Relapse in patients with antineutrophil cytoplasmic antibody-associated vasculitis undergoing dialysis: a single-centre retrospective study in South Korea

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Abstract

Objective

The disease activity of antineutrophil cytoplasmic antibody-associated vasculitis (AAV) can decrease after dialysis, and relapse after dialysis is not well-studied. We investigated the clinical manifestations and factors associated with relapse in patients with AAV undergoing dialysis.

Methods

This retrospective study included data of patients with AAV undergoing dialysis due to renal involvement from July 2005 to March 2021 in a single tertiary centre in Seoul, Korea. Cox regression analysis was performed to identify relapse-associated factors.

Results

The study cohort included 38 patients with a median age of 64.0 years; 28 (73.7%) were female, and 35 (92.1%) patients were diagnosed with microscopic polyangiitis (MPA). At diagnosis, the mean Birmingham vasculitis activity score (BVAS) was 18.3 and 66.3% of the patients exhibited pulmonary manifestations. During follow-up, 12 patients experienced AAV relapse, including nine patients with diffuse alveolar haemorrhage (DAH), two patients with aggravated interstitial lung disease, and one patient with DAH accompanied with neuropathy. Clinical features including age, sex, and baseline BVAS did not significantly differ between the relapse and non-relapse groups. By univariable analysis, lung infiltration, DAH, corticosteroid pulse therapy for induction, and mean corticosteroid dose were significantly associated with relapse. Multivariable analysis revealed that DAH (adjusted hazard ratio 5.509, 95% CI 1.569–19.339; p=0.008) and mean corticosteroid dose (adjusted hazard ratio 1.381, 95% CI 1.161–1.642; p<0.001) were significantly associated with relapse.

Conclusion

In patients with AAV undergoing dialysis, DAH and mean corticosteroid dose were significantly associated with relapse, highlighting the importance of close monitoring.

Key words

vasculitis, dialysis, recurrence

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic small-vessel vasculitis that affects various organs including the renal, respiratory, and nervous systems (1). Renal involvement is particularly common, with approximately 70% of patients with granulomatosis with polyangiitis (GPA) and nearly 100% of patients with microscopic polyangiitis (MPA) experiencing renal involvement as an AAV manifestation (2). Furthermore, even when disease remission is achieved after immunosuppressive treatment, relapses of AAV can occur throughout the course of the disease (3, 4). Despite advances in disease management, a considerable proportion of patients with AAV and renal involvement progress to end-stage renal disease during follow-up (4–6).

Although induction and maintenance therapies are recommended for patients with AAV, specific guidelines are lacking for the management of those undergoing dialysis (7, 8). Previous studies have revealed that AAV disease activity generally declines after dialysis initiation. However, AAV can relapse despite ongoing dialysis (9-11). Clinical manifestations of relapse during dialysis vary across studies. For instance, one study including 46 patients with AAV in dialysis reported relapse in six patients with GPA, whereas none of the patients with MPA experienced relapse. In that study, the relapses included pulmonary haemorrhage in one patient and minor relapse involving the skin, joints, and upper respiratory tract in five patients (9). In another study with a median follow-up duration of 63 months, 10 of the 93 patients relapsed after dialysis initiation (10), with involvement observed in lungs, upper respiratory tract, and musculoskeletal system. However, most of these studies have focused on Caucasian populations and factors associated with relapse have not been extensively studied.

Therefore, we aimed to investigate the clinical manifestations of AAV relapse during dialysis and to identify factors associated with relapse in an East Asian patient population.

Materials and methods

Patients and data collection

In this study conducted in a single tertiary centre in Seoul, Korea, the data of patients diagnosed with AAV and initiated dialysis between July 2005 and March 2021 due to renal involvement were retrospectively reviewed. Data were collected from the period between July 2005 and April 2023. AAV diagnosis was based on the International Chapel Hill Consensus Conference on the nomenclature of systemic vasculitides (12), and renal involvement was confirmed by either histologic or clinical evaluation. Patients who were undergoing dialysis at the time of AAV diagnosis or during the follow-up period were eligible. Patients who discontinued dialysis, underwent kidney transplantation, or expired before remission and those lost to follow-up before achieving remission were excluded from the study.

Data on the following variables were extracted from the electronic medical records: age, sex, ANCA type, complete blood count, estimated glomerular filtration rate, urinalysis, erythrocyte sedimentation rate, C-reactive protein level, and details of treatments that were administered including corticosteroid dose and plasmapheresis. Disease activity was determined using the Birmingham vasculitis activity score (BVAS) version 3.0 (13). Disease remission was defined as a one-time BVAS of 0 or a persistent BVAS of 1 lasting more than 1 month and requiring treatment with lower than 7.5 mg of prednisolone or an equivalent dose (14, 15).

Ethics

The Institutional Review Board of Asan Medical Centre approved the study (IRB no. 2021-1357). Because of the retrospective nature of the study, the requirement for informed consent was waived. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its subsequent amendments.

Statistical analysis

Categorical variables were presented as percentages and compared using the chi-square or Fisher's exact test.

Continuous variables were presented as medians (IQR) or means (SD) and compared using Student's t and Mann-Whitney U-tests for parametric and non-parametric data, respectively. Cox regression analysis was performed to identify variables associated with AAV relapse.

All statistical analyses were performed using SPSS software, v. 21.0 (IBM, Armonk, NY). A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 69 patients with AAV underwent dialysis due to renal involvement during the study period. During the follow-up period, eight patients discontinued dialysis shortly before achieving remission, one patient underwent kidney transplantation, and 11 patients were lost to follow-up within 6 months before remission. In addition, 11 patients expired before achieving remission due to infection (n=6), vasculitis (n=4), and lymphoma (n=1). Thus, the final analysis included 38 patients. The median age was 64.0 (IQR 52.5–71.3) years, and 28 patients (73.7%) were female (Table I).

At the time of diagnosis, 92.1% (35/38) of the patients were positive for anti-myeloperoxidase and the mean BVAS was 18.3 (±4.0). All patients exhibited renal manifestations, and 66.3% of the patients presented with pulmonary manifestations, including diffuse alveolar haemorrhage (DAH) observed in six patients.

In the overall study cohort (n=38), 12 patients experienced AAV relapse during a median follow-up period of 59.7 (±50.4) months after dialysis. The comparison between the patients with and without relapse revealed no significant differences in age, sex, or mean BVAS. Pulmonary involvement was more common in the relapse group than in the non-relapse group (91.7% *vs*. 69.2%), albeit without statistical significance (p=0.130). Platelet count and C-reactive protein level at baseline, *i.e*. time of AAV diagnosis, were significantly lower in patients with relapse compared with those who did not experience relapse.

Table I. Baseline characteristics of patients with or without relapse.

	All (n=38)	Relapse		p
		Yes (n=12)	No (n=26)	
At the time of diagnosis				
Age, years	64.0 (52.5–71.3)	58.0 (50.3–67.8)	64.0 (57.5–72.3)	0.353
Female, n (%)	28 (73.7)	9 (75.0)	19 (73.1)	0.900
BVAS at diagnosis	18.3 ± 4.0	18.5 ± 3.4	18.3 ± 4.3	0.871
Renal involvement	38 (100)	12 (100)	26 (100)	0.179
Pulmonary involvement	29 (66.3)	11 (91.7)	18 (69.2)	0.130
ENT	3 (7.9)	1 (8.3)	2 (7.7)	>0.999
Neurologic involvement	3 (7.9)	1 (8.3)	2 (7.7)	0.946
Myalgia	8 (21.1)	1 (8.3)	7 (26.9)	0.393
Fever	10 (26.3)	3 (25.0)	7 (26.9)	>0.999
Weight loss	10 (26.3)	3 (25.0)	7 (26.9)	>0.999
AAV type				0.946
MPA	35 (92.1)	11 (91.7)	24 (92.3)	
GPA	3 (7.9)	1 (8.3)	2 (7.7)	
ANCA type by ELISA				0.687
Anti-PR3	2 (5.3)	0 (0)	2 (7.7)	
Anti-MPO	35 (92.1)	12 (100)	23 (88.5)	
ANCA type by IF				>0.999
p-ANCA	18 (90.0)	7 (100)	11 (84.6)	
c-ANCA	1 (5.0)	0 (0)	1 (7.7)	
Laboratory data				
WBC, μL	9800 (7400–14300)	9500 (7450–12300)	10250 (7400–15125)	0.379
Neutrophil, %	79.1 ± 10.5	81.5 ± 12.7	78.0 ± 9.3	0.352
Lymphocyte, %	13.4 ± 8.1	11.7 ± 8.7	14.1 ± 7.8	0.412
Hb, g/dL	8.4 ± 1.6	8.8 ± 2.2	8.3 ± 1.3	0.417
Platelet, $\times 10^3/\mu L$	299.3 ± 129.5	233.3 ± 90.4	329.7 ± 134.8	0.031
ESR, mm/h	74.9 ± 31.0	58.2 ± 29.3	80.2 ± 30.3	0.132
CRP, mg/dL	11.0 ± 9.2	5.3 ± 5.0	13.0 ± 9.6	0.039
Albumin, g/dL	2.7 ± 0.6	3.0 ± 0.6	2.6 ± 0.5	0.039
Creatinine, mg/dL	5.8 ± 3.0	5.0 ± 2.6	6.2 ± 3.2	0.250

Data are expressed as mean ± SD, median (IQR), or n (%).

BVAS: Birmingham vasculitis activity score; ENT: ear, nose, and throat; AAV: ANCA-associated vasculitis; ANCA: antineutrophil cytoplasmic antibody; MPA: microscopic polyangiitis; GPA: granulomatosis polyangiitis; ELISA: enzyme-linked immunosorbent assay; Anti-PR3: anti-proteinase 3; Anti-MPO: anti-myeloperoxidase; IF: immunofluorescence; WBC: white blood cell; Hb: haemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table II. Treatment approaches of patients with or without relapse during dialysis.

	All (n = 38)	Relapse		p
		Yes (n=12)	No (n=26)	
Induction therapy				
IV cyclophosphamide	5 (13.2)	0 (0)	5 (19.2)	0.158
PO cyclophosphamide	31 (81.6)	9 (75.0)	22 (84.6)	0.656
Rituximab	3 (7.9)	2 (16.7)	1 (3.8)	0.229
Azathioprine	2 (5.3)	2 (16.7)	0 (0)	0.094
Plasmapheresis	10 (26.3)	2 (16.7)	8 (30.8)	0.365
Corticosteroid doses during induction				0.627
Medium (≥0.5 mg/kg/day)	6 (15.8)	1 (8.3)	5 (19.2)	
High (≥1 mg/kg/day)	9 (23.7)	5 (41.7)	4 (15.4)	
Pulse (≥250 mg/day)	23 (60.5)	6 (50.0)	17 (65.4)	
Maintenance therapy				
Azathioprine	21 (55.3)	8 (66.7)	13 (50.0)	0.486
Mycophenolate mofetil	2 (5.3)	0 (0.0)	2 (7.7)	>0.999
Cumulative corticosteroid dose, g	10.1 (5.8–17.2)	13.6 (9.9–16.8)	11.5 (5.3–18.1)	0.209
Mean corticosteroid dose, mg/day	6.0 (3.9–12.0)	6.3 (4.3–13.8)	5.8 (3.3–11.7)	0.530

Data are expressed as n (%). IV: intravenous; PO: per oral.

Table III. Clinical characteristics of patients with relapse (n=12).

Age/sex at diagnosis	BVAS at diagnosis	Initial manifestation	Time from dialysis to relapse, months	Relapse manifestation	Treatment after relapse	Outcome
85/F	20	Fever, DAH	23.5	DAH	Corticosteroid pulse	Remission
49/F	20	Weight loss, DAH	86.2	DAH	Corticosteroid pulse	Remission
67/M	27	Skin vasculitis, ILD, Mononeuritis multiplex	15.2	ILD	Medium-dose corticosteroid	No remission
68/M	13	Myalgia	20.6	DAH	Corticosteroid pulse, PE	Remission
75/F	20	Fever, DAH	25.9	DAH	High-dose corticosteroid	Remission*
51/F	18	Weight loss, DAH	9.6	DAH	High-dose corticosteroid, CYC	Expire
62/M	19	Fever, weight loss, ILD	12.0	ILD	Corticosteroid pulse	Expire
61/F	16	Lung infiltration	15.2	DAH	Medium-dose corticosteroid, AZA	Remission*
48/F	18	DAH	87.6	DAH, neuropathy	High-dose corticosteroid, CYC	Remission*
55/F	18	DAH	89.5	DAH	Corticosteroid pulse	Remission
54/F	15	Conjunctivitis, PNS	50.5	DAH	High-dose corticosteroid	Remission
50/F	18	DAH	34.3	DAH	Medium-dose corticosteroid, AZA	Remission

BVAS: Birmingham vasculitis activity score; DAH: diffuse alveolar haemorrhage; ILD: interstitial lung disease; PE: plasmapheresis; CYC: cyclophosphamide; AZA: azathioprine; PNS: paranasal sinus; initial manifestation excludes renal manifestation.
*Subsequent relapse after achieving remission.

Treatment approaches of patients with or without AAV relapse during dialysis

Next, we examined the medications administered for AAV treatment in patients undergoing dialysis. Induction therapy with intravenous or oral cyclophosphamide was administered in 33 of the 38 patients (86.8%), including three patients who received both intravenous and oral cyclophosphamide (Table II). In addition, three patients (7.9%) were treated with rituximab, whereas plasmapheresis was performed in 10 patients (26%). As for corticosteroids, pulse (≥250 mg/day of methylprednisolone), high-dose, and medium-dose corticosteroid therapy were administered in 23 (60.5%), 9 (23.7%), and 6 (15.8%) patients, respectively. The mean prednisolone-equivalent corticosteroid dose was 6.3 (4.3–13.8) mg/day in the relapse group and 5.8 (3.3–11.7) mg/day in the non-relapse group (p=0.530). As maintenance therapy, 21 patients (55.3%) received azathioprine, of whom 2 (5.3%) were switched to mycophenolate mofetil due to adverse reactions such as liver function abnormalities related to azathioprine use. In the case of the remaining 17 patients, maintenance therapy consisted of low-dose corticosteroids without immunosuppressive agents. The rates of induction therapy, maintenance therapy, and plasmapheresis were not significantly different between the relapse and non-relapse groups.

Clinical characteristics of the patients with relapse

Table III shows the detailed clinical characteristics of 12 patients who experienced relapse during the follow-up period in the present study. The median time from dialysis to first relapse was 24.7 (IQR 15.2–77.3) months. Among those who experienced relapse, 10 patients presented with DAH, and two patients experienced aggravation of interstitial lung disease (ILD) as a manifestation of AAV relapse. One patient experienced DAH along with neuropathy. For relapse, all patients received treatment with corticosteroids, alone or combination with immunosuppressants or plasmapheresis. Following treatment, remission was achieved in nine of the 12 patients (75%). However, three of the nine patients who achieved remission subsequently experienced another relapse in the form of DAH, during which two patients had discontinued all medications and one was receiving low-dose corticosteroids. After their first relapse, two patients were administered azathioprine or cyclophosphamide as maintenance therapy for 11 and 36 months, respectively; however, therapy was then discontinued due to infectious events or stable disease status. After the second relapse, all three patients were able to achieve remission once again solely with medium- to high-dose corticosteroid therapy, without using immunosuppressants. They remained relapse-free during further follow-up periods of 4, 22, and 110 months after the second relapse, respectively.

Factors associated with relapse

Cox regression analysis to determine the clinical characteristics and treatments associated with relapse during dialysis indicated that age and sex were not significantly associated with AAV relapse (Table IV). Univariable analysis revealed several factors that were significantly associated with relapse, including lung infiltration, DAH, platelet count, corticosteroid pulse for induction therapy (compared with high-dose corticosteroid therapy), and mean corticosteroid dose. In multivariable analysis, DAH (adjusted hazard ratio 5.509, 95% CI 1.569–19.339; p=0.008) and mean corticosteroid dose (adjusted hazard ratio 1.381, 95% CI 1.161–1.642; p<0.001) were found to be significantly associated with AAV relapse during dialysis. Furthermore, when the analysis was restricted only to patients with MPA, we also observed the significance of DAH and mean corticosteroid dose in relation to the risk of AAV relapse (Supplementary Table S1).

Discussion

In the present study, we found that approximately one third of patients undergoing dialysis experienced AAV relapse during a mean follow-up pe-

Table IV. Univariable and multivariable analyses of factors associated with relapse.

Variable	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*p*
At time of diagnosis				
Age, years	1.019 (0.972–1.069)	0.440		
Female	0.378 (0.098–1.451)	0.156		
BVAS at diagnosis	1.032 (0.898–1.185)	0.659		
Pulmonary involvement	5.574 (0.713–43.561)	0.101		
Lung infiltration	5.580 (1.168–26.659)	0.031		
DAH	4.594 (1.449–14.562)	0.010	5.509 (1.569–19.339)	0.008
ENT	0.946 (0.120–7.479)	0.958		
Neurologic involvement	0.578 (0.074–4.508)	0.601		
Myalgia	0.650 (0.083–5.112)	0.682		
Fever	1.655 (0.440–6.218)	0.456		
Weight loss	0.617 (0.163–2.341)	0.478		
WBC, /μL	1.000 (1.000–1.000)	0.846		
Hb, g/dL	1.080 (0.794–1.468)	0.624		
Platelet, $\times 10^3/\mu L$	0.992 (0.986–0.999)	0.031		
ESR, mm/h	0.981 (0.956–1.006)	0.141		
CRP, mg/dL	0.917 (0.822–1.022)	0.117		
Albumin, g/dL	1.752 (0.695–4.414)	0.235		
Treatment				
Corticosteroid pulse for induction	0.281 (0.080–0.990)	0.048		
Plasma exchange for induction	0.655 (0.142–3.026)	0.588		
Mean corticosteroid doses, mg/day	1.360 (1.155–1.602)	<0.001	1.381 (1.161–1.642)	<0.001
Cumulative cyclophosphamide doses, g	0.977 (0.908–1.051)	0.533		
Maintenance therapy	1.762 (0.529–5.873)	0.356		

HR: hazard ratio; CI: confidence interval; BVAS: Birmingham vasculitis activity score; DAH: diffuse alveolar haemorrhage; ENT: ear, nose, and throat; WBC: white blood cell count; Hb: haemoglobin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

riod of 59.7 (±50.4) months after the initiation of dialysis. Pulmonary involvement, particularly DAH, was significantly associated with relapse in patients with AAV undergoing dialysis. Furthermore, DAH was the most common and recurrent manifestation of relapse. Our analyses to determine the contribution of treatment on relapse revealed that mean corticosteroid dose was significantly associated with relapse. In addition, the present study population provides a detailed description of relapse manifestations including treatments during dialysis.

The prevalence of ILD is higher in patients with MPA, whereas necrotising granulomatous inflammation and tracheobronchial inflammation are more common in those with GPA (16, 17). Recent studies have also reported a higher DAH prevalence in patients with MPA compared with those with GPA (18). It has been known that AAV exhibits geographical variation, wherein MPA is more prevalent in East Asian countries (1). Thus, the higher prevalence of DAH observed in the present study conducted in South Korea might be attributable to the higher proportion of enrolled patients with MPA (92.1%) compared with previous studies, in which 49–52% of the patients had MPA (9, 10). Nevertheless, it is noteworthy that DAH was more common than ILD exacerbation as a main manifestation in patients who experienced relapse in this study cohort.

In the present study, we investigated the medications administered to patients after relapse and the subsequent outcomes to evaluate their efficacy and gain a deeper understanding of AAV relapse management in patients undergoing dialysis. We found that the majority of patients achieved remission being treated with steroids or other immunosuppressants following relapse. However, some patients experienced a subsequent episode of relapse and DAH was a common presentation in these cases, highlighting the importance of close and continuous monitoring of patients with DAH for the potential development of recurrent pulmonary haemorrhage even during dialysis.

We evaluated the association of relapse with treatment approaches and laboratory findings in patients with AAV undergoing dialysis. A study investigating the predictive value of cyclophosphamide as initial treatment for relapse did not find a significant association between treatment and relapse (19). In contrast, we observed a significant association between mean corticosteroid dose and relapse risk in the present study. However, we advise caution in the interpretation of this finding as a causal relationship. It is possible that patients with higher disease activity might have required higher doses of corticosteroids for effective disease control during the follow-up period. From another therapeutic perspective, it was observed that patients experienced a second relapse during period when they were not receiving immunosuppressants, and these relapsed patients were able to achieve remission once more solely with corticosteroid treatment. Further studies are warranted for a clearer understanding of the relationship between specific treatments, including corticosteroids, and relapse in patients with AAV undergoing dialysis.

In the present study, the rate of relapse during dialysis was 0.08 relapses per person-year, which was similar to the previously reported rates ranging from 0.03 to 0.07 relapses per person-year (19-21). The rate of relapse observed in patients undergoing dialysis, including that observed in the present study, appears to be lower compared with that reported in patients not undergoing dialysis; while not a direct comparison, this difference suggests that AAV disease activity is generally decreased after dialysis.

Limitations of the present study include the single-centre design and the relatively small sample size. Specifically, the analysis of associations between certain treatments and relapse was limited by the small number of patients who received maintenance immunosuppressive treatment and studies with larger cohorts are necessary to further investigate these associations. In addition, survivorship bias could not be ruled out as patients with a shorter follow-up period and those who did not

achieve remission were excluded from the analyses.

In conclusion, we found that pulmonary manifestations, including DAH at baseline, were significantly associated with relapse in patients with AAV undergoing dialysis and that mean corticosteroid dose was significantly associated with relapse. Therefore, close monitoring during dialysis is important in patients with pulmonary manifestations of AAV, especially DAH.

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