



Rituximab Biosimilar Prevents Poor Outcomes of Microscopic Polyangiitis and Granulomatosis with Polyangiitis as Effectively as Rituximab Originator

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Purpose: There has been no extensive study to compare the efficacy between rituximab originator (Mabthera[®]) and its biosimilar (Truxima[®]) for microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA). Here, we investigated the clinical effects of rituximab on poor outcomes of MPA and GPA in Korean patients, and compared those between Mabthera[®] and Truxima[®].

Materials and Methods: We retrospectively reviewed the medical records of a total of 139 patients, including 97 MPA patients and 42 GPA patients. At diagnosis, antineutrophil cytoplasmic antibody positivity and comorbidities were assessed. During follow-up, all-cause mortality, relapse, end-stage renal disease, cerebrovascular accident and acute coronary syndrome were evaluated as poor outcomes. In this study, rituximab was used as either Mabthera[®] or Truxima[®].

Results: The median age at diagnosis was 60.1 years and 46 patients were men (97 MPA and 42 GPA patients). Among poor outcomes, patients receiving rituximab exhibited a significantly lower cumulative relapse-free survival rate compared to those not receiving rituximab ($p=0.002$). Nevertheless, rituximab use did not make any difference in other poor outcomes of MPA and GPA except for relapse, which might be a rebuttal to the fact that rituximab use after relapse eventually led to better prognosis. There were no significant differences in variables at diagnosis and during follow-up between patients receiving Mabthera[®] and those receiving Truxima[®]. Patients receiving Truxima[®] exhibited a similar pattern of the cumulative survival rates of each poor outcome to those receiving Mabthera[®].

Conclusion: Truxima[®] prevents poor outcomes of MPA and GPA as effectively as does Mabthera[®].

Key Words: Rituximab, biosimilar, microscopic polyangiitis, granulomatosis with polyangiitis, prognosis

INTRODUCTION

Microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA) are classified as antineutrophil cytoplasmic an-

tibody (ANCA)-associated vasculitis (AAV). MPA and GPA share the pathological characteristics of small-vessel necrotizing vasculitis, as described in the 2012 Chapel Hill Consensus Conferences Nomenclature of Vasculitis (2012 CHCC definitions).^{1,2} However, clinical features of MPA and GPA are quite different: MPA has a predilection to cause necrotizing glomerulonephritis and pulmonary capillaritis, whereas GPA often induces the formation of granuloma at the upper and lower respiratory tracts and occasionally causes necrotizing glomerulonephritis.³

Rituximab, a monoclonal antibody against CD20 of B lymphocytes, has been widely used as one of the standard therapies for MPA and GPA. The efficacy of rituximab on MPA and GPA as both induction and maintenance therapies has been shown in the two large clinical trials.^{4,5} Moreover, rituximab

Received: May 11, 2020 **Revised:** June 6, 2020

Accepted: June 16, 2020

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•The authors have no potential conflicts of interest to disclose.

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has also been validated to be effective as a remission maintenance therapy in refractory GPA cases.⁶ The European League Against Rheumatism (EULAR) and the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recognized the therapeutic potential of rituximab as effective as that of cyclophosphamide (CYC), suggesting that a combination of glucocorticoid with either CYC or rituximab be administered to newly diagnosed patients with life-threatening AAV.⁷

Currently, two types of rituximab are widely used, including originator (Mabthera[®], Roche) and biosimilar (Truxima[®], Celltrion). Truxima[®] is the first rituximab biosimilar, and it has been approved for the treatment of medical conditions for which Mabthera[®] was also approved.⁸ The clinical effects of Truxima[®] were compared with those of Mabthera[®] via several clinical trials, and were proved to be effective and safe in patients with follicular lymphoma and rheumatoid arthritis.^{9,10} However, there was no extensive study to analyse the efficacy of Truxima[®] for MPA and GPA with a considerable number of patients. Here, we investigated whether Truxima[®] could prevent poor outcomes of MPA and GPA as effectively as Mabthera[®].

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of 139 patients with MPA and GPA from the Severance Hospital ANCA-associated VasculitidEs (SHAVE) cohort between October 2000 and March 2019, at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, Seoul, Republic of Korea. The diagnosis of MPA and GPA was based on the 2007 European Medicines Agency algorithm for AAV and polyarteritis nodosa (the 2007 EMA algorithm) and the 2012 CHCC definitions.^{1,2} All patients had well-documented medical records with which we could obtain the information on ANCA positivity, clinical data, and comorbidities at diagnosis, as well as outcomes and medications that were administered during follow-up. This study was approved by the Institutional Review Board (IRB) of Severance Hospital (4-2017-0673), which waived the need for patients' written informed consent, as this was a retrospective study.

Clinical data and ANCA positivity at diagnosis and during follow-up

In regard to variables at diagnosis, age and gender were collected as demographic data. We check the positivity of four types of ANCA was, including perinuclear (P)-ANCA, cytoplasmic (C)-ANCA, myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA. In patients who tested positive in the indirect fluorescence assay, but negative in antigen-specific assays, P-ANCA positivity was considered as MPO-ANCA

positivity and C-ANCA positivity as PR3-ANCA positivity.¹¹ We also assessed the comorbidities of MPA and GPA at the time prior to the initiation of any immunosuppressive drug, such as hypertension, chronic kidney disease (CKD) (stage III-V), dyslipidaemia, diabetes mellitus, interstitial pneumonia and diffuse alveolar haemorrhage.

With regard to variables during follow-up, all-cause mortality, relapse, end-stage renal disease (ERSD), cerebrovascular accident and acute coronary syndrome were evaluated as poor outcomes. The follow-up duration was defined as the period between the date of AAV diagnosis and the date of the last visit for the survived patients. In cases of the deceased patients, it was defined as the period between the diagnosis of AAV and the time of death. For patients who had any poor outcomes, it was defined as the period starting from the diagnosis of AAV until the time when each poor outcome appeared. Medications administered during follow-up were also examined.

Rituximab

Two types of rituximab, Mabthera[®] and Truxima[®], were used; and both were considered as rituximab in this study. Based on the EULAR recommendation, in real clinical settings, we have explained that Mabthera[®] is rituximab originator and Truxima[®] is rituximab biosimilar. Also, we have evenly recommended two drugs for patients in need of rituximab and encouraged patients to choose Mabthera[®] or Truxima[®] to date.

Statistical analyses

All statistical analyses were conducted using SPSS software (version 23 for Windows; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median (interquartile range), and categorical variables were expressed as number and percentage. Significant differences in categorical variables between the two groups were analysed using chi-square and Fisher's exact tests. Significant differences in continuous variables between the two groups were compared using Mann-Whitney test. Comparison of cumulative survivals between the two groups, based on the administration of rituximab, was analysed by Kaplan-Meier survival analysis with log-rank test. The relative risk (RR) of A for B was analysed using contingency tables and chi-square test. *p*-values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of 139 patients with MPA and GPA

The median age at diagnosis was 60.1 years, and 46 patients were men (97 MPA patients and 42 GPA patients). At diagnosis, ANCA was detected in 120 patients (92.3%) and MPO-ANCA (or P-ANCA) was positive in 99 patients (71.2%). The most common comorbidity at diagnosis was hypertension (44.6%),

followed by CKD (30.2%). During follow-up, the most common poor outcome was relapse (36.0%), followed by ESRD (23.2%). The most commonly administered immunosuppressive drug after glucocorticoid (92.1%) was CYC (48.2%), followed by azathioprine (47.5%). Twenty-six patients (18.7%) received rituximab (Table 1).

Comparison of variables between patients receiving rituximab and those not receiving rituximab

We compared various clinical aspects between patients who received rituximab and those who did not receive rituximab. First, we did not observe any significant differences in demographic data, and AAV variants were found. All patients receiving rituximab had ANCA at diagnosis, whereas 84.1% of patients not receiving rituximab had ANCA at diagnosis ($p=0.024$). For the pre-existing comorbidities at diagnosis, patients in the rituximab group exhibited higher frequencies of having CKD (50.0% vs. 25.7%, $p=0.015$) and dyslipidaemia (46.2% vs. 25.7%, $p=0.039$) compared to those in the non-rituximab group, but other comorbidities were not different between the two groups. Furthermore, the two groups had comparable follow-up durations. Patients receiving rituximab presented relapse more often than those not receiving rituximab (61.5% vs. 30.1% $p=0.003$). Azathioprine (65.4% vs. 43.4%, $p=0.043$) and mycophenolate mofetil (34.6% vs. 8.8%, $p=0.001$) had been supplied frequently to patients receiving rituximab, compared to those not receiving rituximab (Table 2).

Comparison of the cumulative survival rates of poor outcomes between patients receiving rituximab and those not receiving rituximab

Using Kaplan-Meier analysis, we analysed and compared the cumulative survival rates of poor outcomes of MPA and GPA during the follow-up period between patients receiving rituximab and those not receiving rituximab. Among poor outcomes during the follow-up period, patients receiving rituximab exhibited a significantly lower cumulative relapse-free survival rate compared to those not receiving rituximab ($p=0.002$) (Fig. 1).

Comparison of the cumulative survival rates of poor outcomes between Mabthera[®] and Truxima[®]

We compared the clinical effects of rituximab on poor outcomes of MPA and GPA between Mabthera[®] and Truxima[®]. There were no significant differences in demographic, ANCA positivity and comorbidity data at diagnosis, as well as the frequency of poor outcomes and medications administered during follow-up between patients receiving Mabthera[®] and Truxima[®] (Table 3). Moreover, among poor outcomes, patients receiving Truxima[®] exhibited a similar pattern of cumulative survival rates of each poor outcome compared to those receiving Mabthera[®] (Fig. 2).

DISCUSSION

In this study, we investigated the clinical effects of rituximab on poor outcomes of MPA and GPA in Korean patients and found that the cumulative relapse-free rate in patients receiving rituximab was much lower than that in patients not receiving rituximab during follow-up. We interpret this result to mean that rituximab was more frequently administered to patients experiencing any relapse rather than rituximab having insufficient efficacy for preventing relapse. To support our

Table 1. Characteristics of 139 Patients with MPA or GPA

Variables	Values
At diagnosis	
Demographic data	
Age (yr)	60.1 (19.5)
Male gender	46 (33.1)
Variants	
MPA	97 (69.8)
GPA	42 (30.2)
ANCA positivity at diagnosis	
MPO-ANCA (or P-ANCA)	99 (71.2)
PR3-ANCA (or C-ANCA)	25 (18.0)
MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA)	4 (2.9)
ANCA negative	19 (13.7)
Comorbidities at diagnosis	
Hypertension	62 (44.6)
CKD (stage III–V)	42 (30.2)
Dyslipidaemia	41 (29.5)
Diabetes mellitus	39 (28.1)
Interstitial lung disease	34 (24.5)
Diffuse alveolar haemorrhage	7 (5.0)
During follow-up	
Poor outcomes during follow-up	
Relapse	50 (36.0)
ESRD	32 (23.2)
All-cause mortality	14 (10.1)
CVA	12 (8.6)
ACS	9 (6.5)
Medications administered during follow-up	
Rituximab	26 (18.7)
Glucocorticoid	128 (92.1)
Cyclophosphamide	67 (48.2)
Azathioprine	66 (47.5)
Methotrexate	17 (12.2)
Mycophenolate mofetil	19 (13.7)
Tacrolimus	10 (7.2)

MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; CKD, chronic kidney disease; ESRD, end-stage renal disease; CVA, cerebrovascular accident, ACS, acute coronary syndrome.

Values are expressed as median (interquartile range) or n (%).

claim, we compared the frequencies of rituximab use between patients with and without relapse, and found that rituximab was prescribed more often to patients with relapse than those without relapse [16 of 50 patients (32.0%) vs. 10 of 89 patients (11.2%), $p=0.003$]. In addition, we obtained a RR of 3.718 for having serious vasculitis status requiring rituximab use in relation to the presence of relapse over the absence of relapse.

In order to get a more accurate analysis in this context, it is preferred to compare the variables before and after the use of rituximab. However, since we only had one case of relapse after rituximab administration, statistical analysis of the preventive potential of rituximab for relapse of MPA and GPA was not possible. Nevertheless, we believed that the lack of difference in other poor outcomes of MPA and GPA, except for re-

Table 2. Comparison of Variables between MPA or GPA Patients Receiving Rituximab and Those Not Receiving Rituximab

Variables	Patients receiving rituximab (n=26)	Patients not receiving rituximab (n=113)	p value
At diagnosis			
Demographic data			
Age (yr)	57.3 (13.9)	61.0 (20.4)	0.595
Male gender	10 (38.5)	36 (31.9)	0.519
Variants			
MPA	17 (65.4)	80 (70.8)	0.588
GPA	9 (34.6)	33 (29.2)	
ANCA positivity at diagnosis			
MPO-ANCA (or P-ANCA)	21 (80.8)	78 (69.0)	0.337
PR3-ANCA (or C-ANCA)	6 (23.1)	19 (16.8)	0.453
ANCA double positive	1 (3.8)	3 (2.7)	0.568
ANCA negative	0 (0)	19 (15.9)	0.024
Comorbidities during at diagnosis			
Hypertension	16 (61.5)	46 (40.7)	0.054
CKD (stage III–V)	13 (50.0)	29 (25.7)	0.015
Dyslipidaemia	12 (46.2)	29 (25.7)	0.039
Diabetes mellitus	6 (23.1)	33 (29.2)	0.531
Interstitial lung disease	8 (30.8)	26 (23.0)	0.407
Diffuse alveolar haemorrhage	2 (7.7)	5 (4.4)	0.615
During follow-up			
Follow-up duration (months)	26.0 (57.7)	34.9 (59.7)	0.691
Poor outcomes			
Relapse	16 (61.5)	34 (30.1)	0.003
Follow-up duration for relapse (months)	11.4 (23.3)	19.6 (39.3)	0.227
ESRD	7 (26.9)	25 (22.1)	0.600
Follow-up duration for ESRD (months)	27.1 (49.0)	16.1 (52.9)	0.157
All-cause mortality	3 (11.5)	11 (9.7)	0.726
Follow-up duration for death (months)	26.0 (57.7)	34.9 (59.7)	0.701
CVA	3 (11.5)	9 (8.0)	0.697
Follow-up duration for CVA (months)	22.1 (42.3)	28.1 (58.2)	0.679
ACS	2 (7.7)	7 (6.2)	0.675
Follow-up duration for ACS (months)	26.0 (41.4)	33.8 (60.2)	0.666
Medications administered during follow-up			
Glucocorticoid	26 (100)	102 (90.3)	0.218
Cyclophosphamide	17 (65.4)	50 (44.2)	0.052
Azathioprine	17 (65.4)	49 (43.4)	0.043
Methotrexate	2 (7.7)	15 (13.3)	0.522
Mycophenolate mofetil	9 (34.6)	10 (8.8)	0.001
Tacrolimus	2 (7.7)	8 (7.8)	1.000

MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; CKD, chronic kidney disease; ESRD, end-stage renal disease; CVA, cerebrovascular accident, ACS, acute coronary syndrome. Values are expressed as median (interquartile range) or n (%).

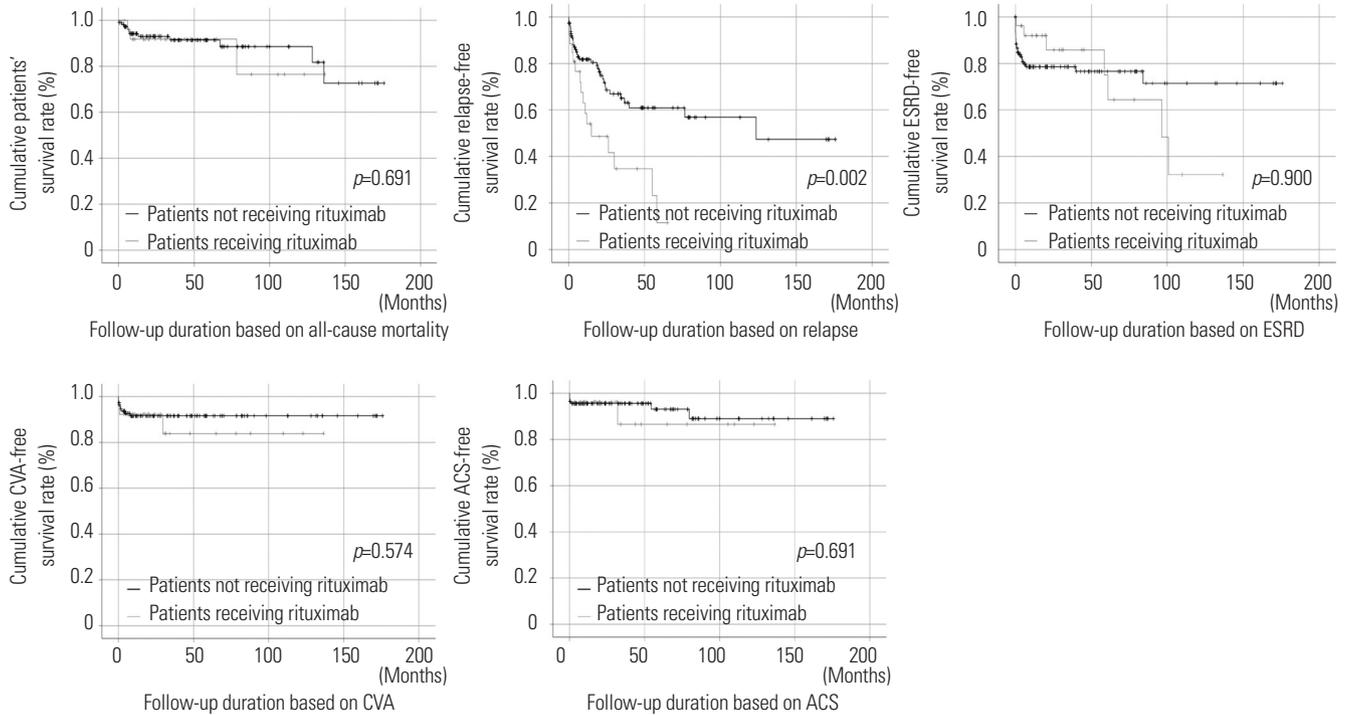


Fig. 1. Comparison of cumulative survival rates of poor outcomes based on the administration of rituximab. Among five poor outcomes during the follow-up period, patients receiving rituximab exhibited a significantly lower cumulative relapse-free survival rate than those compared to receiving rituximab. ESRD, end-stage renal disease; CVA, cerebrovascular accident, ACS, acute coronary syndrome.

lapse, might be a rebuttal to the fact that rituximab use after relapse eventually led to good.

There was another evidence for the positive effect of rituximab on poor outcomes of MPA and GPA. At diagnosis, the frequency of CKD (stage III-V) in patients receiving rituximab was higher than that in patients not receiving rituximab. In other words, this result may reflect that the extent of kidney involvement of MPA and GPA was more severe in patients receiving rituximab compared to the other group. However, the two groups exhibited similar cumulative ESRD-free survival rates during follow-up. This result was in line with the results of previous studies;^{5,12} therefore, we also assumed that rituximab might have a preventive potential against the progression to ESRD in Korean patients with MPA and GPA.

Like many European countries, the National Health Insurance Service (NHIS) in Korea provides universal healthcare to South Korean patients. However, the coverage of rituximab for MPA and GAP patients by NHIS is somewhat different than those of European countries. Since January 2013, NHIS in Korea has provided coverage for rituximab to MPA and GPA patients under special circumstances, such as the following: cases of MPA or GPA which are refractory to CYC, or cases that exhibit serious adverse events caused by CYC. Therefore, in Korea, the rituximab-based therapy for MPA and GPA is still recognized as a secondary induction therapeutic option after the use of CYC. If rituximab could be used as a primary induction therapeutic option for MPA and GPA treatment, we would expect a better prognosis for patients with MPA and GPA.

Here, we compared the two brands of rituximab: Mabthera[®] and Truxima[®] with respect to therapeutic effects on the outcomes of MPA and GPA. The Korean NHIS has offered coverage of Mabthera[®] for treating MPA and GPA since January 2013, whereas, Truxima[®] has been covered since February 2017. For this reason, the therapeutic effects and long-term outcomes by Truxima[®] in patients with MPA and GPA have been not well-known compared to those by Mabthera[®]. In the present study, we found that the clinical effects of Truxima[®] on poor outcomes of MPA and GPA were not significantly different from those of Mabthera[®]. This result suggests that Truxima[®] is as effective as Mabthera[®] in the treatment of MPA and GPA, without worsening any outcomes.

At diagnosis, the frequency of ANCA positivity in patients receiving rituximab was significantly higher compared to those not receiving rituximab (Table 2). In addition, during follow-up, patients receiving rituximab had experienced relapse more often compared to those not receiving rituximab (Fig. 1). Taking these results into consideration, we expected that the frequency of relapse in patients with ANCA would be meaningfully higher than that in those without ANCA. We investigated whether ANCA positivity at diagnosis might enhance the occurrence of poor outcomes of MPA and GPA during follow-up using Kaplan Meier survival analysis with log-rank test. Among poor outcomes, ANCA positivity at diagnosis could predict lower cumulative relapse-free survival rate than ANCA negativity does at diagnosis ($p=0.049$). Moreover, among poor outcomes other than relapse, patients with

ANCA at diagnosis exhibited significantly reduced cumulative ESRD-free survival rate compared to those without ANCA at diagnosis ($p=0.020$) (Supplementary Fig. 1, only online), similar to previous studies.^{13,14} Therefore, we concluded that ANCA positivity at diagnosis might be closely associated with relapse, which more often required rituximab use compared to ANCA negativity.

In addition, interstitial lung disease and diffuse alveolar haemorrhage at diagnosis have been known as important risk factors for all-cause mortality during follow-up in patients with AAV.^{15,16} The cumulative survival rates were significantly lower in patients with interstitial lung disease and those with diffuse alveolar haemorrhage at diagnosis compared to those

without lung manifestations ($p=0.034$ and $p=0.006$, respectively) (Supplementary Fig. 2, only online).

Our study had several limitations. First, it was designed as a monocentric study. For this reason, the number of patients receiving rituximab was not large enough to represent the current clinical situation in Korea regarding MPA and GPA. Also, due to the study's retrospective design, we could not exclude the possibility of missing data at diagnosis. In addition, as mentioned earlier, there was a difference in follow-up durations between Mabthera®-based group and Truxima®-based group, due to the NHIS coverage policy in Korea. This could have caused a problem in comparing the clinical effects between the two groups. However, we believe that our study may

Table 3. Comparison of Variables between MPA or GPA Patients Receiving Mabthera® and Those Receiving Truxima®

Variables	Patients receiving Mabthera® (n=11)	Patients receiving Truxima® (n=15)	p value
At diagnosis			
Demographic data			
Age (yr)	55.0 (15.7)	57.5 (13.5)	0.675
Male gender	3 (27.3)	7 (46.7)	0.315
Variants			
MPA	8 (72.7)	9 (60.0)	0.683
GPA	3 (27.3)	6 (40.0)	0.683
ANCA positivity at diagnosis			
MPO-ANCA (or P-ANCA)	9 (81.8)	12 (80.0)	1.000
PR3-ANCA (or C-ANCA)	3 (27.3)	3 (20.0)	1.000
ANCA double positive	1 (9.1)	0 (0)	0.423
ANCA negative	0 (0)	0 (0)	N/A
Comorbidities during at diagnosis			
Hypertension	6 (54.5)	10 (66.7)	0.530
CKD (stage III–V)	4 (36.4)	9 (60.0)	0.428
Dyslipidaemia	5 (45.5)	7 (46.7)	0.951
Diabetes mellitus	3 (27.3)	3 (20.0)	1.000
Interstitial lung disease	4 (36.4)	4 (26.7)	0.683
Diffuse alveolar haemorrhage	1 (9.1)	1 (6.7)	1.000
During follow-up			
Poor outcomes			
Relapse	8 (72.7)	8 (53.3)	0.428
ESRD	4 (36.4)	3 (20.0)	0.407
All-cause mortality	2 (18.2)	1 (6.7)	0.556
CVA	2 (18.2)	1 (6.7)	0.556
ACS	2 (18.2)	0 (0)	0.169
Medications administered during follow-up			
Glucocorticoid	11 (100)	15 (100)	N/A
Cyclophosphamide	6 (54.5)	11 (73.3)	0.419
Azathioprine	7 (63.6)	10 (66.7)	1.000
Methotrexate	2 (18.2)	0 (0)	0.169
Mycophenolate mofetil	4 (36.4)	5 (33.3)	1.000
Tacrolimus	2 (18.2)	0 (0.0)	0.169

MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; N/A, not applicable; CKD, chronic kidney disease; ESRD, end-stage renal disease; CVA, cerebrovascular accident; ACS, acute coronary syndrome.

Values are expressed as median (interquartile range) or n (%).

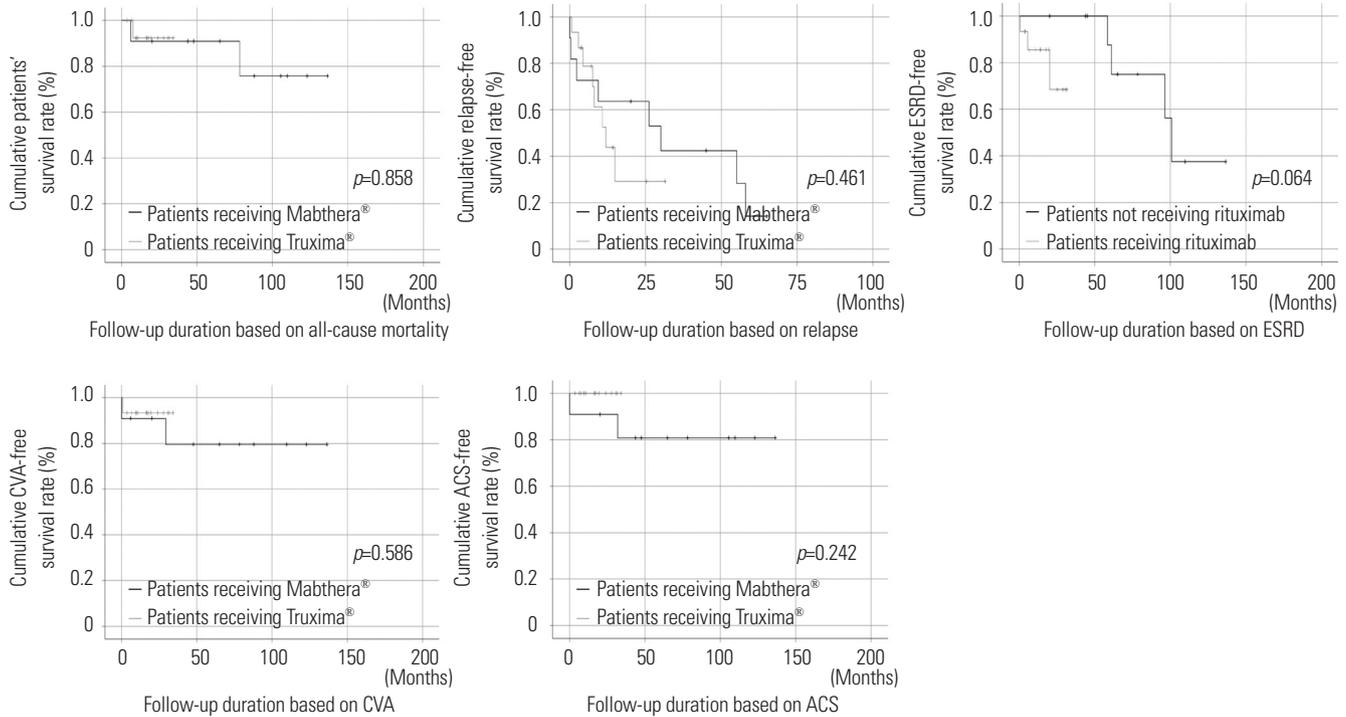


Fig. 2. Comparison of cumulative survival rates of poor outcomes between rituximab originator (Mabthera®) and biosimilar (Truxima®). Among five poor outcomes, patients receiving Truxima® exhibited a similar pattern of cumulative survival rates for each poor outcome compared to those receiving Mabthera®. ESRD, end-stage renal disease; CVA, cerebrovascular accident, ACS, acute coronary syndrome.

still offer some clinical significance to demonstrate the effect of rituximab use on the prognosis of MPA and GPA in Korean patients, as the first pilot study conducted in the biggest AAV cohort in Korea. Furthermore, this study was the first to compare the effect of Truxima® on poor outcomes of MPA and GPA with that of Mabthera®.

In conclusion, rituximab is an effective therapeutic modality for treating severe MPA and GPA in Korean patients. Also, Truxima® prevents poor outcomes of MPA and GPA as effectively as does Mabthera®.

ACKNOWLEDGEMENTS

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (HI14C1324).

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