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Efficacy of tacrolimus as maintenance therapy after cyclophosphamide for treating antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Azathioprine (AZA), methotrexate, or rituximab is used for the maintenance therapy of antineutrophil cytoplasmic antibody-associated vasculitis (AAV). Although the efficacy of tacrolimus (TAC) in various autoimmune diseases has been demonstrated, there have been few reports on the efficacy of TAC in AAV. We investigated the efficacy of TAC as maintenance therapy for AAV and compared its efficacy with that of AZA.

We retrospectively analyzed the medical records of 81 patients with AAV who received cyclophosphamide as induction therapy and AZA or TAC as maintenance therapy. All-cause death, relapse, and progression to end-stage renal disease (ESRD) were analyzed.

Among 81 patients with AAV, 69 patients received AZA alone, 6 patients received TAC alone, and 6 patients received TAC after AZA for maintenance therapy. Overall, 11 patients (13.6%) died, 30 patients (37.0%) experienced relapse, and 16 patients (19.8%) progressed to ESRD during a median of 33.8 months. No significant differences were observed in cumulative patients', relapse-free, and ESRD-free survival rates between patients administered AZA alone and TAC alone. There were no significant differences in the cumulative patients' and relapse-free survival rate between patients who received AZA alone and TAC after AZA. However, the cumulative ESRD-free survival rate was lower in patients who received TAC after AZA than in those who received AZA alone ($P=.027$).

Patients who received TAC as maintenance therapy showed a higher incidence of ESRD than those who received AZA; however, this might be attributed to the lack of efficacy of AZA rather than the low ESRD prevention effect of TAC.

Abbreviations: AAV = antineutrophil cytoplasmic antibody-associated vasculitis, ANCA = antineutrophil cytoplasmic antibody, AZA = azathioprine, BVAS = Birmingham vasculitis activity score, C = cytoplasmic, CYC = cyclophosphamide, ESRD = end-stage renal disease, FFS = five-factor score, GPA = granulomatosis with polyangiitis, MMF = mycophenolate mofetil, MPO = myeloperoxidase, MTX = methotrexate, P = perinuclear, PR3 = proteinase 3, RTX = rituximab, TAC = tacrolimus.

Keywords: antibodies, antineutrophil cytoplasmic, chronic kidney disease, tacrolimus, therapeutics

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Consent for publication: Not applicable.

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1. Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis characterized by necrotizing vasculitis, presenting no or few immune complex deposits in organ tissues.[1] AAV is divided into 3 subtypes based on clinical, laboratory, radiological, and histological features—microscopic polyangiitis, granulomatosis with polyangiitis (GPA), and eosinophilic GPA.[2]

The treatment of AAV is categorized into induction therapy and maintenance therapy, with induction therapy particularly aimed at remission induction.[3] For induction therapeutic regimens, in the case of organ or life-threatening diseases, either cyclophosphamide (CYC) or rituximab (RTX), along with glucocorticoids, is recommended.[4–7] Particularly, for serious diffuse alveolar hemorrhage with rapidly progressive renal failure, plasma exchange should be considered.[4,8] In cases of non-organ or life-threatening disease, either methotrexate (MTX) or mycophenolate mofetil (MMF), along with glucocorticoids, is recommended.[4,9] For maintenance therapeutic regimens after remission, azathioprine (AZA), MTX, or RTX, along with glucocorticoids, is recommended.[4,10] Moreover, maintenance therapy is recommended for at least 2 years.[4]

Tacrolimus (TAC) is a macrolide calcineurin inhibitor and has been widely used for treating autoimmune diseases and preventing graft failure after organ transplantation.[11,12]

In autoimmune diseases, pro-inflammatory cytokines, including tumor necrosis factor-α and interleukin-1, can enhance intracellular ionized calcium (Ca^{++}) concentration; thus, activity of calcineurin/nuclear factor of activated T cells increases. Consequently, alterations in autoreactive immune cells may occur; for instance, T cell activation, proliferation, and differentiation from naive T cells to TH1 and TH17 cells may be noticeably augmented.[13] TAC inhibits calcineurin phosphatase and downregulates calcium-dependent pathways.

Considering changes in pro-inflammatory cytokines and the subsequent activation of autoreactive immune cells play an important role in the pathogenesis of AAV,[14–16] it could be postulated that TAC may be a beneficial therapeutic alternative for treating AAV, possibly as effective as AZA or MTX as maintenance therapy. Nevertheless, only a few cases on the efficacy of TAC in treating AAV have been reported.[17,18] Furthermore, there have been no previous reports on the therapeutic potential of TAC in a considerable number of patients with AAV. Hence, in this study, we investigated the efficacy of TAC as maintenance therapy for AAV treatment and compared its efficacy with that of AZA.

2. Methods

2.1. Patients

The medical records of 223 patients with AAV were retrospectively reviewed. All patients were initially diagnosed or reclassified as AAV at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital, from October 2000 to March 2020. Furthermore, all patients met both the 2007 European Medicines Agency algorithm for polyarteritis nodosa and AAV and the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.[1,2] The inclusion criteria were as follows: patients who received CYC as induction therapy and patients who received AZA or TAC as maintenance therapy. The exclusion criteria were as follows: patients who received other immunosuppressive drugs, such as MMF or MTX, for maintenance therapy, patients who had a follow-up period of less than 3 months, and patients presenting serious concomitant medical conditions, such as malignancy, serious infection, and other systemic vasculitides other than AAV.

2.2. Study population

Among 223 patients with AAV, 106 patients who did not receive CYC as induction therapy were excluded. Furthermore, among 117 patients with AAV who received CYC as induction therapy, 7 patients who received MMF alone or MMF after AZA, 22 patients who received MTX alone or MTX after AZA, and 7 patients who received no immunosuppressive agents as maintenance therapy were excluded. Finally, 81 patients with AAV who received AZA alone, TAC alone, or TAC after AZA as maintenance therapy, after induction therapy with CYC, were included in this study (Fig. 1). Glucocorticoid pulse therapy (1 g for 3 days or 500 mg for 5 days) was given to all patients for remission induction therapy, followed by high-dose prednisolone for at least 4 weeks. After the glucocorticoid pulse therapy, 6 cycles of intravenous CYC (15 mg/kg, dose adjusted by renal function and age) was administered. To substantially focus on TAC and AZA, prednisolone or methylprednisolone was deliberately not described for convenience in this study. The present study was performed in accordance with the Declaration of Helsinki Ethical Principles and was approved by the Institutional Review Board of Severance Hospital (**4-2017-0673**); being a retrospective study, the board waived the need for written informed consent.

2.3. Medications administered

We reviewed the medical records to gather information regarding the administration of CYC, RTX, MMF, AZA, MTX, and TAC, along with prednisolone, in patients with AAV during the follow-up. Patients prescribed TAC were subdivided into 2 groups: those taking TAC alone and those prescribed TAC after AZA. Medications administered were monitored under the Korean Drug Utilization Review system to prevent omission of any medications prescribed by other hospitals.

2.4. Data collection

At the time of diagnosis, demographic data were collected, which included data related to age and sex of the patients. In addition to AAV subtypes and ANCA positivity, clinical features based on 9 items of the Birmingham vasculitis activity score (BVAS) were reviewed. As AAV-specific indices, BVAS and five-factor score (FFS) were assessed. The initial results of the white blood cell count, hemoglobin, platelet count, creatinine, serum albumin, aspartate aminotransferase, alanine aminotransferase, erythrocyte sedimentation rate, and C-reactive protein were investigated.

2.5. Evaluation of poor outcomes of AAV

We defined poor outcomes of AAV as all-cause mortality, relapse, and progression to end-stage renal disease (ESRD) during the follow-up period. ESRD was defined as a status that requires renal replacement therapy.

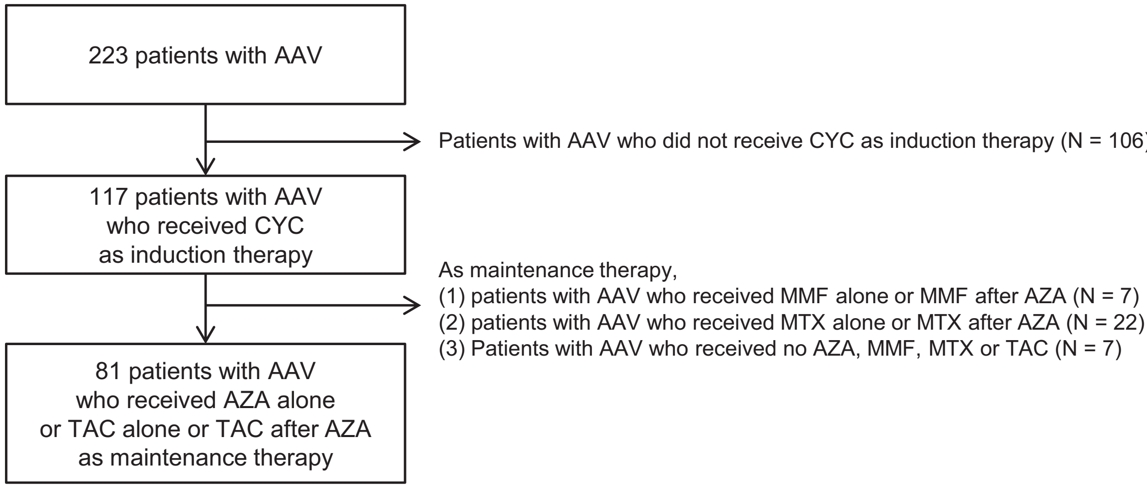

Figure 1. Selection of the study population. AAV = ANCA-associated vasculitis, AZA = azathioprine, CYC = cyclophosphamide, MMF = mycophenolate mofetil, TAC = tacrolimus.

2.6. Follow-up period

For the surviving patients, the follow-up duration was defined as the period since initial AAV diagnosis until the last visit. For deceased patients, the follow-up duration based on all-cause mortality was defined as the period since initial AAV diagnosis until death. For patients who presented poor outcomes, the follow-up duration was defined as the period since initial AAV diagnosis until each poor outcome appeared.

2.7. Statistical analyses

All statistical analyses were conducted using SPSS (version 25 for Windows; IBM Corp., Armonk, NY). Continuous variables are expressed as median and interquartile range, and categorical variables are expressed as number and percentage. Significant differences in categorical variables between groups were analyzed using the χ^2 and Fisher exact tests. Significant differences in continuous variables between groups were compared using the Mann–Whitney test. A comparison of cumulative survival rates between groups was performed using Kaplan-Meier survival analysis with the log-rank test. P values <.05 were considered statistically significant.

3. Results

3.1. Data at diagnosis

The median age was 59.0 years, and 50 patients (61.7%) were women. Among 81 patients, 55 patients were diagnosed with microscopic polyangiitis, 13 with GPA, and 16 with eosinophilic granulomatosis with polyangiitis. ANCA was positive in 63 patients. The most common clinical feature was renal manifestations (67.9%), followed by pulmonary manifestations (54.3%). The median BVAS, FFS, erythrocyte sedimentation rate, and C-reactive protein were 13.0, 1.0, 63.0 mm/h, and 19.1 mg/L, respectively. The median values of other routine laboratory test results are described in Table 1.

3.2. Data during follow-up period

Among 81 patients, 11 patients (13.6%) died of any cause. Thirty patients (37.0%) experienced relapse, and 16 patients (19.8%) required renal replacement therapy. Among 81 patients, AZA was administered to 75 patients (92.6%) and TAC was prescribed to 12 patients (14.8%) for maintenance therapy after induction therapy with CYC. Six patients were prescribed AZA, with subsequent administration of TAC (Table 1).

3.3. Comparison of variables between patients administered AZA alone and those administered TAC alone or TAC after AZA

Regarding data at the time of diagnosis, no significant differences were observed in demographics, AAV subtypes, ANCA positivity, and clinical features between patients prescribed AZA alone and those administered TAC alone or TAC after AZA. AAV-specific indices, routine laboratory results, and acute-phase reactants did not differ between the groups. In terms of data during the follow-up period, the period based on all-cause mortality was longer in patients prescribed TAC alone or TAC after AZA than in those administered AZA alone (62.8 vs 32.4 months, respectively). Additionally, patients prescribed TAC alone or TAC after AZA exhibited a higher rate of ESRD occurrence than those administered AZA alone (41.7% vs 15.9%), but did not demonstrate any significant difference (Table 1).

3.4. Comparison of cumulative survival rates between patients administered AZA alone and those administered TAC alone or TAC after AZA

Patients prescribed TAC alone or TAC after AZA exhibited a lower cumulative ESRD-free survival rate than those prescribed AZA alone (P = .026). However, no significant differences were observed in the cumulative patients' and relapse-free survival rates between the groups (Fig. 2).

3.5. Comparison of variables among patients who received AZA alone, TAC alone, and TAC after AZA

First, regarding patients administered AZA alone and TAC alone, all patients administered TAC alone exhibited pulmonary

Table 1

Demographics of patients with antineutrophil cytoplasmic antibody-associated vasculitis who received azathioprine alone and those who received tacrolimus alone or after azathioprine.

Variables	All patients (N=81)	AZA alone (N=69)	TAC alone or TAC after AZA (N=12)	*P*
At the time of diagnosis				
Demographic data				
Age, y	59.0 (23.0)	59.0 (23.0)	61.0 (22.0)	.519
Female sex, N (%)	50 (61.7)	43 (62.3)	7 (58.3)	1.000
AAV subtypes (N, (%))				.324
MPA	52 (64.2)	42 (60.9)	10 (83.3)	
GPA	13 (16.0)	12 (17.4)	1 (8.3)	
EGPA	16 (19.8)	15 (21.7)	1 (8.3)	
ANCA positivity, N (%)				
MPO-ANCA (or P-ANCA) positive	55 (67.9)	47 (68.1)	8 (66.7)	1.000
PR3-ANCA (or C-ANCA) positive	12 (14.8)	11 (15.9)	1 (8.3)	.683
Both ANCA positive	4 (4.9)	4 (5.8)	0 (0)	1.000
ANCA negative	18 (22.2)	15 (21.7)	3 (25.0)	.724
Clinical features based on BVAS				
General manifestations	39 (48.1)	30 (43.5)	9 (75.0)	.061
Cutaneous manifestations	17 (21.0)	16 (23.2)	1 (8.3)	.444
Mucous and ocular manifestations	2 (2.5)	1 (1.4)	1 (8.3)	.276
Otorhinolaryngologic manifestations	34 (42.0)	29 (42.0)	5 (41.7)	1.000
Pulmonary manifestations	44 (54.3)	35 (50.7)	9 (75.0)	.208
Cardiovascular manifestations	19 (23.5)	15 (21.7)	4 (33.3)	.462
Gastrointestinal manifestations	5 (6.2)	5 (7.2)	0 (0)	1.000
Renal manifestations	55 (67.9)	46 (66.7)	9 (75.0)	.743
Nervous systemic manifestations	32 (39.5)	27 (39.1)	5 (41.7)	1.000
AAV-specific indices				
BVAS	13.0 (9.0)	13.0 (8.0)	16.5 (14.8)	.531
FFS	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	.890
Comorbidities at diagnosis (n (%))				
Chronic kidney disease (stage 3–5)	33 (40.7)	30 (43.5)	3 (25.0)	.229
Diabetes mellitus	25 (30.9)	20 (29.0)	5 (41.7)	.380
Hypertension	32 (39.5)	25 (78.1)	7 (58.3)	.148
Dyslipidemia	18 (22.2)	14 (20.3)	4 (33.3)	.316
Routine laboratory results				
WBC count (/mm^3)	9500.0 (7455.0)	9740.0 (7475.0)	8690.0 (5072.5)	.175
Hb, g/dL	10.6 (3.6)	10.9 (3.7)	9.8 (3.6)	.186
PLT count ($\times$1000/mm^3)	292.0 (152.5)	295.0 (153.5)	221.0 (181.5)	.128
Creatinine, mg/dL	1.1 (1.6)	1.1 (1.3)	1.3 (5.6)	.242
Serum albumin, g/dL	3.6 (1.1)	3.6 (1.2)	3.7 (0.9)	.608
Aspartate aminotransferase, IU/L	18.0 (8.5)	18.0 (9.0)	16.0 (3.5)	.218
Alanine aminotransferase, IU/L	15.0 (13.0)	15.0 (13.0)	14.0 (7.5)	.324
Acute phase reactants				
ESR, mm/h	63.0 (81.0)	63.0 (80.5)	51.0 (82.3)	.558
CRP, mg/L	19.1 (63.2)	19.1 (59.9)	21.0 (91.0)	.489
During the follow-up period				
Poor outcomes and follow-up periods				
All-cause mortality, N (%)	11 (13.6)	9 (13.0)	2 (16.7)	.663
Follow-up period based on all-cause mortality, mo	36.5 (78.3)	32.4 (76.6)	62.8 (123.4)	.053
Relapse, N (%)	30 (37.0)	24 (34.8)	6 (50.0)	.314
Follow-up period based on relapse, mo	24.7 (39.7)	19.8 (37.9)	26.6 (53.2)	.730
ESRD, N (%)	16 (19.8)	11 (15.9)	5 (41.7)	.054
Follow-up period based on ESRD, mo	26.2 (55.3)	26.2 (65.3)	26.6 (54.0)	.581
Medications administered, N (%)				
CYC	81 (100)	69 (100)	12 (100)	N/A
AZA	75 (92.6)	69 (100)	6 (50.0)	N/A
TAC	12 (14.8)	0 (0)	12 (100)	N/A

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

AAV=ANCA-associated vasculitis, ANCA=antineutrophil cytoplasmic antibody, AZA=azathioprine, BVAS=Birmingham vasculitis activity score, C=cytoplasmic, CRP=C-reactive protein, CYC=cyclophosphamide, EGPA=eosinophilic granulomatosis with polyangiitis, ESR=erythrocyte sedimentation rate, ESRD=end-stage renal disease, FFS=five-factor score, GPA=granulomatosis with polyangiitis, Hb=haemoglobin, MPA=microscopic polyangiitis, MPO=myeloperoxidase, N/A=not applicable, P=perinuclear, PLT=platelet, PR3=proteinase 3, TAC=tacrolimus, WBC=white blood cell.

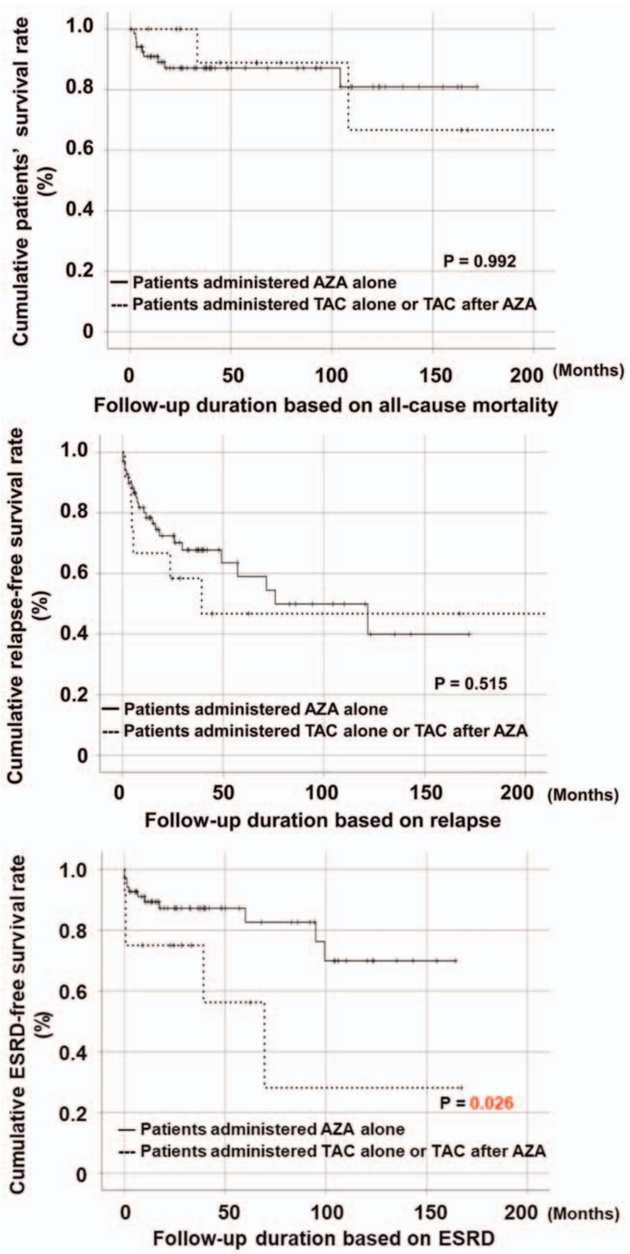

Figure 2. Kaplan-Meier curves comparing patients who received AZA alone and TAC alone or TAC after AZA. There were no differences in the cumulative patients' and relapse-free survival rates between patients prescribed TAC alone or TAC after AZA. Patients prescribed TAC alone or TAC after AZA exhibited a lower cumulative ESRD-free survival rate than those prescribed AZA alone ($P=.026$). AZA=azathioprine, ESRD=end-stage renal disease, TAC=tacrolimus.

manifestations at diagnosis, whereas 50.7% of patients administered AZA alone exhibited these manifestations ($P=.029$). Other variables did not differ between these groups. Second, regarding patients administered AZA alone and administered TAC after AZA, patients administered TAC after AZA had more underlying hypertension than those administered AZA alone ($P=.035$). Third, regrading patients administered TAC alone and administered TAC after AZA, FFS at diagnosis was significantly higher in patients administered TAC alone than in those administered TAC after AZA ($P=.044$). However, its statistical significance was too low to propose clinical implications. The incidence rates of poor AAV outcomes did not differ among the 3 groups (Table 2).

3.6. Comparison of cumulative survival rates among patients administered AZA alone, TAC alone, and TAC after AZA

Between patients who received AZA alone and TAC alone, no significant differences were observed in the cumulative patients', relapse-free, and ESRD-free survival rates. Meanwhile, patients who received TAC after AZA exhibited a lower cumulative ESRD-free survival rate than those who received AZA alone ($P=.027$). Other cumulative survival rates did not differ between patients who received AZA alone and those who received TAC after AZA. The cumulative patients', relapse-free, and ESRD-free survival rates did not differ between patients who received TAC alone and those who received TAC after AZA (Fig. 3).

4. Discussion

Our study is the first to investigate the therapeutic potential of TAC as maintenance therapy for AAV treatment in a considerable number of patients, to the best of our knowledge. In the present study, we demonstrated that patients who received TAC for maintenance therapy showed comparable outcomes for survival and relapse with those who received AZA for maintenance therapy. However, the risk for ESRD occurrence was higher in patients who received TAC than those who received AZA.

In this study, the most significant difference was observed in the incidence rates of ESRD in patients who received TAC and those who received AZA alone during the follow-up period. More precisely, patients administered TAC after AZA as maintenance therapy showed a high incidence rate of ESRD. What factors influenced these outcomes?

First, we questioned whether glomerulonephritis was more severe or renal function had decreased more at the time of diagnosis in patients administered TAC after AZA than in those who received AZA alone. As a result, baseline serum creatinine level was higher in patients administered TAC after AZA than in those administered AZA alone (2.8 vs 1.1 mg/dL). Furthermore, we pondered whether there were any factors other than kidney-related variables that present a distinct difference at the time of diagnosis between patients who received TAC after AZA and those administered AZA alone. A greater proportion of patients who received TAC after AZA had underlying hypertension than those who received AZA alone (83.3% vs. 36.2%) (Table 2). These factors may have resulted in high incidence of ESRD in patients administered TAC after AZA.

We focused on the reasons for switching from AZA to TAC. Among six patients administered TAC after AZA, five patients switched from AZA to TAC due to lack of efficacy and one patient owing to elevated levels of hepatic enzymes.[19] Among 5 patients who switched medications due to a lack of efficacy, 4 suffered from decreased renal function, three of whom progressed to ESRD. In other words, before drug switching, a sudden decline in kidney function had commenced. However, there was little need for drug switching in patients who maintained AZA, as no sudden decline in kidney function was observed. Therefore, it can be concluded that the decline in renal function while receiving AZA was the key reason for progression to ESRD, rather than that TAC was less effective in maintaining renal functions than

Table 2

Comparison of variables among patients with antineutrophil cytoplasmic antibody-associated vasculitis who were administered azathioprine alone, tacrolimus alone, and tacrolimus after azathioprine.

Variables	AZA alone [1] (N=69)	TAC alone [2] (N=6)	TAC after AZA [3] (N=6)	*P* (1 vs 2)	*P* (1 vs 3)	*P* (2 vs 3)
At the time of diagnosis						
Demographic data						
Age, y)	59.0 (23.0)	64.0 (16.8)	58.5 (31.8)	.333	.984	.520
Female sex, N (%)	43 (62.3)	4 (66.7)	3 (50.0)	1.000	.671	1.000
AAV subtypes, N (%)				.417	.460	.368
MPA	42 (60.9)	5 (83.3)	5 (83.3)			
GPA	12 (17.4)	1 (16.7)	0 (0)			
EGPA	15 (21.7)	0 (0)	1 (16.7)			
ANCA positivity, N (%)						
MPO-ANCA (or P-ANCA) positive	47 (68.1)	4 (66.7)	4 (66.7)	1.000	1.000	1.000
PR3-ANCA (or C-ANCA) positive	11 (15.9)	1 (16.7)	0 (0)	1.000	.583	1.000
Both ANCA positive	4 (5.8)	0 (0)	0 (0)	1.000	1.000	N/A
ANCA negative	15 (21.7)	1 (16.7)	2 (33.3)	1.000	.613	1.000
Clinical features based on BVAS						
General manifestations	30 (43.5)	5 (83.3)	4 (66.7)	.092	.401	1.000
Cutaneous manifestations	16 (23.2)	0 (0)	1 (16.7)	.331	1.000	1.000
Mucous and ocular manifestations	1 (1.4)	1 (16.7)	0 (0)	.155	1.000	1.000
Otorhinolaryngologic manifestations	29 (42.0)	1 (16.7)	4 (66.7)	.392	.395	.242
Pulmonary manifestations	35 (50.7)	6 (100)	3 (50.0)	.029	1.000	.182
Cardiovascular manifestations	15 (21.7)	3 (50.0)	1 (16.7)	.145	1.000	.545
Gastrointestinal manifestations	5 (7.2)	0 (0)	0 (0)	1.000	1.000	N/A
Renal manifestations	46 (66.7)	5 (83.3)	4 (66.7)	.657	1.000	1.000
Nervous systemic manifestations	27 (39.1)	2 (33.3)	3 (50.0)	1.000	.678	1.000
AAV-specific indices						
BVAS	13.0 (8.0)	17.0 (17.5)	16.5 (12.3)	.604	.688	.688
FFS	1.0 (1.0)	2.0 (2.0)	1.0 (1.3)	.149	.214	.044
Comorbidities at diagnosis, n (%)						
Chronic kidney disease (stage 3–5)	30 (43.5)	2 (33.3)	1 (16.7)	.630	.391	1.000
Diabetes mellitus	20 (29.0)	3 (50.0)	2 (33.3)	.284	1.000	1.000
Hypertension	25 (36.2)	2 (33.3)	5 (83.3)	.887	.035	0.242
Dyslipidemia	14 (20.3)	2 (33.3)	2 (12.5)	.602	.602	1.000
Routine laboratory results						
WBC count (/mm^3)	9740.0 (7475.0)	8690.0 (6375.0)	9190.0 (7112.5)	.319	.319	1.000
Hb, g/dL	10.9 (3.7)	10.0 (2.0)	8.7 (5.2)	.429	.249	.335
PLT count (×1000/mm^3)	295.0 (153.5)	221.0 (174.8)	230.5 (201.5)	.257	.270	.749
Creatinine, mg/dL	1.1 (1.3)	1.2 (6.7)	2.8 (5.8)	.435	.348	.936
Serum albumin, g/dL	3.6 (1.2)	3.7 (1.3)	3.7 (0.8)	.519	.914	.748
Aspartate aminotransferase, IU/L	18.0 (9.0)	16.0 (6.5)	16.0 (12.5)	.544	.229	.618
Alanine aminotransferase, IU/L	15.0 (13.0)	14.0 (16.8)	12.0 (17.8)	.822	.222	.333
Acute phase reactants						
ESR, mm/h	63.0 (80.5)	34.0 (83.5)	76.0 (63.3)	.252	.777	.297
CRP, mg/L	19.1 (59.9)	10.5 (48.3)	70.0 (112.1)	.799	.204	.336
During the follow-up period						
Poor outcomes and follow-up periods						
All-cause mortality, N (%)	9 (13.0)	0 (0)	2 (33.3)	1.000	.211	.455
Follow-up period based on all-cause mortality, mo	32.4 (76.6)	53.8 (140.7)	68.6 (111.2)	.125	.191	.873
Relapse, N (%)	24 (34.8)	2 (33.3)	4 (66.7)	1.000	.188	.567
Follow-up period based on relapse, mo	19.8 (37.9)	26.6 (71.7)	31.5 (99.0)	.961	.646	.631
ESRD, N (%)	11 (15.9)	2 (33.3)	3 (50.0)	.277	.075	1.000
Follow-up period based on ESRD, mo	26.2 (65.3)	23.8 (62.6)	36.3 (57.4)	.500	.891	.378

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

AAV=ANCA-associated vasculitis, ANCA=antineutrophil cytoplasmic antibody, AZA=azathioprine, BVAS=Birmingham vasculitis activity score, C=cytoplasmic, CRP=C-reactive protein, EGPA=eosinophilic granulomatosis with polyangiitis, ESR=erythrocyte sedimentation rate, ESRD=end-stage renal disease, FFS=five-factor score, GPA=granulomatosis with polyangiitis, Hb=haemoglobin, MPA=microscopic polyangiitis, MPO=myeloperoxidase, N/A=not applicable, P=perinuclear, PLT=platelet, PR3=proteinase 3, TAC=tacrolimus, WBC=white blood cell.

AZA. We believe that only 2 of 6 patients who received TAC only as maintenance therapy progressed to ESRD, which supports our hypothesis.

Follow-up period based on all-cause mortality was longer in patients administered TAC alone or TAC after AZA than those administered AZA alone. Nine patients died among patients administered AZA alone, whereas those administered TAC alone had no mortality. Two cases of mortality among patients treated with TAC was among those treated with TAC after AZA, not TAC alone. This might be the factor affecting the difference in follow-up period, because patients who switched taking AZA to TAC inevitably have a longer follow-up duration because they

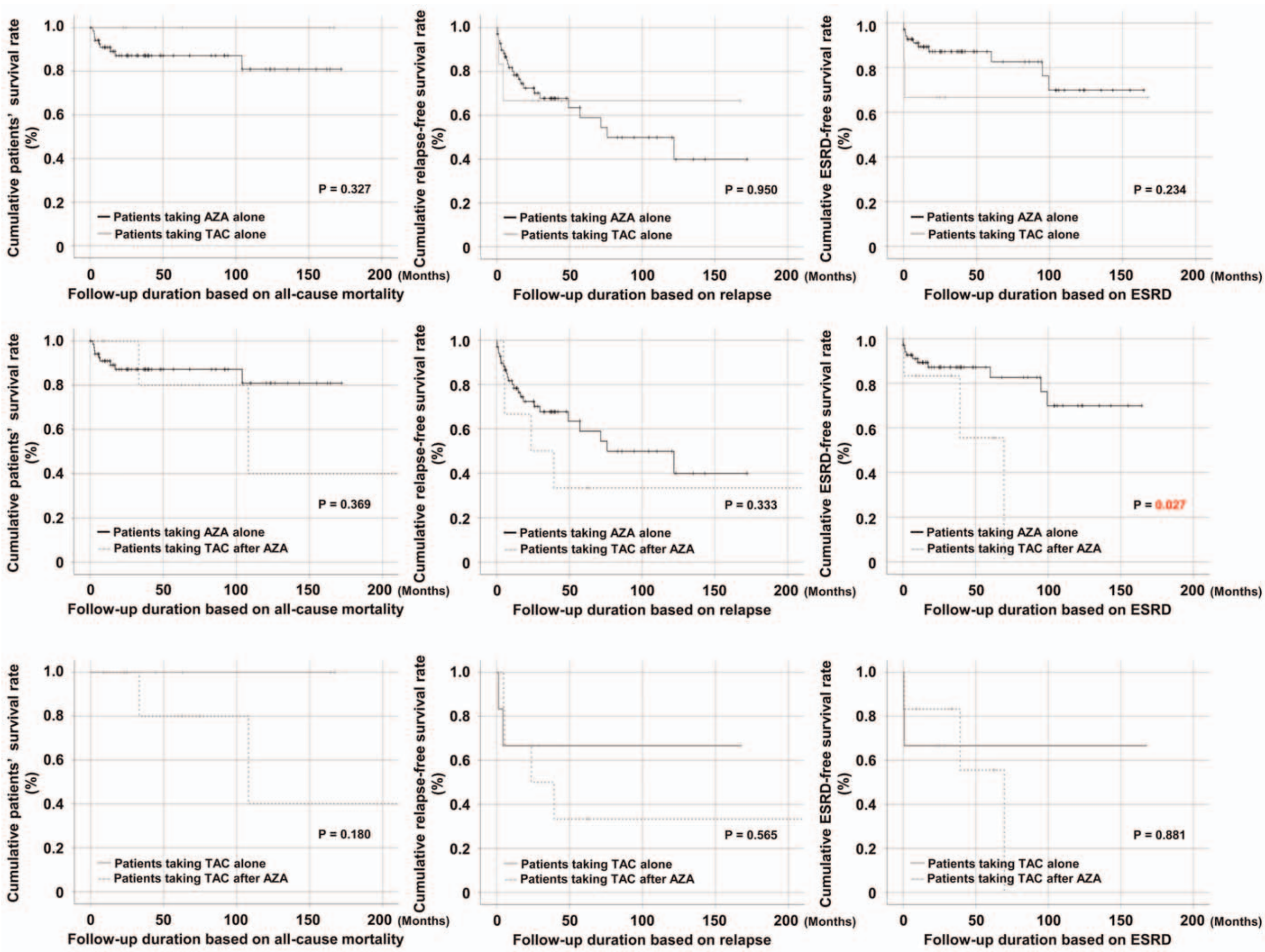

Figure 3. Kaplan-Meier curves comparing patients who received AZA alone, TAC alone, and TAC after AZA. No differences were observed in the cumulative patients', relapse-free, and ESRD-free survival rates between patients who received AZA alone and TAC alone or between patients who received TAC alone and those who received TAC after AZA. Patients who received TAC after AZA showed a lower cumulative ESRD-free survival rate than those who received AZA alone (P=0.027), but cumulative patients', and relapse-free survival rates did not differ between the groups. AZA=azathioprine, ESRD=end-stage renal disease, TAC=tacrolimus.

include the period of taking AZA. Although the number of patients was small, despite the follow-up period was numerically longer in patients treated with TAC alone than those treated with AZA alone there were no deaths in the patients treated with TAC alone, indicating the efficacy of TAC.

For maintenance therapy, drugs that have demonstrated efficacy through randomized controlled trials include AZA, MTX, and RTX.[20] Among these, MTX is recommended as maintenance therapy in patients with relatively nonsevere AAV. In a study demonstrating the effectiveness of MMF and AZA as maintenance therapy after induction therapy, the relapse rate in patients who received MMF was higher than that in those who received AZA.[21] Based on these findings, AZA has been the most widely used drug for maintenance therapy in the current general clinical settings.[4]

Nevertheless, in this study, TAC was selected as maintenance therapy for the following reasons. With respect to patients who received TAC after AZA, all 6 patients who demonstrated a lack of AZA efficacy strongly opposed the re-administration of CYC, as well as RTX administration, owing to concerns regarding adverse drug reactions. MMF was excluded from consideration as the risk of recurrence with MMF was higher than that with AZA.[21]

In contrast, with TAC as the first maintenance therapeutic regimen, all six patients demonstrated reasons for difficulties with AZA—2 patients presented elevated liver enzyme levels and four patients presented leukocytopenia.[19,22] The rate of kidney involvement was high (83.3%) in these 6 patients; however, RTX did not meet the criteria for health insurance coverage and the effectiveness of MTX as maintenance therapy for treating patients with AAV and kidney involvement was not confirmed.[23] TAC seemed to have significantly prevented ESRD, considering that only 2 of 5 patients with kidney involvement who were prescribed TAC as the first maintenance therapy developed ESRD.

Presently, TAC has proven efficacy in lupus nephritis and is actively recommended for treating lupus nephritis as a combination therapy with prednisolone or prednisolone plus

MMF based on randomized controlled trials.[24–26] Although lupus nephritis is characterized by the deposition of immune complexes, demonstrating considerably different pathological findings from AAV, the therapeutic effect of TAC could be significant as TH1, TH17, and effector T cells are actively involved in the pathogenesis of both diseases.[16,27] Notably, this study provided evidence that the efficacy of TAC is comparable to that of AZA as an alternative therapeutic option in patients with AAV. Therefore, a prospective clinical study to investigate the efficacy of TAC for treating AAV, particularly AAV with renal involvement, is warranted.

To the best of our knowledge, our report is the first pilot study investigating the therapeutic potential of TAC as maintenance therapy for AAV treatment in a considerable number of patients. However, our study has several limitations owing to its retrospective design and the small number of patients who received TAC. The most significant limitation is that the disease status at the time of drug switching may differ between the groups. Additionally, there may have been a selection bias because our study is a retrospective single-center study, and the number of patients was insufficient to verify the statistical significance. Furthermore, cumulative dose of glucocorticoids may differ between patients who received TAC and those who received AZA because disease status such as disease duration, inflammatory burden, and relapsed or not may differ for each patient. For these reasons, our results should be interpreted with caution, and well-designed prospective studies are needed. Nevertheless, our study has clinical implication in investigating the potential efficacy of TAC as a maintenance therapy for AAV, which has only limited drug options. Future prospective studies with a larger patient population could overcome these limitations and validate our results. We believe that our study will make a significant contribution to patients with AAV in clinical settings and anticipate that our study will serve as an opportunity to initiate clinical studies demonstrating the therapeutic effect of TAC in the treatment of AAV.

5. Conclusions

Patients who received TAC as maintenance therapy showed a higher incidence of ESRD than those who received AZA, but this might be attributed to the lack of efficacy of AZA rather than the low ESRD prevention effect of TAC as maintenance therapy after CYC.

Author contributions

Conceptualization: Jung Yoon Pyo, Jason Jungsik Song, Yong-Beom Park, Sang-Won Lee.
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Writing – review & editing: Sang-Won Lee.

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