Protective effect of different doses of trimethoprim-sulfamethoxazole prophylaxis for early severe infections among patients with antineutrophil cytoplasmic autoantibody-associated vasculitis

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ABSTRACT

Objective. *To analyse the protective effect of different doses of trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis for early severe infections in antineutrophil cytoplasmic autoantibody-associated vasculitis (AAV), considering time-varying changes.*

Methods. *In this retrospective observational study, we assessed the protective effect of TMP/SMX within the first 6 months of diagnosis among Japanese patients with AAV. We included 250 consecutive patients with AAV who were admitted to our hospital. The protective effect of TMP/SMX against early severe infections was verified using Cox regression analysis along with potential confounding factors. Cox regression with inverse probability treatment weights for early severe infections was also performed as a sensitivity analysis.*

Results. *Cox regression analysis showed that the reduced TMP/SMX exposure group had a significant protective effect against early severe infections (standard-dose group versus no TMP/SMX group: hazard ratio [HR] 0.393, 95% confidence interval [CI]: 0.139–1.11, p=0.077; reduced-dose group versus no TMP/SMX group: HR 0.418, 95%CI: 0.216–0.807, p=0.009), even when considering time-dependent changes. In the sensitivity analysis, the reduced-dose group still had a significantly lower risk of early severe infections than the no TMP/SMX group (HR=0.393, 95%CI: 0.177–0.873, p=0.022). During follow-up, 18.0% of the patients discontinued TMP/SMX due to side effects.*

Conclusion. *TMP/SMX is highly effective in preventing severe infections among patients with AAV despite the high incidence of side effects. Further studies are needed to determine the optimal dose of TMP/SMX for preventing severe infections, especially considering renal impairment.*

Introduction

Disease control of antineutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) and the prognosis of AAV have dramatically improved due to the application of immunosuppressive therapy combined with corticosteroids and cyclophosphamide (CYC) or rituximab (RTX) (1-4). However, controlling the side effects of treatment, particularly for severe life-threatening infections, remains challenging. Recent studies have shown that severe infection is a major cause of death as well as active vasculitis. The majority of severe infections occur within the first 6 months of starting remission induction therapy (5-8). Although several risk factors for severe infections have been suggested, prophylactic methods against them have not yet been established. Trimethoprim-sulfamethoxazole (TMP/SMX) is routinely prescribed as prophylaxis for *Pneumocystis jirovecii* pneumonia in daily practice and is also expected to reduce disease flare-ups in granulomatosis with polyangiitis (GPA) (9). A recent observational study has reported that TMP/SMX reduced the risk of severe infections among European patients with AAV with predominant GPA (10). However, the protective effect of TMP/SMX against severe infections in patients with AAV in different parts of the world remains unclear.

Although the side effects of TMP/SMX are relatively frequent, previous studies did not consider TMP/SMX exposure as a time-varying factor; some studies have reported that as many as

20% of patients needed to discontinue TMP/SMX because of side effects (9, 11). Moreover, we frequently prescribe TMP/SMX at a reduced dosage to effectively prevent *Pneumocystis jirovecii* pneumonia due to concerns about the high incidence of side effects. This study aimed to assess the protective effect of TMP/SMX for severe infections in Japanese patients with AAV considering time-varying changes and to investigate the differences in the protective effect among different TMP/SMX dosage groups.

Materials and methods

Study population

This study was conducted as a retrospective observational study. We screened newly diagnosed patients admitted to our hospital for AAV between January 2000 and January 2020 and collected the data retrospectively. All patients were diagnosed according to the European Medicines Agency algorithm as having GPA, microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) (12). Clinical manifestations and laboratory data for comparing patient characteristics were recorded at the time of diagnosis except for the following: having steroid-induced diabetes mellites (DM), received haemodialysis (HD), cumulative doses of corticosteroids, vasculitis damage index, and receiving TMP/SMX dose.

Patients with incomplete or missing records regarding vasculitis activity or treatment regimen were excluded from final analyses. Patients with missing records regarding the history of infectious episodes for more than 6 months until loss to follow up were excluded. Patients with classic polyarteritis nodosa (cPAN), unclassified vasculitis, or secondary vasculitis who did not receive immunosuppressive treatment, or who died within 1 week after diagnosis, were also excluded.

Finally, 250 patients were included in this study. Our research was performed according to the principles outlined in the Declaration of Helsinki and approved by the ethics committee of our hospital (approval number: 3430). Informed consent was obtained through an opt-out methodology. Patient data were recorded at each follow-up visit and collected from medical records until loss to follow-up or 6 months after diagnosis. The date of diagnosis was defined as the day that remission induction therapy was started.

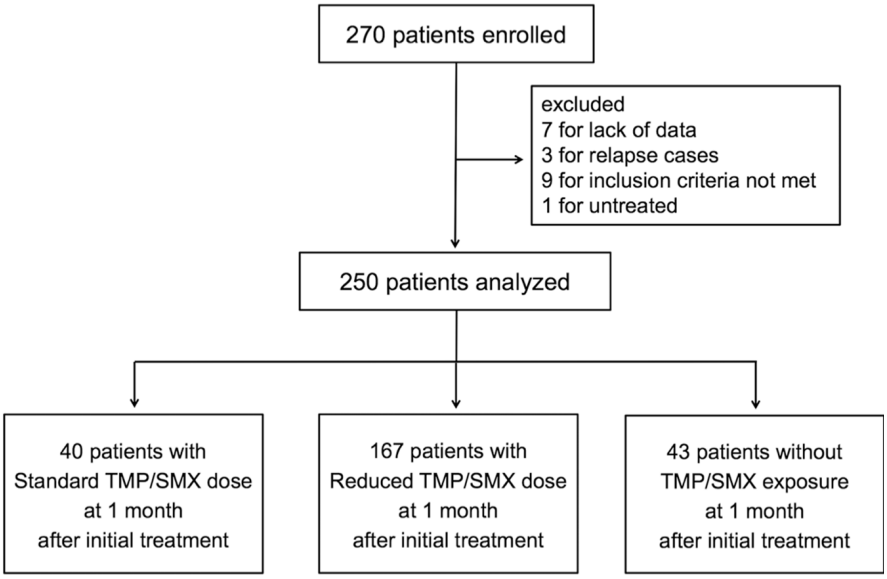

Fig. 1. Flow diagram of patient selection.
A total of 254 patients were included in this retrospective observational study after excluding 20 patients due to various reasons. The patients were categorised into three groups according to the received dosage of trimethoprim-sulfamethoxazole (TMP/SMX) at 1 month after diagnosis.

All included patients had not received any immunosuppressive therapy before the diagnosis of AAV. Remission induction therapy included oral or intravenous CYC, RTX, mycophenolate mofetil, methotrexate, azathioprine, calcineurin inhibitors, intravenous immunoglobulin, and plasma exchange, in addition to corticosteroids. Treatment regimens were selected at the discretion of each physician. In general, initial doses of corticosteroids were continued for 2 weeks, with gradual tapering of the dose every 2 weeks. Prophylactic methods against *Pneumocystis jirovecii* pneumonia were also used at the discretion of each physician. Since there is no authorised prophylaxis regimen of TMP/SMX against *Pneumocystis jirovecii* pneumonia regarding renal impairment, physicians generally chose from two regimens: 160 mg/800 mg TMP/SMX three times a week or 80 mg/400 mg TMP/SMX once daily for patients without renal impairment (13, 14). These are the most common dosages for prophylaxis against *Pneumocystis jirovecii* pneumonia. The prescriber reduced the dose by half for patients with impaired renal function (creatinine clearance ≤30 ml/min) according to drug package inserts of pharmaceuticals and medical devices agency in Japan. Patients with severely impaired renal function (creatinine clearance ≤15 ml/min) were generally not prescribed TMP/SMX according to drug package inserts. The decision to reduce the dosage of TMP/SMX or change the prophylactic drug was the physician's discretion when side effects were observed. We analysed the sample's risk factor for severe infections within 6 months, including TMP/SMX exposure. Because TMP/SMX exposure is a time-dependent variable due to the high incidence of adverse effects, which mainly occur within the first month of prescription, patient characteristics were compared among different TMP/SMX exposure groups at 1 month after diagnosis.

Definition

Among the different TMP/SMX dosage groups, the standard-dose group was defined as receiving 160 mg/800 mg TMP/SMX three times a week or 80 mg/400 mg TMP/SMX once daily. The reduced-dose group received a lower dosage of TMP/SMX per week,

Table I. Patient characteristics.

	Standard-dose group (n=40)	Reduced-dose group (n=167)	No TMP/SMX group (n=43)	Reduced-dose group *vs.* No TMP/SMX group *p*-value	TMP/SMX exposure *vs.* No TMP/SMX group *p*-value
Sex				0.734	0.504
Female, n (%)	26 (65.0)	91 (54.5)	22 (51.2)		
Male, n (%)	14 (35.0)	76 (45.5)	21 (48.8)		
Age at diagnosis, median [IQR]	66.5 [60.3-76.0]	76.0 [68.0-81.0]	75.0 [67.0-81.5]	0.743	0.233
Past history of smoking, n (%)	15 (40.5)	70 (46.1)	19 (46.3)	1.000	0.864
Past history of CKD, n (%)	3 (7.9)	35 (22.0)	7 (17.1)	0.667	0.666
Past history of lung disease, n (%)	12 (30.8)	38 (23.0)	11 (25.6)	0.692	1.000
Steroid DM or past history of DM, n (%)	15 (38.5)	95 (57.2)	17 (39.5)	0.041	0.07
ANCA, n (%)				1.000	0.862
MPO-ANCA/p-ANCA	28 (70.0)	137 (82.0)	36 (83.7)		
PR3-ANCA/c-ANCA	5 (12.5)	14 (8.4)	3 (7.0)		
Both negative	7 (17.5)	16 (9.6)	4 (9.3)		
Type of AAV, n (%)				0.567	0.323
MPA	20 (50.0)	118 (70.7)	31 (72.1)		
GPA	14 (35.0)	29 (17.4)	5 (11.6)		
EGPA	6 (15.0)	20 (12.0)	7 (16.3)		
BVAS[†], median [IQR]	8.0 [6.0-16.0]	14.0 [12.0-18.0]	15.0 [12.0-18.0]	0.538	0.197
VDI, median [IQR]	2.0 [1.0-3.0]	3.0 [2.0-3.0]	3.0 [2.0-3.0]	0.901	0.364
Serum IgG (mg/dL), median [IQR]	1876.0 [1496.5-2161.0]	1537.0 [1274.5-2023.0]	1531.0 [1217.5-1891.0]	0.549	0.48
Serum lymphocyte (/μL), median [IQR]	1413.3 [1135.1-1701.5]	1155.6 [869.2-1593.2]	1089.0 [780.5-1378.7]	0.169	0.074
CRP (mg/dL), median [IQR]	7.9 [4.8-11.4]	6.4 [1.1-10.7]	6.6 [2.3-10.9]	0.427	0.759
Serum creatinine (mg/dL), median [IQR]	0.66 [0.54-0.74]	1.56 [0.67-3.76]	1.50 [0.65-2.95]	0.628	0.302
eGFR (mL/min per 1.73 m^2) median [IQR]	68.2 [58.4-85.9]	23.9 [8.5-65.5]	24.8 [11.6-66.6]	0.597	0.314
Revised FFS[‡] ≥2, n (%)	14 (35.0)	128 (76.6)	30 (69.8)	0.428	0.859
Renal involvement, n (%)	8 (20.0)	115 (68.9)	31 (72.1)	0.853	0.124
Pulmonary involvement, n (%)	28 (70.0)	68 (40.7)	14 (32.6)	0.383	0.181
Initial doses of CS/weight (mg/kg/day)[§], median [IQR]	0.99 [0.80-1.00]	0.75 [0.63-1.00]	0.95 [0.66-1.00]	0.023	0.07
MPSL pulse therapy, n (%)	10 (25.0)	104 (62.3)	25 (58.1)	0.726	1.000
Cumulative CS/weight at 1 month (mg/kg)[§], median [IQR]	25.3 [21.1-27.3]	20.6 [17.2-26.7]	25.1 [17.7-27.7]	0.08	0.237
CYC	21 (52.5)	37 (22.2)	9 (20.9)	1.000	0.351
RTX	0	9 (5.4)	7 (16.3)	0.025	0.002
Other immunosuppressants[¶]	4 (10.0)	16 (9.6)	4 (9.3)	1.000	0.777
Received HD, n (%)	0	13 (7.8)	3 (7.0)	1.000	1.000

Interquartile range (IQR): data are presented as median [1st quartile to 3rd quartile].
[†]BVAS = Birmingham Vasculitis Activity Score version 3 (16).
[‡]revised FFS = the revised Five-Factor Scores reported in 2009 (17).
[§]Different types of corticosteroids were converted to equivalent doses of prednisolone.
[¶]mycophenolate mofetil, methotrexate, azathioprine, and calcineurin inhibitors.
TMP/SMX: trimethoprim-sulfamethoxazole; SD: standard deviation; CKD: chronic kidney disease; DM: diabetes mellitus; ANCA: anti-neutrophil cytoplasmic antibody; MPO: myeloperoxidase; PR3: perinuclear proteinase-3; AAV: antineutrophil cytoplasmic autoantibody-associated vasculitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; cPAN: classic polyarteritis nodosa; BVAS: Birmingham Vasculitis Activity Score; VDI: vasculitis damage index; IgG: Immunoglobulin G; CRP: C-reactive protein; IQR: interquartile range; eGFR: estimated glomerular filtration rate; FFS: Five Factor Score; CS: corticosteroids; MPSL: methylprednisolone; CYC: cyclophosphamide; RTX: rituximab; HD: haemodialysis.

and the no TMP/SMX group did not receive TMP/SMX. Patients with any TMP/SMX exposure were assigned to the combined standard-dose group and reduced-dose group.

A history of chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) <50 mL/min/1.73 m^2 at least 6 months before the date of diagnosis. The eGFR was calculated according to the Japanese eGFR equation based on standardised serum creatinine levels (15). Past history of DM was defined as receiving antidiabetic treatment at disease onset, and steroid DM was defined as receiving antidiabetic treatment within 1 month after diagnosis. Received HD was defined as receiving HD at 1 month after diagnosis. The Birmingham Vasculitis Activity Score (BVAS) at the time of diagnosis was calculated according to BVAS version 3, and pulmonary and renal involvement were also scored according to the BVAS (16). The Five-Factor Score (revised FFS) at diagnosis was calculated according to Five-Factor Score 2009 (17). Indirect immunofluorescence or antigen-specific enzyme-linked immunosorbent assay tests were used to detect ANCA. We defined "severe infections" as viral, bacterial, or fungal infections requiring

hospitalisation or intravenous antibiotics. Disseminated herpes zoster recurrences, *Pneumocystis jirovecii* pneumonia, cytomegalovirus (CMV) hepatitis, gastrointestinal infections with CMV, mycobacterium tuberculosis, expanded nontuberculous mycobacterium infection, and febrile neutropenia were also included as severe infections. The first episode of severe infection was recorded in each patient, and duplicate counts of the infectious episode were avoided.

Statistical analyses

Differences between the groups (any TMP/SMX exposures versus no TMP/SMX group, reduced-dose group *versus* no TMP/SMX group at 1 month after diagnosis) were analysed using the Mann-Whitney U-test for continuous variables and Fisher's exact test for categorical variables. All analyses excluded patients with missing data. As mentioned above, TMP/SMX exposure was entered as a discrete time-varying covariate in the survival analysis and multivariate analysis.

The Kaplan-Meier method was used to estimate severe infection-free survival, and the log-rank test was used to evaluate the differences between the groups. The adjusted Kaplan-Meier estimator to reduce confounding effects using inverse probability treatment weights (IPTW) was used for sensitivity analysis (18). Censoring was performed on the day of loss to follow-up or completion of follow-up until 6 months after diagnosis. IPTW were generated using propensity scores, which were generated on the basis of the probability of being in three different TMP/SMX exposure groups at 1 month after diagnosis (standard-dose group, reduced-dose group, and no TMP/SMX group). The multinomial regression model was used to estimate the propensity scores, including age, sex, serum lymphocyte at diagnosis, eGFR at diagnosis, revised FFS, BVAS, lung involvement, received immunosuppressants, and initial dose of corticosteroids as covariates. These covariates have been suggested as risk factors for severe infections in AAV by previous studies (5-8, 19-26). IPTW were truncated at the 5th and 95th percentile. Different TMP/SMX exposure groups and the variables that were significantly different (p.value <0.1) between any TMP/SMX exposures and the no TMP/SMX group at 1 month after diagnosis were selected for the Cox regression model for severe infections within 6 months. Adjusted Cox regression analysis using IPTW was also performed for sensitivity analysis. The differences were considered to indicate statistical significance if the two-tailed p-value was less than 0.05. All analyses were performed using R software version 4.0.2 (R Development Core Team, Vienna, Austria). The following R software packages were used for statistical processing and creation of graphs: WeightIt (v. 0.10.2), survival (v. 3.1-12), and ggplot2 (v. 3.3.2).

Results

Demographics

The final sample included 250 patients (Fig. 1). Patient data at baseline are shown in Table I. The distribution of diagnoses among the patients was as follows: 169 with MPA, 48 with GPA, and 33 with EGPA.

All patients had prophylaxis for *Pneumocystis jirovecii*, including inhaled pentamidine or oral atovaquone, and 207 patients (82.8%) had TMP/SMX at 1 month after diagnosis. In these patients, 40 received a standard dose of TMP/SMX for prophylaxis against *Pneumocystis jirovecii* pneumonia, and 167 received a reduced dose of TMP/SMX. No patient received combination drugs for prophylaxis. Patients prescribed TMP/SMX tended to receive lower amounts of corticosteroids as remission induction therapy (any TMP/SMX exposures *versus* no TMP/SMX group: median [IQR] 0.80 [0.63–1.00] *vs*. 0.95 [0.66-1.00] mg/kg/day, p=0.07). The TMP/SMX exposure group received less RTX than no TMP/SMX group (4.3% *vs*. 16.3%, p=0.002), while other proposed risk factors for severe infections, including onset age, sex, eGFR or renal function at diagnosis, pulmonary involvement, revised FFS, BVAS, and rate of receiving CYC were not significantly different between any TMP/SMX exposures and the no TMP/SMX group. Serum lymphocyte concentrations at diagnosis showed a tendency to be higher in all the TMP/SMX exposures compared with that in the no TMP/SMX group (median [IQR] 1184 [896-1598] *vs*. 1096 [717–1422] /μL, p=0.074). The frequency of steroid DM or a history of DM at 1 month after diagnosis tended to be higher in all the TMP/SMX exposures compared with that in the no TMP/SMX group (53.1% *vs*. 39.5%, p=0.07). Serum eGFR was significantly lower in patients in the reduced-dose group compared with that of those in the standard-dose group (median [IQR] 23.9 [8.6–65.5] *vs*. 68.2 [58.4–85.9] ml/min per 1.73 m^2, p<0.001). In all patients, there were changes in TMP/SMX dose in 79 episodes within 6 months. Prescription pattern of TMP/SMX within 6 months are shown in the Supplementary Table S1.

Protective effect of TMP/SMX for severe infections after induction therapy

According to the univariate analysis comparing all TMP/SMX exposures and the no TMP/SMX group, serum lymphocyte, steroid DM, or history of DM, initial dose of corticosteroids, and receiving RTX were selected as potential confounding factors for early severe infections. Therefore, we performed Cox regression analysis, including these factors and TMP/SMX exposure as a time-varying factor (Table II).

The results showed that the reduced-dose group had a significant protective effect for early severe infections (reduced-dose group *vs*. no TMP/SMX group: hazard ratio [HR] 0.418, 95% confidence interval [CI]: 0.216–0.807, p=0.009), although protective effect among the standard-dose group against early severe infections could not be confirmed statistically (standard-dose group *vs*. no TMP/SMX group: HR 0.393, 95%CI: 0.139–1.11, p=0.077). Multivariate analysis revealed that a lower serum lymphocyte count at diagnosis was a significant risk factor for early severe infections (HR 0.943 for every 100/μL increase, 95% CI: 0.890–0.998, p=0.043).

Among the different TMP/SMX dosage groups, the survival analysis showed that the reduced-dose group had a sig-

Table II. Multivariate analysis for early severe infections.

Risk factor	Hazard ratio	95% CI	*p*-value
TMP/SMX exposure[a]			
Standard-dose group *vs*. No TMP/SMX group	0.393	(0.139-1.11)	0.077
Reduced-dose group *vs*. No TMP/SMX group	0.418	(0.216-0.807)	0.009
Steroid DM or past history of DM	0.902	(0.493-1.649)	0.737
Serum lymphocyte count[b]	0.943	(0.890-0.998)	0.043
Initial dose of CS/weight[c]	2.446	(0.536-11.580)	0.248
Receiving RTX	1.923	(0.804-4.597)	0.142

[a]TMP/SMX exposure was entered as a discrete time-varying covariate.
[b]For every 100/μL increase.
[c]Different types of corticosteroids were converted to equivalent doses of prednisolone.
TMP/SMX: trimethoprim-sulfamethoxazole; DM: diabetes mellitus; CS: corticosteroids; CI: confidence interval; RTX: rituximab.

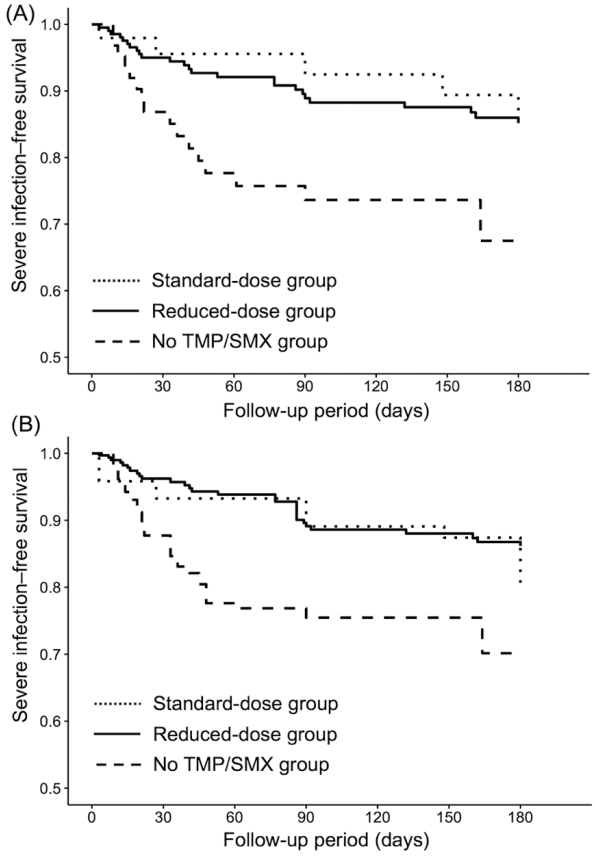

Fig. 2. Severe infection-free survival rates within 6 months among the three groups.
A: Kaplan-Meier curve showing the reduced-dose group had a significantly lower risk of early severe infections than the no trimethoprim-sulfamethoxazole (TMP/SMX) group (Bonferroni-corrected p=0.012).
B: The adjusted Kaplan-Meier curve using IPTW among the three groups.

nificantly lower risk of early severe infections than the no TMP/SMX group (Bonferroni-corrected p=0.012) (Fig. 2A).

Sensitivity analysis

The adjusted Cox regression analysis using IPTW revealed that TMP/SMX still had a significant protective effect for early severe infections in the reduced-dose group (HR 0.393, 95%CI: 0.177–0.873, p=0.022) (Table III). Protective effect of TMP/SMX for early severe infections in the standard-dose group could not be confirmed statistically (HR 0.595, 95%CI: 0.196–1.806, p=0.359). The adjusted Kaplan-Meier curves using IPTW are shown in Fig. 2B.

Aetiologies of early severe infections

We identified 45 severe infections during 6 months after diagnosis (Table IV). Bacterial pneumonia was most frequent type of infection in the total patient cohort (n=15, 33.3%). Unfortunately, two patients in the TMP/SMX group had *Pneumocystis jirovecii* pneumonia; these patients had received a reduced dose of TMP/SMX because of severe renal insufficiency. Other severe infections included sepsis of unknown origin (n=6), cytomegalovirus infections (n=5), skin and soft tissue infections (n=4), disseminated herpes zoster recurrences (n=3), fungal infections (n=2), biliary tract infections (n=2), intestinal infections (n=2), mycobacterium avium complex infections (n=1), disseminated nocardia infections (n=1), urinary tract infections (n=1), and suppurative parotitis (n=1).

The exact pathogen was identified in 31 instances of severe infections. *P. aeruginosa* and cytomegalovirus were the most common pathogens (both n=5), followed by *E. coli* (n=4), herpes zoster (n=3), *S. aureus* (n=3), *P. jirovecii* (n=2), *Aspergillus spp*. (n=2), *S. pneumoniae* (n=1), *Nocardia cyriacigeorgica* (n=1), *Mycobacterium avium complex* (n=1), *K. oxytoca* (n=1), *E. faecium* + *P. aeruginosa* (n=1), *E. cloacae* (n=1), and *C. perfringens* (n=1).

Reasons for discontinuing TMP/SMX

Among the total sample, 45 patients (18.0%) discontinued TMP/SMX within 6 months. The most frequent reason for discontinuation was cytopenia (n=19), followed by rash (n=9), liver dysfunction (n=7), hyperkalaemia (n=4), unknown (n=4), renal dysfunction (n=1), and the end of treatment for AAV at the patient's request (n=1). After discontinuation of TMP/SMX, all patients received alternative prophylaxis for *Pneumocystis jirovecii* pneumonia.

Discussion

Our study demonstrated that reduced TMP/SMX exposure has a protective effect for severe infections within the first 6 months in Japanese patients with AAV, considering time-varying changes. These results are in line with those of previous studies.

Despite remarkable advances in treatment, the mortality rate for patients with AAV remains higher than that for age- and sex-matched persons in the general population and the main cause of death within the first year is infection (27). The current European League

Table III. Multivariate analysis for early severe infections using an inverse probability-weighted Cox regression model.

Risk factor	Hazard ratio	95% CI	*p*-value
TMP/SMX exposure†			
Standard-dose group *vs*. No TMP/SMX group	0.595	(0.196-1.806)	0.359
Reduced-dose group *vs*. No TMP/SMX group	0.393	(0.177-0.873)	0.022
Steroid DM or past history of DM	1.001	(0.441-2.276)	0.998
Serum lymphocyte count‡	0.917	(0.845-0.995)	0.037
Initial dose of CS/weight§	3.636	(0.701-18.666)	0.122
Receiving RTX	1.588	(0.590-4.279)	0.360

†TMP/SMX exposure was entered as a discrete time-varying covariate.
‡For every 100/μL increase.
§Different types of corticosteroids were converted to equivalent doses of prednisolone.
TMP/SMX: trimethoprim-sulfamethoxazole; DM: diabetes mellitus; CS: corticosteroids; CI: confidence interval.

Table IV. Summary of early severe infections.

Infections	Total n (%)	Standard-dose group (n=5)	Reduced-dose group (n=25)	No TMP/SMX group (n=15)
Bacterial pneumonia	15 (33.3)	3 (60.0)	9 (36.0)	3 (20.0)
Sepsis (unknown origin)	6 (13.3)	1 (20.0)	2 (8.0)	3 (20.0)
Cytomegalovirus infections	5 (11.1)	0	2 (8.0)	3 (20.0)
Skin and soft tissue infections	4 (8.9)	0	2 (8.0)	2 (13.3)
Disseminated herpes zoster infections	3 (6.7)	0	1 (4.0)	2 (13.3)
Fungal infections	2 (4.4)	1 (20.0)	1 (4.0)	0
Biliary tract infections	2 (4.4)	0	2 (8.0)	0
Pneumocystis jirovecii pneumonia	2 (4.4)	0	2 (8.0)	0
Intestinal infections	2 (4.4)	0	1 (4.0)	1 (6.7)
Mycobacterium avium complex infections	1 (2.2)	0	0	1 (6.7)
Disseminated nocardia infections	1 (2.2)	0	1 (4.0)	0
Urinary tract infections	1 (2.2)	0	1 (4.0)	0
Suppurative parotitis	1 (2.2)	0	1 (4.0)	0

TMP/SMX: trimethoprim-sulfamethoxazole.

Against Rheumatism/European Renal Association - European Dialysis and Transplant Association recommendations encourage the use of TMP/SMX as prophylaxis against infection with *Pneumocystis jirovecii* in all patients with AAV who are being treated with cyclophosphamide (28). However, little is known about its protecting effect against severe infections.

In 1996, a double-blind, placebo-controlled trial assessed the efficacy of TMP/SMX in preventing relapses among patients with GPA and found that the number of infectious episodes per patient within 24 months was significantly lower in the TMP/SMX group (9). Kronbichler *et al*. reported that the use of TMP/SMX was associated with a lower frequency of severe infections during follow-up (mean time of 22.7 months) in new-onset and relapsed patients with AAV receiving RTX (10). Previous studies have focused primarily on European patients with AAV, in whom GPA is predominant; these studies also did not consider time-varying changes related to TMP/SMX exposure, although discontinuation is relatively frequent due to side effects. Moreover, most life-threatening severe infections occur within the first 6 months of starting remission induction therapy (5-8, 20). Our study provides robust evidence of the protective effect of TMP/SMX against early severe infections among patients with AAV in an MPA-predominant sample and considering the time-varying changes that occur with TMP/SMX exposure. We believe our study revealed useful information in the context of the increasing incidence of MPA worldwide (29). In addition, we found that a reduced dose of TMP/SMX was effective in the prevention of severe infections. Whereas previous reports included relapse patients, this study included only new-onset patients with AAV; the results were therefore not affected by previous treatment.

Our study could not prove the presence of a significant protective effect against severe early infection in the standard-dose group, although the survival analysis implied that the standard-dose group seemed to have the same protective effect as the reduced-dose group. We believe that the reason for these results was derived from the relatively small sample size in the standard-dose group. One reason for the inadequate sample size was that in most cases receiving a standard dose of TMP/SMX, the dosage had to be reduced or discontinued due to side effects during the course of study (34.7% among the standard-dose group during the study period, data not shown).

We found that 18.0% of patients needed to discontinue TMP/SMX because of side effects. Although not all side effects may have been due to TMP/SMX and most of the patients received a reduced dose, the frequency of discontinuation was generally consistent with that of previous studies (9, 30-32). The results of some studies have indicated that the side effects of TMP/SMX were reduced by a reduced-dose regimen; however, our sample had a high number of patients with decreased kidney function, which may have increased the toxicity of TMP/SMX (11, 32).

To the best of our knowledge, there is no authorised prophylaxis regimen of TMP/SMX against *Pneumocystis jirovecii* pneumonia for rheumatic diseases patients regarding renal impairment. Although one open randomised trial reported the equal efficacy for preventing *Pneumocystis jirovecii* infection between the standard TMP/SMX dose group and half-dose group at week 24 in patients with various systemic rheumatic diseases, there were two cases of *Pneumocystis jirovecii* infection in the reduced-dose group in our study (32). The optimal TMP/SMX dose for the prevention of infections, including *Pneumocystis jirovecii*, warrants further study.

We acknowledge that there were several limitations to our study. First, given its

retrospective single-centre observational design, there could have been both selection and recall bias. Second, the study may have been unable to comprehensively detect potential confounding factors among all groups, considering TMP/SMX exposure as a time-varying factor. However, it seems reasonable to compare the background among groups at 1 month in the present study in the context of previous reports. Third, the prescription patterns of TMP/SMX varied in our cohort. Prospective comparative studies with defined TMP/SMX dosages according to renal function are warranted in the future.

In conclusion, TMP/SMX is highly effective in preventing severe infections as well as *Pneumocystis jirovecii* infection in patients with AAV, despite the high incidence of side effects. Further prospective studies will be warranted to determine the optimal dose of TMP/SMX for the prevention of severe infections, especially regarding renal impairment.

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