.9%)	60 (80.0%)	0.432
IVCY	24 (16.6%)	23 (30.7%)	0.013
IVCY+CNI	13 (9.0%)	5 (6.7%)	0.379
TAC	26 (17.9%)	15 (20.0%)	0.420
CyA	29 (20.0%)	8 (10.7%)	0.056
MTX	9 (6.2%)	2 (2.7%)	0.211
Biologic DMARDs	2 (1.4%)	0 (0.0%)	0.433
Others	10 (6.9%)	7 (9.3%)	0.346
Initial dose of PSL (mg/day)	40 (15–80)	40 (10–60)	0.383
WBC (/μL)	8900 (400–23200)	10700 (1800–23500)	0.164
Lymphocytes (/μL)	1311 (158–6123)	1280 (188–5982)	0.781
IgG (mg/dL)	1500 (107–3697)	1508 (258–3737)	0.897
Creatinine (mg/dL)	0.57 (0.16–2.19)	0.62 (0.18–8.44)	0.016
eGFR (mL/min/1.73 m^2)	97.0 (22.2–230.9)	86.1 (5.6–265.1)	0.023
Renal dysfunction	13 (9.0%)	21 (28.0%)	<0.001

Renal dysfunction is defined as <60 mL/min/1.73 m^2. Data are presented as the median (~~interquartile~~ range) or as the number (%). The *P* values were determined by using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables.

SLE, systemic lupus erythematosus; *PM*, polymyositis; *DM*, dermatomyositis; *AOSD*, adult onset still's disease; *RA*, rheumatoid arthritis; *ILD*, interstitial lung disease; *IVCY*, intravenous cyclophosphamide; *CNI*, calcineurin inhibitor; *TAC*, tacrolimus; *CyA*, cyclosporin A; *DMARDs*, disease modifying anti-rheumatic drugs; *PSL*, prednisolone; *WBC*, white blood cell; *IgG*, immunoglobulin G; *eGFR*, estimated glomerular filtration rate

Table 2 (final version)

Table 2 Baseline clinical and laboratory characteristics of patients with and without adverse events

	With adverse event (n=43)	Without adverse event (n=177)	*P* value
Age, y	69 (16–86)	58 (16–87)	0.003
Female	30 (69.8%)	114 (64.6%)	0.317
Body mass index	21.1 (16.7–26.9)	21.0 (14.9–34.2)	0.627
Diseases			
SLE	12 (27.9%)	43 (24.3%)	0.377
PM/DM	5 (11.6%)	44 (24.9%)	0.043
Vasculitis syndrome	19 (44.2%)	43 (24.3%)	0.009
AOSD	5 (11.6%)	14 (7.9%)	0.303
RA	0 (0.0%)	14 (7.9%)	0.043
Others	2 (4.7%)	19 (10.7%)	0.178
Comorbidities	24 (55.8%)	99 (55.9%)	0.561
ILD	11 (25.6%)	68 (38.4%)	0.079
Other lung disease	4 (9.3%)	22 (12.4%)	0.395
Diabetes	21 (48.8%)	55 (31.1%)	0.023
Malignancies	1 (2.3%)	10 (6.2%)	0.329
Methylprednisolone pulse	27 (62.8%)	111 (62.7%)	0.569
Immunosuppressive drugs	31 (72.1%)	142 (80.2%)	0.168
IVCY	11 (25.6%)	36 (20.3%)	0.287
IVCY+CNI	4 (9.3%)	14 (7.9%)	0.483
TAC	7 (16.3%)	34 (19.2%)	0.422
CyA	6 (14.0%)	31 (17.5%)	0.381
MTX	1 (2.3%)	10 (5.6%)	0.329
Biologic DMARDs	0 (0.0%)	2 (1.1%)	0.647
Others	2 (4.7%)	15 (8.5%)	0.316
Initial dose of PSL (mg/day)	40 (20–60)	40 (10–80)	0.488
WBC (/μL)	9200 (2700–19500)	9400 (400–23500)	0.299
Lymphocytes (/μL)	1206 (158–3220)	1422 (160–6123)	0.405
IgG (mg/dL)	1620 (107–3250)	1443 (258–3737)	0.118
Creatinine (mg/dL)	0.61 (0.16–4.15)	0.59 (0.18–8.44)	0.136
eGFR (mL/min/1.73 m^2)	78.1 (8.8–167.2)	96.4 (5.6–265.1)	0.003
Renal dysfunction	11 (25.6%)	23 (13.0%)	0.039
Conventional group	35 (81.4%)	110 (62.1%)	0.011

Renal dysfunction is defined as <60 mL/min/1.73 m^2. Data are presented as the median (~~interquartile~~ range) or as the number (%). The *P* values were determined by using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables.

SLE, systemic lupus erythematosus; *PM*, polymyositis; *DM*, dermatomyositis; *AOSD*, adult onset still's disease; *RA*, rheumatoid arthritis; *ILD*, interstitial lung disease; *IVCY*, intravenous cyclophosphamide; *CNI*, calcineurin inhibitor; *TAC*, tacrolimus; *CyA*, cyclosporin A; *DMARDs*, disease modifying anti-rheumatic drugs; *PSL*, prednisolone; *WBC*, white blood cell; *IgG*, immunoglobulin G; *eGFR*, estimated glomerular filtration rate

Table 3 Predictors for adverse events, based on multivariate logistic regression analysis

	Odds ratio	95%CI	*P* value
Conventional group	4.367	0.090-0.581	0.002
eGFR（mL/min/1.73 m^2）	0.986	1.002-1.026	0.025
Age	1.016	0.959-1.010	0.233
Diabetes mellitus	1.656	0.274-1.332	0.211

CI, confidence interval; *eGFR*, estimated glomerular filtration rate

Table 4 (final version)

Table 4 Comparison of adverse events between the conventional group and the dose-reduction group

	Conventional group (n=145)	Dose-reduction group (n=75)	*P* value
Adverse events	35 (24.1%)	8 (10.7%)	0.011
AE required discontinuation	21 (14.5%)	6 (8.0%)	0.119
Electrolyte abnormality	2 (1.4%)	3 (4.0%)	0.219
Drug eruption	10 (6.9%)	3 (4.0%)	0.295
BM suppression	6 (6.2%)	0 (0.0%)	0.079
Renal dysfunction	2 (1.4%)	1 (1.3%)	0.732
Liver dysfunction	5 (3.4%)	0 (0.0%)	0.121
Fever	1 (0.7%)	1 (1.3%)	0.567
AE required a dose reduction	13 (9.0%)	2 (2.7%)	0.064
Electrolyte abnormality	8 (5.5%)	1 (1.3%)	0.127
BM suppression	3 (2.1%)	0 (0.0%)	0.284
Renal dysfunction	3 (2.1%)	0 (0.0%)	0.284
Headache	0 (0.0%)	1 (1.3%)	0.341

Data are presented as the number (%). There is some overlapping in the contents of adverse events. The *P* values were determined by using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. *AE*, adverse event; *BM*, bone marrow