Clinical analysis of ANCA-associated renal vasculitis patients with chronic dialysis

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ABSTRACT

Objective. *Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) constitute a subgroup of life-threatening diseases which affects the kidney in more than half of the patients at diagnosis. Currently, little has been published focusing on AAV patients with dialysis. We analysed AAV patients with chronic dialysis to provide more detailed information.*

Methods. *From 1997 to 2011, AAV patients complicated by renal involvement resulting in end-stage renal disease (ESRD) and had undergone haemodialysis (HD) or peritoneal dialysis (PD) for at least 3 months in Shanghai Ruijin hospital were retrospectively analysed in this study. Their data were also compared to those without dialysis at the same time.*

Results. *We enrolled 49 AAV patients with chronic dialysis. 41 required dialysis at initial presentation and rest 8 progressed to ESRD during follow-up. 19 HD patients died and 6 PD patients died during follow-up, and infection was the most common cause among the patients. There was no significant difference regarding survival between HD patients and PD patients ($p>0.05$). However anaemia and level of triglyceride was more significantly improved in HD patients at the end of observation ($p<0.05$, $p<0.05$ respectively). Compared with patients without dialysis dependency, dialysis patients presented higher percentage of hypertension ($p<0.01$), more severe renal involvement and higher BVAS ($p<0.01$). For the outcome, survival was significantly higher in non-dialysis patients ($p<0.05$).*

Conclusion. *Patients with AAV experienced a high rate of renal failure and dialysis dependence. Our study suggests that haemodialysis and peritoneal dialysis are two comparable dialysis modalities for AAV patients with ESRD. However, AAV patients with dialysis dependency had worse outcome in comparison with those without dialysis.*

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) constitute a subgroup of life-threatening diseases including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formally known as Wegener's granulomatosis), Churg-Strauss syndrome (CSS) and their localised forms (1-3). It is the most common cause of rapidly progressive glomerulonephritis (RPGN) which affects the kidney in more than half of the patients at diagnosis (4, 5). Despite improved treatment strategies and outcome, AAV still leads to end-stage renal disease (ESRD) in about 25% of the patients who require permanent renal replacement therapy (6, 7). Currently, little has been published focusing on AAV patients with dialysis and the results of dialysis in this population remain largely unclear. In this study, we retrospectively analysed AAV patients with chronic dialysis to provide detailed information in this population.

Methods

Patients

From 1997 to 2011, AAV patients complicated by renal involvement resulting in ESRD and had undergone haemodialysis (HD) or peritoneal dialysis (PD) for at least 3 months in our department were enrolled in this study. Patients with acute renal replacement therapy (RRT) and renal function recovery before 3 months of treatment were excluded. Diagnosis was based on the definition of Chapel Hill consensus conference (CHCC) and American College of Rheumatology (ACR) (8-11). Renal involvement was defined as an elevated creatinine level attributable to the disease (serum creatinine >115μmol/l) and/or urinary abnormalities (proteinu-

ria with protein >300 mg/day and microscopic hematuria with>10 erythrocytes/high-power field on two separate occasions in the absence of urinary infection). We also compared the data of patients with dialysis dependency to those without dialysis at the same time. Patients with anti-glomerular basement membrane disease or secondary causes of vasculitis were excluded.

Clinical and laboratory data

Hypertension was defined as systolic pressure greater than 140 mm Hg and/or diastolic pressure greater than 90 mm Hg or if antihypertensive medication was needed. Disease activity at initial clinical presentation was evaluated by the Birmingham Vasculitis Activity Score (BVAS) 2003 (12). The blood samples tested for albumin, total cholesterol, triglyceride, calcium, phosphate, intact-parathyroid hormone (iPTH) and haemoglobin (Hb) were retrieved and analysed at two time points: the first set of data were obtained before the start of dialysis, and the second set of data were the latest values before the end of our observation period.

ANCA analysis

All patients had been tested for the presence of ANCA by IIF (Euroimmun AG, Lübeck, Germany). ELISA was performed to test antimyeloperoxidase (MPO) and antiproteinase 3 (PR3) antibodies in all sera (Euroimmun AG) as we previously reported (13-16).

Treatment protocols

Pulsed intravenous cyclophosphamide (CTX) in combination with corticosteroids in a tapering schedule was administered in patients for remission induction therapy. Oral prednisone was given at an initial dosage of 0.8–1.0 mg/kg/day for 1–2 months tapering to 20mg/d by 3–6 months. Pulsed intravenous CTX was given at 0.5g/m^2 every month and adjusted according to the patients' leukocyte count. Dose reduction of CTX was made for those older than 65 years or leukocyte count less than 4×10^9/l. Pulse methylprednisolone or plasma exchange were added to those patients with severe renal involvement or alveolar haemorrhage. If the patients remained dialysis dependent without extra-renal involvement after three months of remission induction therapy, the administration of cyclophosphamide was suspended, and corticosteroids were gradually reduced. For the remission maintenance therapy, patients were treated with low dose oral prednisone together with mycophenolate mofetil (MMF) or CTX after 3–6 months of remission induction therapy. Cotrimoxazole was added to patients with GPA for *Pneumocystis carinii* (PC) prophylaxis while receiving remission induction therapy.

Statistics

Statistical analysis was calculated using SPSS 11.0 (SSPS Inc., Chicago, Ill., USA) software. Data were presented as mean±SD. Differences of qualitative results were compared using the χ^2 test. Differences of quantitative parameters between groups were performed with the t test (for normally distributed data) or nonparametric test (for non-normally distributed data). Differences of semiquantitative results were performed with the Mann-Whitney U-test. Kaplan-Meier curves were used to analyse patient survival. A p-value <0.05 was considered statistically significant.

Table I. Characteristics of AAV patients with dialysis dependence at diagnosis.

	Haemodialysis (n=37)	Peritoneal dialysis (n=12)
Age (yrs, mean)	57.2 ± 12.3	61.2 ± 12.4
Gender (M,%)	15 (40.5%)	6 (46.2%)
Disease category (n, %)		
GPA	5 (13.5%)	0
MPA	28 (75.7%)	10 (83.3%)
RLV	4 (10.8%)	2 (16.7%)
ANCA		
C-ANCA/PR3-ANCA (%)	7 (18.9%)	0
P-ANCA/MPO-ANCA (%)	30 (81.1%)	12 (100%)
Renal involvement		
Serum creatinine (μmol/L, mean)	717.6 ± 288.3	762.6 ± 340.1
Proteinuira (mg/d, mean)	2313.4 ± 2128.1	2578.4 ± 1811.6
BVAS (median)	23	22
Duration from diagnosis to ESRD (mon, mean)	9.2 ± 20.1	6.2 ± 13.4

GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; RLV: renal limited vasculitis:

Results

Demographic features and dialysis of the patients

In current study, we enrolled 49 AAV patients with chronic dialysis in our department. Among these patients, 41 required dialysis at initial presentation and rest 8 progressed to ESRD during follow-up. For the type of dialysis, 37 patients received haemodialysis and 12 received peritoneal dialysis when dialysis began. Details of patients were summarised in Table 1. Characteristics of AAV patients with dialysis dependence at diagnosis

Follow-up and outcome of the patients on dialysis

During follow-up, 2 peritoneal dialysis patient changed over to haemodialysis. One patient was due to fungal peritonitis and the other was because of technical failure due to recurrent peritonitis; rest patients did not change dialysis therapy during follow-up. Four kidney transplantations were performed in 4 haemodialysis patients. All the grafts were still functioning at the end of this study observation. No kidney transplantations were performed in peritoneal dialysis patients. Clinical course and follow-up are summarised in Figure 1.
In our study, 19 haemodialysis patients and 6 peritoneal dialysis patients died during follow-up. For the cause of the death, our study showed that infection was the most common cause for the deaths (Table II).

Comparison of AAV patients with haemodialysis and peritoneal dialysis

In our study, our results suggest there was no significant difference regarding survival between haemodialysis patients and peritoneal dialysis patients

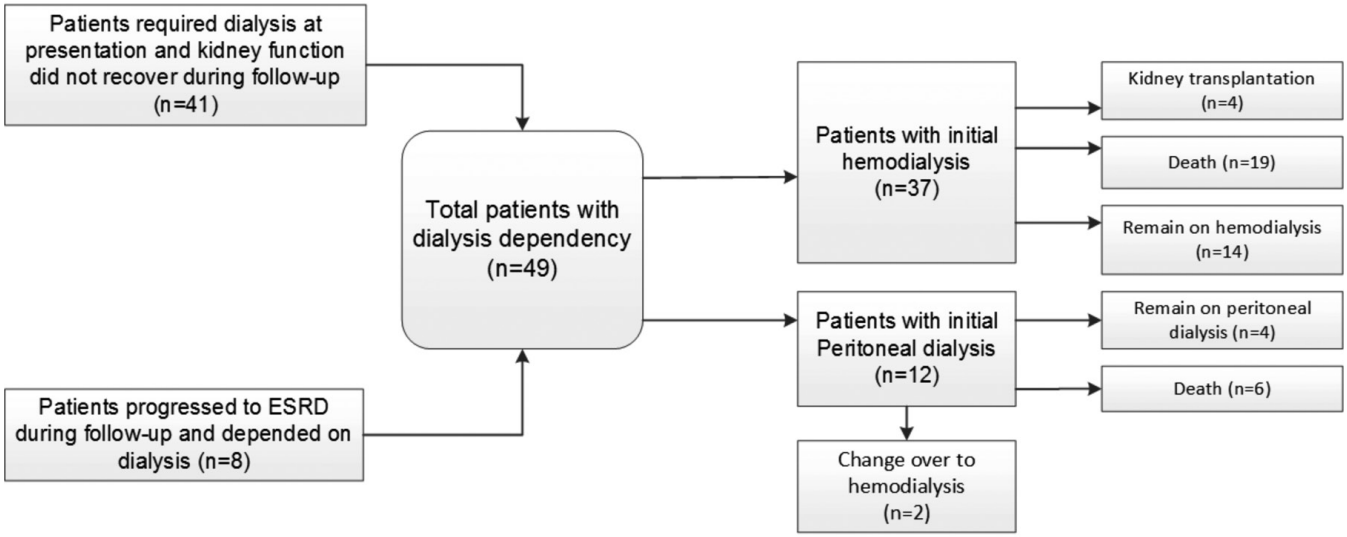

Fig. 1. Clinical course and outcome of the patients with dialysis dependency.

Table II. Cause of the death of the patients.

	Haemodialysis (n=19)	Peritoneal dialysis (n=6)
Infection	9 (47.4%)	4 (66.7%)
Vasculitis-related organ involvement	2 (10.5%)	1 (16.7%)
Cardiovascular events without evidence of vasculitis	7 (36.8%)	1 (16.7%)
Others	1 (5.3%)	0

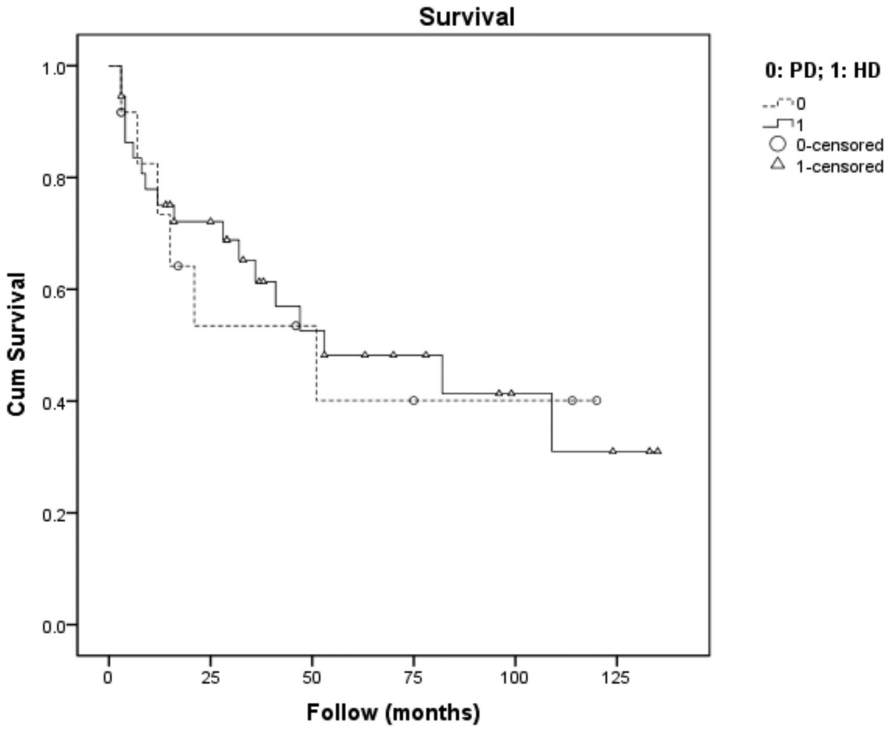

Fig. 2. Comparison of survival of AAV patients with dialysis dependence.
HD: haemodialysis; PD: peritoneal dialysis.
Dash line represented AAV patients with peritoneal dialysis and solid line represented AAV patients with haemodialysis. Survival between haemodialysis and peritoneal dialysis patients were analysed by Kaplan-Meier curves. The results showed that there was no significant difference between two groups of patients ($p>0.05$).

(Fig. 2). In Table IV, we compared the laboratory data of patients with HD and PD before dialysis began and at the end of observation. Our results showed that most data were comparable between the groups, however anaemia and level of triglyceride was more significantly improved in HD patients at the end of observation ($p<0.05$, $p<0.05$ respectively).

Comparison of AAV patients with and without dialysis dependency

Compared with patients without dialysis dependency, dialysis patients presented with a higher percentage of hypertension ($p<0.01$), larger amount of proteinuria ($p<0.001$) and worse kidney function ($p<0.01$). And more dialysis patients presented with gastrointestinal tract involvement ($p<0.05$) at presentation. Accordingly, BVAS of dialysis patients was significantly higher ($p<0.01$). Details are summarised in Table IV. For the outcome between two groups, survival was significantly higher in non-dialysis patients ($p<0.05$) (Fig. 3).

Discussion

Despite the improved therapeutic strategies of AAV, the prognosis of the disease remains poor. Studies showed that the survival of patients with AAV at 5 years was 67–78% (5, 14, 17), and differed among subgroups of the patients (18). Renal involvement is the

Table III. Comparison of laboratory data between AAV patients with hemodialysis and peritoneal dialysis.

	Haemodialysis (n=37)	Peritoneal dialysis (n=12)	*p*-value
Albumin (g/L)			
Pre-dialysis	28.0 ± 4.1	25.1 ± 6.5	NS
dialysis	29.9 ± 5.0	24.0 ± 8.2	NS
Total cholesterol (mmol/L)			
Pre-dialysis	2.5 ± 1.4	2.0 ± 1.3	NS
dialysis	2.0 ± 1.0	2.5 ± 0.8	NS
Triglyceride (mmol/L)			
Pre-dialysis	5.4 ± 1.6	4.1 ± 1.9	NS
dialysis	4.8 ± 1.5	5.3 ± 1.6	<0.05
iPTH (pg/L)			
Pre-dialysis	113.9 ± 80.8	191.2 ± 197.6	NS
dialysis	67.4 ± 51.2	76.2 ± 68.0	NS
Haemoglobin (g/L)			
Pre-dialysis	83.2 ± 19.8	68.6 ± 11.1	<0.05
dialysis	98.5 ± 18.5	66.9 ± 41.6	<0.05
Calcium (mmol/L)			
Pre-dialysis	2.1 ± 0.2	2.2 ± 0.3	NS
dialysis	2.2 ± 0.1	2.1 ± 0.4	NS
Phosphate (mmol/L)			
Pre-dialysis	1.6 ± 0.5	1.5 ± 0.3	NS
dialysis	1.3 ± 0.7	1.3 ± 0.5	NS

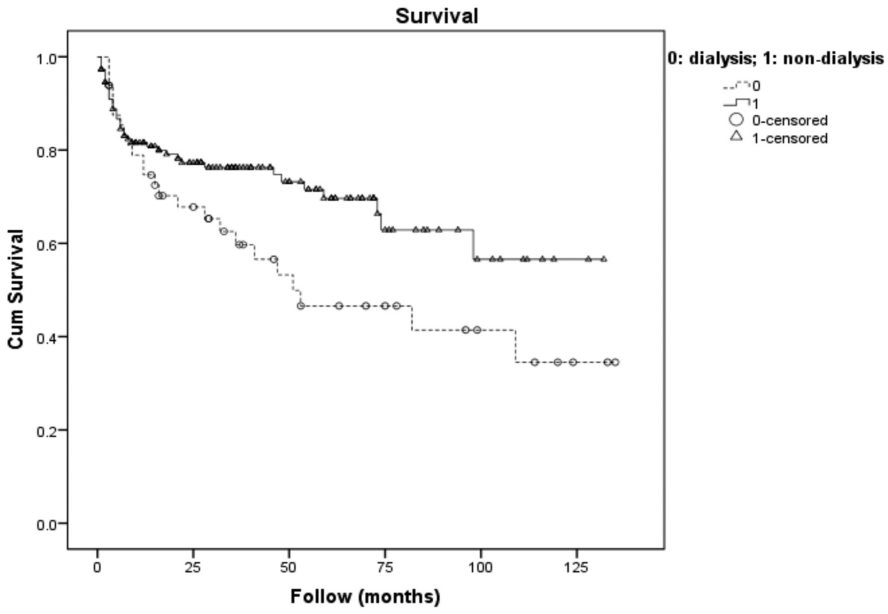

Fig. 3. Comparison of survival of AAV patients with and without dialysis dependency.
Dash line represented non-dialysis AAV patients and solid line represented AAV patients with dialysis dependency (haemodialysis and peritoneal dialysis patients). Survival between two groups of patients were analysed by Kaplan-Meier curves. The results showed that the survival of non-dialysis patients was significantly higher ($p<0.05$).

most common severe manifestations of AAV which is present in more than half of the patients at diagnosis (5). Even being treated with strong immunosuppressant even in combination of plasma exchange, many patients still progressed to ESRD and required dialysis or transplantation (19-21). It is noteworthy that 84% of AAV patients with ESRD in our study presented with dialysis dependency at diagnosis and their renal insufficiency did not recover despite aggressive treatment. The high prevalence of dialysis dependency at presentation and severe involvement of the kidney might thus contribute to the high dialysis dependency for the AAV patients.

In our study, more MPA patients reached ESRD and depended on dialysis in comparison with GPA and RLV patients. No CSS patients progressed to ESRD in our cohort. It is no surprising that CSS patients have the best renal outcome because it is a rare cause of ESRD and the long-term follow-up is usually good (22-24). However, renal survivals for patients with MPA, RLV and GPA were quite different in the studies published elsewhere. In the study by Weidne *et al*. (25), patients with RLV had the highest renal survival rate while patients with GPA had the lowest. Lionaki *et al*. (6) demonstrated in their study that more MPA patients progressed to ESRD than GPA and RLV patients did, which was similar to ours. As certain factors like advanced age, response to the treatment and severity of renal injury might affect renal outcomes among subgroups of AAV patients, the renal outcome would differ accordingly. However it is believed that MPA patients are more likely to have chronic lesions and thus associated worse renal survival (26).

Two of our PD patients changed to haemodialysis due to fungi-related peritonitis or technical failure caused by peritonitis. Though PD is an effective treatment for the patients with ESRD, study showed that there was an increased peritonitis morbidity in patients with immunosuppressive therapies and some authors implied that PD might not be the initial therapy of choice for those high-risk population (27). Since limited studies from the literature prevent drawing any conclusive summaries regarding the preference of HD or PD in this population, more investigations are necessary to study these subjects. In addition to infection, gastrointestinal involvement of the vasculitis could also present with peritonitis which has similar symptoms as infection related peritonitis do (28). As treatment to these two forms of peritonitis would be totally different, distinguishing the pathogenesis at diagnosis is of great importance.

Renal transplantation is one of viable options of the renal replacement therapies for patients with ESRD, however

Table IV. Comparison of dialysis patients and non-dialysis patients.

	Dialysis patients (n=49)	Non-dialysis patients (n=147)	*p*-value
Age (yrs, mean)	57.0 ± 12.4	59.6 ± 16.4	NS
BVAS (median)	23	19	<0.01
Renal involvement			
Peak serum creatinine at diagnosis (μmol/L)	708.8 ± 305.6	225.3 ± 168.5	<0.001
Proteinuria (mg/d)	2416.3 ± 2047.6	1367.2 ± 1677.2	<0.001
Organ involvement (%)			
Lung	35 (71.4%)	99 (67.3%)	NS
ENT	14 (28.6%)	50 (34.0%)	NS
Gastrointestinal tract	6 (12.2%)	5 (3.4%)	<0.05
Nervous system	9 (18.4%)	23 (15.6%)	NS
Fever (%)	19 (38.8%)	61 (41.5%)	NS
Hypertension (%)	43 (87.8%)	77 (52.4%)	<0.001

relapses of the disease leading to malfunction of the grafts remains the concern for the patients and physicians. Since Lyons and colleagues performed the first renal transplantation in GPA patient in 1972 (29), several reports have been published on successful renal transplantations in AAV patients with ESRD (7, 30, 31). As studies demonstrated that vasculitis flare and relapse rate were lower after transplantation in comparison with patients on chronic dialysis (22, 30), renal transplantation could be commenced in AAV patients with complete remission. In our study, no patients had vasculitis relapse or flare after transplantation and all the kidney remain functioning confirmed the established findings. As recurrent of vasculitis and vasculitis flare still occurred in patients received kidney transplantation (32, 33), special attention should pay to those patients regarding safety and effectively of the immunosuppressant as well as the timing of transplantation.

AAV patients with long-term immunosuppressive therapy may experience increased rates of infections, malignancies and cardiovascular events as compared to the general population and dialysis could add incidence of these events (34, 36). Studies demonstrated that infection was an important cause of mortality and morality of patients with AAV (36-38). Further investigations showed that incidence of infection correlated to cumulative dose of immunosuppressant like cyclophosphamide (37, 39). In our study, the main causes of death in HD and PD patients were both infection which further addresses the impact of infection on the prognosis of AAV patients. Considering the burden of infection among AAV patients receiving immunosuppressive therapies, it is a contentious issue that whether continuous immunosuppressive therapy be necessary in vasculitis patients on dialysis. Some studies demonstrated that immune complex clearance by haemodialysis was sufficiently immunosuppressive to obviate the need for additional drugs (40). But other studies showed that even on immunosuppressive therapies, vasculitis patients on dialysis could also present with relapse of the disease which suggested the necessary of continuous immunosuppressive therapies in those population (6, 7, 22). Since the long-term toxicity and side-effects of immunosuppressant are severe, it is suggested that immunosuppressive therapy could be discontinued after 3 months in patients who remain dialysis-dependent without any extra-renal manifestations of disease (41). In this regard, immunosuppressant in AAV patients with dialysis should be administrated according to patients' clinical situations. Recent case studies showed the safety of vaccination in AAV patients which provided attractive strategy for prophylaxis of infection (42, 43), however small number of patients enrolled and short term of follow-up limited its application in clinical practice. And further randomised clinical trials are necessary to address the efficacy and safety of vaccination in this population (36).

In our study, we compared two different dialysis modalities, PD and HD in our AAV patients with ESRD. Our results showed that most laboratory parameters and prognosis were comparable between the patients. Similar results were also found by Allen *et al*. (22) and Merion *et al*. (7) which demonstrated there were no statistical difference regarding survival between patients receiving HD and PD therapies. Though most studies including ours suggest different dialysis modalities might not influence outcome of AAV patients with dialysis, limited patients prevent further conclusion from them. We need more investigations with larger study population to further study these subjects.

In conclusion, patients with AAV experienced a high rate of renal failure and dialysis dependency which is mainly contributed by severe renal involvement at presentation. Though immunosuppressive therapies could suppress activity and relapse of the disease, AAV patients with ESRD are susceptible to infection complication which is associated with significant morbidity and mortality. Making strategies according to patients' clinical situation could be a rational way to improve the outcome.

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