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Original Article

Implication of Serious Infections in Patients With Antineutrophil Cytoplasmic Antibody-Associated Vasculitis for the First Cycle of Rituximab: A Pilot Study in a Single Korean Center

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Objective: This study investigated the clinical implications of serious infections in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV) who received the first cycle of rituximab (RTX) during the first 6 months of follow-up.
Methods: The medical records of 36 AAV patients treated with RTX were reviewed. A weekly dose of 375 mg/m^2 RTX was administered for 4 weeks to all patients along with glucocorticoids. Serious infections were defined as those requiring hospitalization. All-cause mortality during the first 6 months of follow-up was counted. The follow-up duration was defined as the period from the first RTX infusion to 6 months after the first RTX infusion.
Results: The median age was 60.5 years, and 16 patients were male. Seven of 36 patients (19.4%) died and three AAV patients had five cases of serious infection such as enterocolitis, pulmonary aspergillosis, atypical pneumonia, cytomegalovirus pneumonia, and cellulitis. AAV patients with serious infections during the first 6 months of follow-up exhibited a significantly lower cumulative survival rate than those without serious infections ($p<0.001$). However, we found no independent predictor of serious infections using the Cox hazard model analysis.
Conclusion: Serious infection is an important predictor of all-cause mortality in Korean patients with AAV who received their first cycle of RTX but there were no significant variables to predict the occurrence of serious infections at the first RTX. Thus, in cases refractory to other induction therapies, RTX should be strongly considered, despite an increase in mortality rate.

Keywords: Antineutrophil cytoplasmic antibody, Vasculitis, Rituximab, Infection, Mortality

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is one of the systemic vasculitides that involves the smallest vessels, such as the capillaries, arterioles, and venules [1]. AAV is categorized into the following three subtypes; microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic GPA (EGPA), according to its clinical, laboratory, radiological, and histological features [2,3]. AAV treatment consists of two steps, namely induction therapy and maintenance therapy. Currently, cyclophosphamide or rituximab (RTX) with glucocorticoids is strongly recommended

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as an induction therapeutic regimen for patients with organ-threatening disease, whereas methotrexate or mycophenolate mofetil together with glucocorticoids is recommended for patients with non–organ-threatening disease [4-7]. In addition, after remission, azathioprine, methotrexate, or RTX along with tapered glucocorticoids for more than 2 years are currently recommended [4,7,8].

Recently, a study reported that the incidence rate of severe infections increased in patients with AAV receiving RTX during the first 12 months of follow-up, and age and serum creatinine level were independently associated with severe infections [9]. Given that the incidence rate of serious infection and mortality rate in AAV patients may differ based on ethnic and geographical diversity, it is worthwhile to investigate the proportion of Korean patients with AAV affected by serious adverse events and their clinical impact [10]. Hence, in this study, we investigated the clinical implication of serious infection in AAV patients receiving RTX during the first 6 months of follow-up.

MATERIALS AND METHODS

Study subjects

The medical records of 255 patients with AAV who were enrolled in the Severance Hospital ANCA-associated VasculitidEs (SHAVE) cohort were reviewed. The SHAVE cohort is a prospective and observational cohort of patients with AAV and was established in November 2016. Preferentially, 38 AAV patients were chosen who met the following inclusion criteria: i) the classification of AAV should be based on two guidelines namely the classification algorithm for AAV and polyarteritis nodosa proposed by the European Medicine Agency in 2007 (the 2007 algorithm) and the revised nomenclature of vasculitides suggested by the Chapel Hill Conference Consensus in 2012 (the 2012 definitions) [1,2]; ii) the classification of AAV should be made at the Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine; iii) RTX had been administered to patients with AAV after enrollment; iv) the medical records included the necessary information required for the clinical record form regarding clinical, laboratory, and AAV-specific data, medications, all-cause mortality, and infections; and v) the follow-up duration was >3 months after AAV diagnosis; The exclusion criteria were as follows: i) concurrent malignancies, infectious diseases, and systemic autoimmune vasculitis other than AAV at the time of AAV diagnosis as well as at the first RTX infusion; ii) AAV patients who had ever received immunosuppressive drugs for the treatment of AAV prior to AAV diagnosis. Secondarily, since diffuse large B-cell lymphoma developed in two patients with AAV after AAV diagnosis, and RTX was provided for the treatment of lymphoma, they were excluded from this study. Finally, 36 patients with AAV were included in this study (Figure 1). The present study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea, IRB No. 4-2020-1071). The patient's written informed consent was waived by the approving IRB, as this was a retrospective study. Given the retrospective design of the study and the use of anonymized patient data, the requirement for written informed consent was waived.

Variables at the first RTX infusion and for the first 6 months of follow-up

Age, male sex, body mass index, and smoking history were obtained as demographical data. Variables at the first RTX infusion and those for the first 6 months of follow-up, in particular, AAV-specific indices including AAV subtype, ANCA positivity, Birmingham vasculitis activity score (BVAS) [11], and five-factor score (FFS) [12], were collected (Table 1). The total follow-up duration was defined as the period between AAV diagnosis and the last visit for surviving AAV patients, and it was defined as that between AAV diagnosis and death for deceased AAV

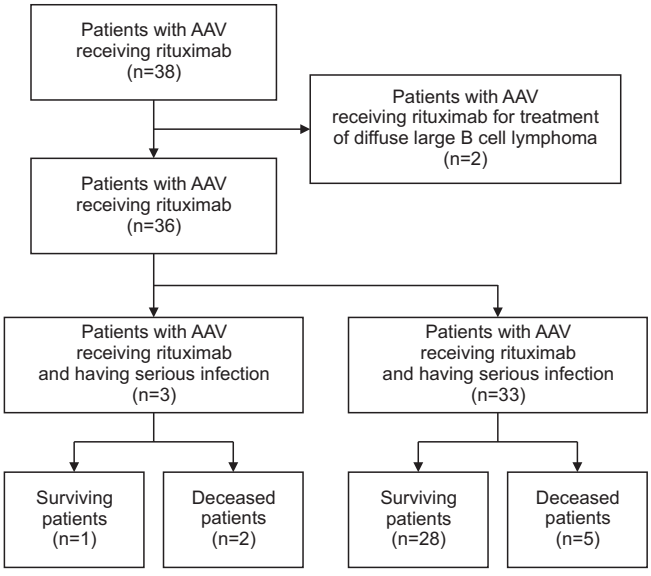

Figure 1. The algorithm of selecting patients. Finally, 36 patients with AAV were included in this study. AAV: antineutrophil cytoplasmic antibody-associated vasculitis.

Table 1. Comparison of characteristics of AAV patients receiving RTX (n=36)

Variable	All AAV patients (n=36)	AAV patientswithout serious infection (n=33)	AAV patients with serious infection (n=3)	p-value
At the first RTX infusion				
Demographic data				
Age (yr)	60.5 (23.0)	62.0 (22.0)	54.0 (N/A)	0.761
No. of male	16 (44.4)	14 (42.4)	2 (66.7)	0.574
Body mass index (kg/m^2)	24.0 (3.2)	22.9 (3.1)	22.8 (N/A)	0.977
Smoking history	8 (22.2)	7 (21.2)	1 (33.3)	0.541
AAV subtype				0.860
MPA	19 (52.8)	17 (51.5)	2 (66.7)	
GPA	16 (44.4)	15 (45.5)	1 (33.3)	
EGPA	1 (2.8)	1(3.0)	0 (0)	
ANCA positivity				
MPO-ANCA (or P-ANCA) positivity	26 (72.2)	24 (72.7)	2 (66.7)	1.000
PR3-ANCA (or C-ANCA) positivity	11 (30.6)	10 (30.3)	1 (33.3)	1.000
Both ANCA positivity	2 (5.6)	2 (6.1)	0 (0)	1.000
Clinical manifestations according to BVAS system				
General manifestations	18 (50.0)	16 (48.5)	2 (66.7)	1.000
Cutaneous manifestations	4 (11.1)	4 (12.1)	0 (0)	1.000
Mucous and ocular manifestations	4 (11.1)	3 (9.1)	1 (33.3)	0.305
Otorhinolaryngological manifestations	17 (47.2)	15 (45.5)	2 (66.7)	0.593
Pulmonary manifestations	24 (66.7)	23 (69.7)	1 (33.3)	0.253
Cardiovascular manifestations	5 (13.9)	4 (12.1)	1 (33.3)	0.370
Gastrointestinal manifestations	1 (2.8)	1 (3.0)	0 (0)	1.000
Renal manifestations	25 (69.4)	22 (66.7)	3 (100)	0.538
Nervous systemic manifestations	12 (33.3)	11 (33.3)	1 (33.3)	1.000
AAV-specific indices				
BVAS	12.0 (11.0)	12.0 (9.0)	20.0 (N/A)	0.121
FFS	1.0 (1.0)	1.0 (1.0)	2.0 (N/A)	0.292
Comorbidity				
Chronic kidney disease without RRT	11 (30.6)	10 (30.3)	1 (33.3)	1.000
Diabetes mellitus	8 (22.2)	7 (21.2)	1 (33.3)	0.541
Hypertension	15 (41.7)	14 (42.4)	1 (33.3)	1.000
Dyslipidaemia	10 (27.8)	10 (30.3)	0 (0)	0.545
Interstitial lung disease	11 (30.6)	10 (30.3)	1 (33.3)	1.000
Chronic obstructive pulmonary disease	2 (5.6)	1 (3.0)	1 (33.3)	0.162
Latent tuberculosis	7 (19.4)	6 (18.2)	1 (33.3)	0.488
Laboratory result				
White blood cell count (/mm^3)	7,505.0 (2,780.0)	7,620.0 (2,980.0)	6,930.0 (N/A)	0.407
Neutrophil count (/mm^3)	6,410.0 (2,490.0)	6,610.0 (2,870.0)	5,920.0 (N/A)	0.627
Lymphocyte count (/mm^3)	825.0 (870.0)	830.0 (760.0)	340.0 (N/A)	0.290
Hemoglobin (g/dL)	10.1 (3.4)	10.1 (3.5)	8.9 (N/A)	0.375
Platelet count (×1,000/mm^3)	229.3 (117.0)	229.0 (128.0)	234.0 (N/A)	0.932
Fasting glucose (mg/dL)	120.0 (68.0)	119.0 (67.0)	129.0 (N/A)	0.457
Blood urea nitrogen (mg/dL)	23.7 (37.0)	23.6 (38.2)	31.2 (N/A)	0.529
Creatinine (mg/dL)	1.5 (1.9)	1.5 (1.9)	2.0 (N/A)	0.627
Total protein (g/dL)	5.6 (1.1)	5.7 (1.0)	5.3 (N/A)	0.108
Serum albumin (g/dL)	3.5 (0.6)	3.4 (0.6)	3.5 (N/A)	0.752

Table 1. Continued

Variable	All AAV patients (n=36)	AAV patientswithout serious infection (n=33)	AAV patients with serious infection (n=3)	p-value
Acute phase reactants				
ESR (mm/h)	15.0 (43.0)	18.0 (45.0)	2.0 (N/A)	0.100
CRP (mg/L)	2.1 (8.0)	2.1 (9.0)	1.7 (N/A)	0.422
During the follow-up duration				
Total follow-up duration (mo)	718.0 (1,140.0)	802.0 (1,139.0)	113.0 (N/A)	0.018
Follow-up duration from the first RTX infusion to 6 months (mo)	5.6 (0)	5.6 (0)	3.8 (N/A)	<0.001
All-cause mortality	7 (19.4)	5 (15.2)	2 (66.7)	0.090
Medications from AAV diagnosis to 6 months after the first RTX infusion				
Glucocorticoid	36 (100)	33 (100)	3 (100)	N/A
Cyclophosphamide	28 (77.8)	26 (78.8)	2 (66.7)	0.541
Mycophenolate mofetil	9 (25.0)	9 (27.3)	0 (0)	0.558
Azathioprine	23 (63.9)	22 (66.7)	1 (33.3)	0.539
Tacrolimus	3 (8.3)	3 (9.1)	0 (0)	1.000
Methotrexate	4 (11.1)	4 (12.1)	0 (0)	1.000
Plasma exchange	8 (22.2)	7 (21.2)	1 (33.3)	0.541
Cumulative dose (mg)				
Glucocorticoids (equivalent to prednisolone)	11,706.6 (9,738.4)	11,781.3 (9,792.8)	10,217.5 (N/A)	0.753
RTX	2,050.0 (578.0)	2,100.0 (750.0)	2,000.0 (N/A)	0.681
Cyclophosphamide	3,000.0 (5,289.0)	3,000.0 (5,108.0)	1,800.0 (N/A)	0.902

Values are presented as number (%) or median (interquartile range). Significant differences between two categorical variables were analyzed using the chi-squared and Fisher's exact tests. The Mann–Whitney U test was used to compare significant differences between two continuous variables. Comparison of the cumulative survival rates between the two groups was performed using Kaplan-Meier survival analysis with the log-rank test. AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, RTX: rituximab, N/A: not applicable, MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiitis, EGPA: eosinophilic granulomatosis with polyangiitis, MPO: myeloperoxidase, P: perinuclear, PR3: proteinase 3, C: cytoplasmic, BVAS: Birmingham vasculitis activity score, FFS: five-factor score, RRT: renal replacement therapy, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

patients. Meanwhile, the follow-up duration was defined as the period during the first 6 months of follow-up after the first RTX infusion for surviving AAV patients, whereas it was defined as the period from the first RTX infusion to death for deceased AAV patients. Medications administered from the AAV diagnosis to 6 months after the first RTX infusion were evaluated. In particular, the cumulative doses of induction therapeutic regimens, glucocorticoids, RTX, and cyclophosphamide were calculated.

RTX treatment and serious infections

A weekly dose of 375 mg/m^2 RTX was administered for 4 weeks to all patients with AAV in this study as an induction therapeutic regimen [5]. Serious infections were defined as those requiring hospitalization, and only serious infection that occurred during the first 6 months of follow-up were assessed in this study.

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as medians with interquartile ranges, and categorical variables are expressed as numbers (percentages). Significant differences between two categorical variables were analyzed using the chi-squared and Fisher's exact tests. The Mann-Whitney U test was used to compare significant differences between two continuous variables. Comparison of the cumulative survival rates between the two groups was performed using Kaplan-Meier survival analysis with the log-rank test. The multivariable Cox hazard model using variables with statistical significance in the univariable Cox hazard model was used to obtain hazard ratios (HRs) during follow-up. p-values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of patients with AAV

At the first RTX infusion, the median age was 60.5 years, and 16 patients were male (19 patients were classified as having MPA, 16 as having GPA, and 1 as having EGPA). The mean body mass index was 24.0 kg/m^2 and eight patients (22.2%) had smoking history. The median BVAS, FFS, erythrocyte sedimentation rate, and C-reactive protein levels were 12.0, 1.0, 15.0 mm/h, and 2.1 mg/L, respectively. During the first 6 months of follow-up, 7 of 36 patients (19.4%) died of any cause. The median cumulative dose of RTX was 2,050.0 mg (Table 1).

Comparative analysis

At the first RTX infusion, there were no significant differences in variables at diagnosis between AAV patients with and without serious infections. The median total follow-up duration was 718.0 months, and that in AAV patients with serious infection was significantly lower than that in AAV patients without serious infection (113.0 vs. 802.0 months, respectively; p=0.018). The follow-up duration after the first RTX infusion exhibited a similar pattern to the total follow-up duration between the two groups (3.8 vs. 5.6 months, respectively; p<0.001). Conversely, patient with AAV with serious infection had a higher mortality rate than those without serious infection (66.7% vs. 15.2%, respectively), but the difference was not statistically significant. There were no significant differences in the number of patients receiving immunosuppressive drugs or the cumulative dose of induction therapeutic regimens between the two groups. In particular, before the first cycle of rituximab, cyclophosphamide had been administered to 28 patients, of whom 2 had serious infections during the first 6 months of follow-up after the first cycle of rituximab, and there were no differences in the frequency and cumulative doses of cyclophosphamide between AAV patients with serious infections and those without (Table 1).

AAV patients with serious infection

Three patients with AAV experienced five cases of serious infection during the first 6 months of follow-up. One 79-year-old female patient with MPA (patient #1) had myeloperoxidase (MPO)-ANCA and exhibited general, otolaryngological, pulmonary, and renal manifestations at the first RTX. The patient had both concurrent enterocolitis and invasive pulmonary aspergillosis for 4.4 months after the first RTX. Another 54-year-

Table 2. Patients with AAV who received RTX and had serious infection during the first 6 months of follow-up

Patient	AAV type	Sex	Age at the first RTX (yr)	Follow-up duration (mo)	ANCA	BVAS at the first RTX	FFS at the first RTX	Clinical manifestations at the first RTX	Period from the first RTX to serious infection (mo)	Serious infection	Death
#1	MPA	Female	79	3.4	MPO-ANCA	23	1	G, O, P, R	4.4	Enterocolitis, Pulmonary aspergillosis	Death
#2	MPA	Male	54	5.3	MPO-ANCA	12	3	R	3.8	Atypical pneumonia	Death
#3	GPA	Male	28	126.7	PR3-ANCA	20	2	G, M, O, C, R, N	1.9	Cytomegalovirus pneumonia, Cellulitis	Survival

AAV: ANCA-associated vasculitis, ANCA: antineutrophil cytoplasmic antibody, RTX: rituximab, MPA: microscopic polyangiitis, GPA: granulomatosis with polyangiitis, MPO: myeloperoxidase, P: perinuclear, PR3: proteinase 3, C: cytoplasmic, BVAS: Birmingham vasculitis activity score, FFS: five-factor score, G: general manifestations, O: otorhinolaryngological manifestations, P: pulmonary manifestations, R: renal manifestations, M: mucous and ocular manifestations, C: cardiovascular manifestations, N: nervous systemic manifestations.

old male patient with MPA (patient #2) also had MPO-ANCA and exhibited only renal manifestations at the first RTX. The patient had presented with atypical pneumonia, in which the pathogen was not identified, for 3.8 months after the first RTX. A third 28-year-old male patient had proteinase 3 (PR3)-ANCA and exhibited general, mucous and ocular, otolaryngological, cardiovascular, renal, and nervous systemic manifestations. The patients had both cytomegalovirus pneumonia and cellulitis. Two patients with MPA died (Table 2) and they died of the infection mentioned above. In AAV without serious infection, 5 patients died. The causes of death were brain hemorrhage, pneumonia, idiopathic pulmonary fibrosis, candida sepsis, and sepsis related cholangitis.

Comparison of the cumulative survival rates

In the comparative analysis between the two groups based on the presence of current serious infections, patient with AAV with serious infections during the first 6 months of follow-up exhibited a significantly lower cumulative survival rate than those without serious infections (p<0.001) (Figure 2).

Cox hazards model analysis

However, in the univariate analysis, there were no significant variables to predict the occurrence of serious infections. Chronic obstructive pulmonary disease tended to predict serious infection (HR=7.977; 95% confidence interval [CI]: 0.725, 88.203); however, this was not statistically significant (Supplementary Table 1).

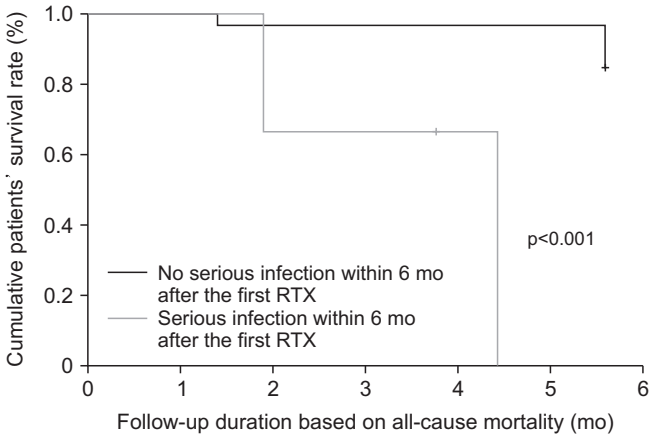

Figure 2. Comparison of the cumulative survival rates. Patient with AAV with serious infections during the first 6 months of follow-up exhibited a significantly lower cumulative survival rate than those without serious infections. AAV: antineutrophil cytoplasmic antibody-associated vasculitis, RTX: rituximab.

DISCUSSION

There were two reasons for investigating the incidence rate of serious infections and its influence on all-cause mortality in patients with AAV receiving RTX only during the first 6 months of follow-up. One was the reimbursement of the medical expenses. Until November 2020, only the reimbursement for RTX infusion as an induction therapy, but not as maintenance therapy, was approved by the Korean National Health Insurance Service. For this reason, most patients with AAV included in this study received only one cycle of RTX infusion (weekly for 4 weeks) as induction therapy under medical insurance. The other is an increased chance of confounding factors contribute to the occurrence of serious infections, such as elevated cumulative doses of glucocorticoids and rituximab, the possibility of worsening of AAV, and an increase in age, leading to increased susceptibility to infections.

There has been known to be that age, smoking, pulmonary involvement, immunosuppressive therapy with mycophenolate mofetil, cyclophophamide, and dose of corticosteroid can increase the risk of infection those who administered with RTX in AAV patients.

Therefore, it was expected that the first 6 months of follow-up would yield clear results.

Serious infections were clearly and independently associated with all-cause mortality in patients with AAV receiving RTX. Therefore, if a factor to predict the occurrence of serious infections at the first RTX infusion can be identified, it will be possible to improve the clinical course by reducing the possibility of all-cause mortality during the first 6 months of follow-up. To obtain independent predictive factors at the time of initiating RTX for the occurrence of serious infections during the first 6 months of follow-up, Cox hazards model analysis for serious infections was conducted. However, in this study, no statistically significant predictors of the occurrence of serious infections were identified (Supplementary Table 1).

We also investigated the effect of high-dose glucocorticoids on the occurrence of serious infection in AAV patients receiving the first cycle of RTX. First of all, when 'high-dose glucocorticoids' is considered as a dose of 1 mg/day equivalent to prednisolone, 'high-dose glucocorticoids' was administered to AAV patients only during the first four weeks of the first cycle

of RTX. During the follow-up after the first cycle of RTX, 'glucocorticoids' was provided to three AAV patients, of whom 1 patient with serious infections received a dose of 62.5 mg/day equivalent to methylprednisolone, whereas, both two patients without serious infections took a dose of 62.5 mg/day equivalent to methylprednisolone. And there were no significant differences in the frequency and doses of 'high-dose glucocorticoids' between AAV patients with serious infections and those without (p=0.236 for the frequency).

Among the various risk factors for serious infections, we focused on four variables at the first cycle of RTX such as obesity, a smoking history and functional status in AAV patients. First, we investigated body mass index for obesity status and a smoking history at the time of the first cycle of RTX. The mean body mass index was 24.0 kg/m^2 and eight patients (22.2%) had smoking history (no current smoker), however, no statistically significant differences in those variables between the two groups were observed (Table 1). Whereas, in terms of functional status, all AAV patients were discharged and none of them was transferred to other hospitals after the first cycle of RTX. Therefore, although we could not obtain clear information on functional status from the medical records, it is assumed that most patients did not have seriously reduced functional states and thus functional status was not likely to contribute to the development of the serious infection in AAV patients.

The five cases of serious infections comprised three cases of pneumonia, one case of enterocolitis, and one case of cellulitis. There were no cases of bacterial pneumonia was not included, but there were cases of viral, fungal, and atypical pneumonia. Of these three patients, two patients died, one from invasive pulmonary aspergillosis (fungal infection) and the other from pneumonia due to cytomegalovirus infection. We believe that these results have two clinical implications. First, in terms of serious infections associated with AAV, all serious infections that caused death were infections that invaded the lungs. Therefore, it could be inferred that although pulmonary manifestation was not directly associated with serious infections, pulmonary involvement in AAV may increase the likelihood of infectious lung disease and ultimately increase the frequency of death. In terms of serious infections not associated with AAV, chronic obstructive pulmonary disorder (COPD) at the time of first RTX infusion tended to be associated with serious infections, although there was no statistical significance in the univariable Cox hazards model analysis (HR=7.997; 95% CI: 0.725, 88.203; p=0.090) (Supplementary Table 1). Therefore, it could be inferred that the presence or absence of COPD may also serve as a predictor for monitoring the occurrence of serious infections but was not useful in this study.

The advantage of this study is that we investigated and proved the clinical significance of serious infections after the first RTX infusion in Korean patients with AAV for the first time, although we could not identify predictors for the occurrence of serious infections in patients with AAV receiving RTX. However, this study had several limitations such as the small number of AAV patients and the retrospective design of this study. In particular, serum immunoglobulin levels should have been checked at baseline and monitored after RTX treatment because hypogammaglobinaemia following RTX may increase infectious risk [12-14]. However, due to the retrospective design of this study, we could not provide immunoglobulin levels before and after RTX treatment in AAV patients [15]. We realized that vaccinations may be associated with the risk of serious infections, but we could not obtain information on the performance of vaccination generally recommended, because it is almost impossible in Korea's medical reality to collect information on vaccinations other than information provided by patients. Also, since two of three AAV patients with serious infection passed away during the first 6 months after the first cycle of RTX, we could not clarify the association between therapeutic responses to RTX and serious infections in this study. We believe that future prospective studies with a larger number of patients who receive more than the second cycle of RTX infusion will clarify and validate the results of our study.

In conclusion, serious infection is an important predictor of all-cause mortality in Korean patients with AAV who received their first RTX infusion but there were no significant variables to predict the occurrence of serious infections at the time of initiating RTX. Therefore, if the necessity for RTX infusion is increased in patients with AAV that is refractory to other induction therapeutic regimens and which should be controlled, physicians should begin RTX infusion beyond concerns about the occurrence of serious infection which might provoke all-cause mortality.

CONCLUSION

Among 36 Korean patients who received RTX, five patients experienced serious infections for the first 6 months of follow-

up. AAV patients with serious infections during the first 6 months of follow-up exhibited a significantly lower cumulative survival rate than those without. No independent predictors of serious infections at the first RTX were obtained in the Cox hazard model analysis.

SUPPLEMENTARY DATA

Supplementary data can be found with this article online at https://doi.org/10.4078/jrd.22.0033.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

H.D., J.Y.P. and S.-W.L. contributed to the study design and data collection, analysis, and interpretation. J.J.S. and Y.-B.P. contributed to the data interpretation. All authors revised the manuscript and gave final approval for submission.

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