Improving clinical management in ANCA-associated vasculitis

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Renal survival in proteinase 3 and myeloperoxidase anti-neutrophil cytoplasmic antibody (ANCA) associated systemic vasculitis.

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Clin J Am Soc Nephrol 2013; 8: 1709-1717.

SUMMARY

Background and objective

This study evaluated predictors for patient and renal survival in patients with ANCA associated vasculitis (AAV) with and without renal involvement.

Design, setting, participants and measurements

There were 273 consecutive AAV patients from January 1990 until December 2007, who were followed until death, loss to follow up or December 2010. Based on organ-involvement, patients were divided into renal (n=212) and nonrenal groups (n=61). The primary endpoint was ESRD requiring for renal replacement therapy (RRT) or renal transplantation or death.

Results

Patient survival was significantly better in nonrenal group compared with the renal group (hazard ratio, 0.55; 95% confidence interval, 0.33-0.92; P=0.02).

In the renal group, renal survival was significantly worse in MPO-ANCA-positive patients (n=65) compared to PR3-ANCA- positive patients (n= 138) (hazard ratio, 2.1, 95% confidence interval, 1.11-3.8; P= 0.01). Of 48 patients who needed RRT at diagnosis, 11 patients (23%) died within 6 months and 14 patients (29%) did not regain renal function.

Of all 23 patients who regained renal function after RRT, 7 patients (30%) were temporarily dialysis independent and needed dialysis later (range 13-63 months). Five patients had a renal relapse in the 6 months before restart of RRT.

Of all 203 PR3-ANCA- positive patients and MPO-ANCA- positive patients with renal involvement, 12 patients (6%) developed ESRD during follow-up. These patients were classified as CKD stage 4 or 5 after initial treatment and eight patients had a renal relapse before becoming dialysis dependent.

Conclusions

AAV-patients with renal involvement who needed RRT had the worst survival probability. In multivariate analysis, the only major determinants for long-term renal survival were renal function at 6 months and renal relapses.

INTRODUCTION

Systemic small vessel vasculitis and necrotizing GN with little or no immune deposits (pauci-immune) is frequently associated with the presence of ANCA against proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA)(1-3). It is estimated that PR3-ANCA or MPO-ANCA are found in > 90% of patients with ANCA-associated vasculitis (AAV), with a specificity as high as 98% for PR3-ANCA and of 91% for MPO-ANCA (2,4,5).
Both types of antibodies are associated with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and renal limited vasculitis (1-3). It is recognized that there are meaningful clinical differences between patients with PR3- AAV and MPO-AAV and it has been suggested that PR3-AAV and MPO-AAV are distinct diseases since PR3-ANCA-positive patients and MPO-ANCA- positive patients demonstrate a different disease-spectrum (2,6,7). In general, patients with PR3-ANCA have more widespread extrarenal organ involvement and more active renal lesions at time of diagnosis compared with MPO-ANCA positive patients who have more chronic lesions (2,8,9). Another important difference is the higher relapse rate found in PR3-ANCA positive AAV-patients, which may be a major prognostic factor for renal survival during long-term follow up (3).
In clinical practice, the differences between PR3-AAV and MPO-AAV could possibly be used for therapeutic diversity in future treatment, such as intensity of treatment or duration of maintenance therapy. Questions also remain about differences in prognosis between AAV without and with renal involvement, especially in those patients who need renal replacement therapy (RRT).
To answer these questions, we retrospectively studied our cohort of patients with systemic AAV to determine the differences between PR3-ANCA-positive patients and MPO-ANCA-positive patients and to evaluate other determinants for renal outcome (renal function at 6 months, relapse, hypertension and proteinuria) during long-term follow up.

MATERIALS AND METHODS

We included all 273 consecutive patients diagnosed and treated with systemic AAV at our centre between January 1990 and December 2007. Patients were followed until death, loss to follow up or December 2010. Median duration of follow up for all patients was 88 months (interquartile range [IQR], 47.5-144.5 months). Thirty-two (12%) patients were lost to follow-up, mainly because of transfer of care to other hospitals. In our cohort, 155 patients (64%) were alive at December 2010.
First, we divided all 273 AAV-patients into groups with (n=212) and without (n= 61) renal involvement at diagnosis and compared clinical characteristics and outcome.

Then, we divided all patients with renal involvement according to ANCA-specificity, i.e. PR3-ANCA (n=138), MPO-ANCA (n=65) and PR3-ANCA- negative patients and MPO-ANCA-negative patients (n=9). In these groups, we compared clinical characteristics and patient and renal outcome according to ANCA-specificity as well as the influence of relapses on renal function.
Finally, we looked for differences in all patients with renal involvement who were in need of RRT at diagnosis (n=48) and compared outcomes with the renal-involvement group who did not need RRT (n=164).

Clinical diagnosis and ANCA-analysis
Based on clinical characteristics, patients were suspected of having AAV and tested for ANCA. When a positive ANCA was found in indirect immunofluorescence (IIF), its specificity was confirmed by antigen specific ELISA, as previously described (10).
When clinically indicated, biopsies were performed. Disease severity at diagnosis and relapse was scored using the Birmingham Vasculitis Activity Score (BVAS)(11).

Definitions
Renal involvement was based on clinical data (active urinary sediment, proteinuria, impaired renal function) or by biopsy.
Need for dialysis at baseline was defined as RRT within 6 weeks after diagnosis.
Relapse was defined as recurrence or new appearance of organ involvement attributable to active vasculitis and requiring increase in or reintroduction of immunosuppression. Renal relapse was defined as a rise in or appearance of new proteinuria and haematuria, a rise in serum creatinine (mg/dl) > 10% with active urinary sediment or renal biopsy showing disease activity. During follow up, renal function was assessed as estimated GFR (eGFR)(ml/min per 1.73m^2) using the Modification of Diet in Renal Disease-formula.

Treatment
Induction treatment consisted of daily oral cyclophosphamide (2 mg/kg, and adjusted for age > 65 years to 1.5 mg/kg) and prednisolone (1 mg/kg; maximal dosage of 60 mg/day). The patients with severe renal involvement (serum creatinine > 5,66, dialysis dependency at diagnosis or progressive disease during the first weeks) received additional therapy with plasma exchange (three times per week for three weeks). Doses of cyclophosphamide were adjusted to maintain the white blood cell count above 4 x 10*9/L. After 4-6 weeks, the daily prednisolone dose was tapered by 10 mg every 2 weeks until the dose reached 30 mg, and thereafter by 5 mg every 2-4 weeks.
During the period 1990-1996, once remission was achieved, maintenance therapy consisted of oral cyclophosphamide with a daily dose tapered by 25 mg every 3 months (n=117). From 1996 onward, patients were switched to azathioprine maintenance therapy

(1.5-2 mg/kg body weight daily) after 3 months of stable remission (n=156). From 1 year after diagnosis azathioprine was tapered by 25 mg every 3 months.

Statistical analysis.

Data were analysed using SPSS16 and GraphPad Prism (version 5.01) software. Values are given as mean ± SD and median (range). Groups were compared using the unpaired t-test or chi-squared test. For paired data, a paired t-test was used. Relapse-free survival was assessed with actuarial survival curves, calculated using Kaplan-Meier estimates for survival distribution. Differences between groups in survival were analysed with the log-rank test. Multivariate backward stepwise Cox proportional hazard analysis with time to death, time to start or restart RRT and relapse as the time-dependent variables was performed to determine the significance of different risk factors in patient and renal outcomes. Other co-variates in our multivariable model were age, sex, ANCA specificity, dialysis at diagnosis, nonrenal relapse, hypertension and proteinuria at 6 months and eGFR at 6 months. A two-sided P-value < 0.05 was considered statistically significant. Decline in renal function was estimated as the slope (ml/min per 1.73m^2) per year of the individual linear regression line of eGFR over time until relapse or end of follow-up. Frequency of relapse was expressed as number of relapses per patient-year.

RESULTS

Patient Baseline Clinical Characteristics

Patients were divided according to presence (n=212) or absence (n=61) of renal involvement at diagnosis (Table 1). Compared with patients without renal involvement at diagnosis, patients in the renal involvement group were older (P= 0.01), and had higher levels of baseline C-reactive protein RP (P= 0.001) and BVAS (P < 0.001). A higher creatinine level at baseline was also found in the renal group.

Within the renal involvement group, we divided the cohorts to differences in ANCA specificity (Table 2). Patients in the PR3 group were more often men (66%) compared with the MPO-group (48%) (P= 0.01). MPO-ANCA- positive patients were older (P= 0.02), and had higher levels of creatinine (P < 0.001) at baseline. Of patients with MPO-AAV, 31% needed dialysis at diagnosis versus 20% in PR3-group (P=0.10). PR3-ANCA- positive patients more often had ear, nose and throat involvement (p < 0.001) and had higher C-reactive protein and BVAS at baseline (p<0.001).

Patient survival

During follow-up, 87 patients (32%) died; cumulative estimated patient survival rates at 1, 5 and 10 years were 90%, 83% and 74% respectively.

Table 1 Clinical characteristics at baseline of 273 patients with AAV: differences between patients without (NR) and with renal involvement (R).

	NR	R	p-value
Number	61	212	
Age (mean)	52 (14)	58 (16)	0.01*
Sex (n)	32	126	0.94
Diagnosis			
GPA (n)	55	132	< 0.0001*
MPA (n)	6	52	0.01*
Renal limited vasc	0	28	
Comorbidity			
Hypertension	1	4	0.90
DM	1	15	0.11
CVD	6	20	0.34
AID**	1	9	0.34
Malignancy	4	15	0.89
ENT (n)	52	124	0.0001*
Pulm (n)	26	40	0.0001*
BVAS med (range)	13 (7-27)	23 (7-48)	< 0.0001*
Creat mean (SD)	0.94 (0.20)	3.63 (3.42)	< 0.0001*
CRP mean (SD)	7.6 (8.3)	10.8 (9.0)	0.001*
Proteinuria (gr/24 hr)	0.09	1.7	< 0.0001*
RRT	0	49***	
Plasmapheresis	0	48	

Abbreviations:
GPA=granulomatosis with polyangiitis, MPA=microscopic polyangiitis, DM=diabetes mellitus, CVD=cardiovascular disease, AID= auto-immune diseases, ENT=ear, nose and throat, BVAS=Birmingham Vasculitis Activity Score, Creat=Creatinine (mg/dL), CRP=C-reactive protein, RRT=renal replacement therapy.

** Concomitant auto-immune diseases:

NR	R	
Morbus Crohn	Morbus Sjogren	1
	Sarcoidosis	1
	Psoriasis	1
	Hypothyroidism	4
	Hyperthyroidism	2

***: 48 PR3- and MPO-positive patients, one PR3- and MPO-ANCA-negative patient.

Table 2 Clinical characteristics at baseline of 212 AAV-patients with renal involvement: differences between PR3-ANCA positive patients, MPO-ANCA positive patients and PR3- and MPO-ANCA negative patients (=ANCA neg) (statistical analysis for PR3 vs MPO).

	PR3	MPO	p-value	ANCA neg
Number	138	65		9
Age (mean)	56 (16)	61 (15)	0.02*	60 (15)
Sex (n)	91	31	0.01*	4
Comorbidity				
Hypertension	3	0	0.23	1
DM	8	7	0.21	0
CVD	10	8	0.24	2
AID**	3	5	0.06	1
Malignancy	12	2	0.14	1
Diagnosis				
GPA (n)	122	7		3
MPA (n)	13	38		1
Renal limited vasc	3	20		5
ENT (n)	106	15	< 0.0001*	3
Pulm (n)	31	8	0.08	1
BVAS med (range)	26 (7-48)	18 (10-32)	< 0.0001*	18 (12-25)
Creat mean (SD)	3.04 (2.84)	4.82 (4.22)	0.0008*	3.54 (2.75)
CRP mean (SD)	13 (9.5)	7.2 (6.5)	<0.0001*	4.3 (4.2)
Proteinuria (gr/24 hr)	1.6	2.4	0.004*	1.4
RRT (n)	28	20	0.10	1
Plasmapheresis (n)	33	15	0.90	0

Abbreviations:
PR3=proteinase 3, MPO=myeloperoxidase, ANCA= anti-neutrophil cytoplasmic antibody, DM=diabetes mellitus, CVD=cardiovascular disease, AID= auto-immune diseases, GPA=granulomatosis with polyangiitis, MPA=microscopic polyangiitis, ENT=ear, nose and throat, BVAS=Birmingham Vasculitis Activity Score, Creat=Creatinine (mg/dL), CRP=C-reactive protein, RRT=renal replacement therapy.

** Concomitant auto-immune diseases:

PR3		MPO		ANCA NEG	
Hypothyroidism	2	Hypothyroidism	2	Hyperthyroidism	1
Psoriasis	1	Hyperthyroidism	1		
		Sarcoidosis	1		
		Morbus Sjogren	1		

Patients without renal involvement showed higher survival rates compared with all patients with renal involvement (hazard ratio[HR], 0.55; 95% confidence interval [95% CI], 0.33-0.92; P= 0.02). The need for RRT at diagnosis accounted for this difference (HR, 0.27; 95% CI, 0.15-0.47; P< 0.001) (Figure 1), because mortality in patients with renal involvement who did not need RRT was not different compared with patients in the nonrenal involvement group (HR, 0.72; 95% CI, 0.38-1.46; P=0.32). In addition, patients who needed RRT were more prone for death due to infectious disease compared with patients who did not need RRT (P = 0.04).

We compared patient survival according to ANCA specificity in all patients with renal involvement (Figure 2). During the first 6 months after diagnosis, a survival disadvantage was found for patients with MPO-ANCA compared with PR3-ANCA (HR, 0.38; 95% CI, 0.22-0.65; P= 0.003). However, in multivariate analysis with inclusion of age at diagnosis, this survival difference was no longer significant (95% CI, 0.35-2.14; P= 0.76). As shown, during follow- up after 6 months, the survival curves are parallel in course.

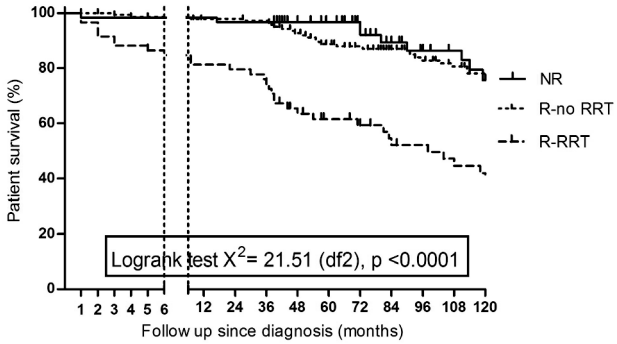
Renal survival

In the nonrenal group, no patient developed ESRD during follow up, despite occurrence of 17 renal relapses in 13 patients in this group (1 MPO-ANCA- positive patient and 12 PR3-ANCA- positive patients).

In the renal involvement group, renal survival was worse in MPO-ANCA positive patients, compared with PR3-ANCA-positive patients and ANCA- negative patients (HR, 2.1; 95% CI, 1.11-3.8; P=0.01) (Figure 3).

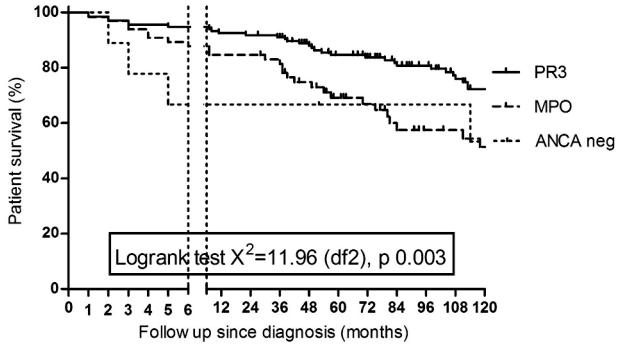
Forty-eight PR3-ANCA- positive patients and MPO-ANCA- positive patients needed RRT at diagnosis. Eleven patients (23%) died within 6 months (2 patients where independent of RRT at time of death) and 14 patients (29%) did not regain renal function at all. Seven patients (15%) regained renal function only temporarily and needed RRT later (range 13-63 months after diagnosis). Sixteen patients (33%) regained and maintained renal function. Of all 164 patients with renal involvement who were dialysis independent at diagnosis, 12 patients (7%) developed ESRD during follow-up and then needed RRT. Further details are given in Figure 4.

Of all PR3-ANCA- positive patients who became dialysis dependent during follow up (n=14), mean eGFR at 6 months was 27 ml/min per 1.73m^2. Thirteen patients experienced relapse in the 6 months before becoming dialysis dependent; only one patient, whose eGFR was 20 ml/min per 1.73m^2 at 6 months, showed a slow decline in renal function during follow up and reached ESRD 178 months after diagnosis. All five MPO-ANCA- positive patients who became dialysis dependent during follow up were classified as CKD stage 4 or 5 after initial treatment. They did not experience relapses, but showed a more rapid decline in renal function (range in slope -1.3 to -4.75 ml/min per year) compared with the mean slope of 0.06 ml/min per year in the other MPO-ANCA- positive patients.



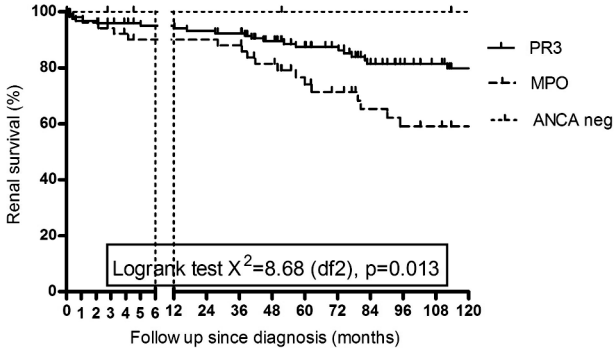
No at risk	0	6	12	60	96	120
NR	61	61	60	48	28	19
R-no RRT	164	142	138	102	77	65
R-RRT	48	39	39	19	11	6

Figure 1 Patient survival in ANCA-associated vasculitis without renal involvement (non-renal=NR) compared to patients with renal-involvement and renal replacement therapy (R-RRT) and renal involvement without renal replacement therapy (R-no RRT)



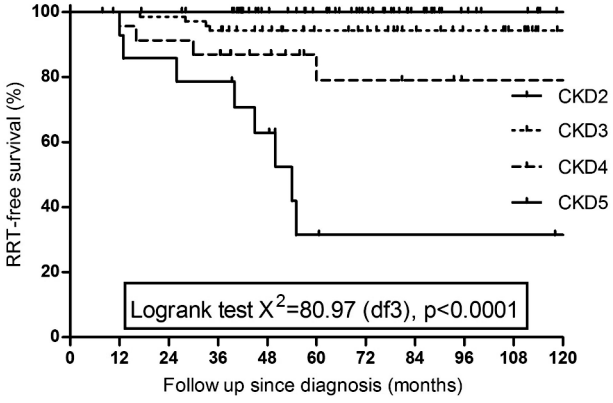
No at risk	0	6	12	60	96	120
PR3	138	128	123	98	75	59
MPO	65	57	56	35	22	18
ANCA neg	9	7	7	6	6	5

Figure 2 Differences in patient survival in PR3-ANCA, MPO-ANCA positive patients and ANCA negative patients (statistical analysis for PR3 versus MPO).



No at risk	0	3	6	12	60	96	120
PR3-ANCA	138	126	113	108	83	58	49
MPO-ANCA	65	54	48	44	30	20	17
ANCA neg	9	8	7	7	6	5	5

Figure 3 Renal survival according to ANCA-specificity in ANCA-associated vasculitis patients with renal involvement.



No at risk	6	12	60	96	120
CKD2	101	101	78	47	37
CKD3	63	60	47	32	22
CKD4	23	23	12	8	8
CKD5	14	14	4	3	2

Figure 4 Renal replacement therapy-free survival according to CKD-stage for all patients with renal involvement alive > 6 months after diagnosis.

These findings indicate that renal function after initial treatment is a major prognostic factor for reaching ESRD (P< 0.001), also shown in Figure 4. In multivariate analysis renal relapses were also significantly associated with the development of ESRD (P=0.02), whereas other covariates were not (Table 3).
Of all 212 AAV patients with renal involvement, 138 patients were PR3-ANCA positive and 65 patients were MPO-ANCA positive at diagnosis.
No statistical difference was found in number of patients who needed RRT at diagnosis between MPO-ANCA- positive patients (31%) versus PR3-ANCA- positive patients (20%) (P= 0.10), or the number of patients who recovered renal function (P=0.29). However, for patients who presented with CKD stage 4 or 5 at diagnosis, recovery of renal function in the first 6 months was less for MPO-ANCA- positive patients (median 8.5; IQR 1.75-15), compared with PR3-ANCA- positive patients (median 12.5, IQR 5-21) (data not shown, Supplemental Figures). For patients with eGFR > 30 ml/min per 1.73m2, recovery was not different. Overall, we found a difference in renal function at baseline and during follow- up (P< 0.001) between MPO-ANCA- positive patients and PR3-ANCA- positive patients with renal involvement (Figure 6). Within both groups, no differences were found comparing eGFR at 6 months and at 5 years. During follow up, 11% of MPO-positive patients had a decline in renal function of 1 CKD-stage, compared with 3% of PR3-positive patients. In those patients who did not experience a relapse, the slope of decline in renal function was -0.06 ml/min per year (SD 3.13) for MPO-ANCA positive patients, compared with a slope of -0.26 ml/min per year (SD 3.18) for PR3-positive patients. Therefore, we concluded that although MPO-ANCA-positive patients present with more advanced renal damage and show less recovery of eGFR after induction therapy, long-term outcome shows little tendency to deterioration to ESRD. Inclusion of patients without renal involvement did not substantially change this finding.

Table 3 Relative risk for renal failure for CKD stage and renal relapse in multivariate analysis.

CKD	RR (95% CI)	p-value
3	ref	
4	16.4 (4.5-59.7)	< 0.0001*
5	43.1 (11.7-158.6)	< 0.0001*
Renal relapse	3.27 (1.24-8.63)	0.01*
Mean arterial pressure (per mmHg)	0.99 (0.96-1.01)	p= 0.29
Proteinuria (per gr/24 hr)	1.14 (0.62-2.1)	p= 0.62

Variables in multivariate analysis: time to death, time to (re)start of renal replacement therapy, relapse as time-dependent variables. Other co-variates are age, sex, ANCA-specificity, dialysis at diagnosis, non-renal relapse, hypertension and proteinuria and eGFR at six months.

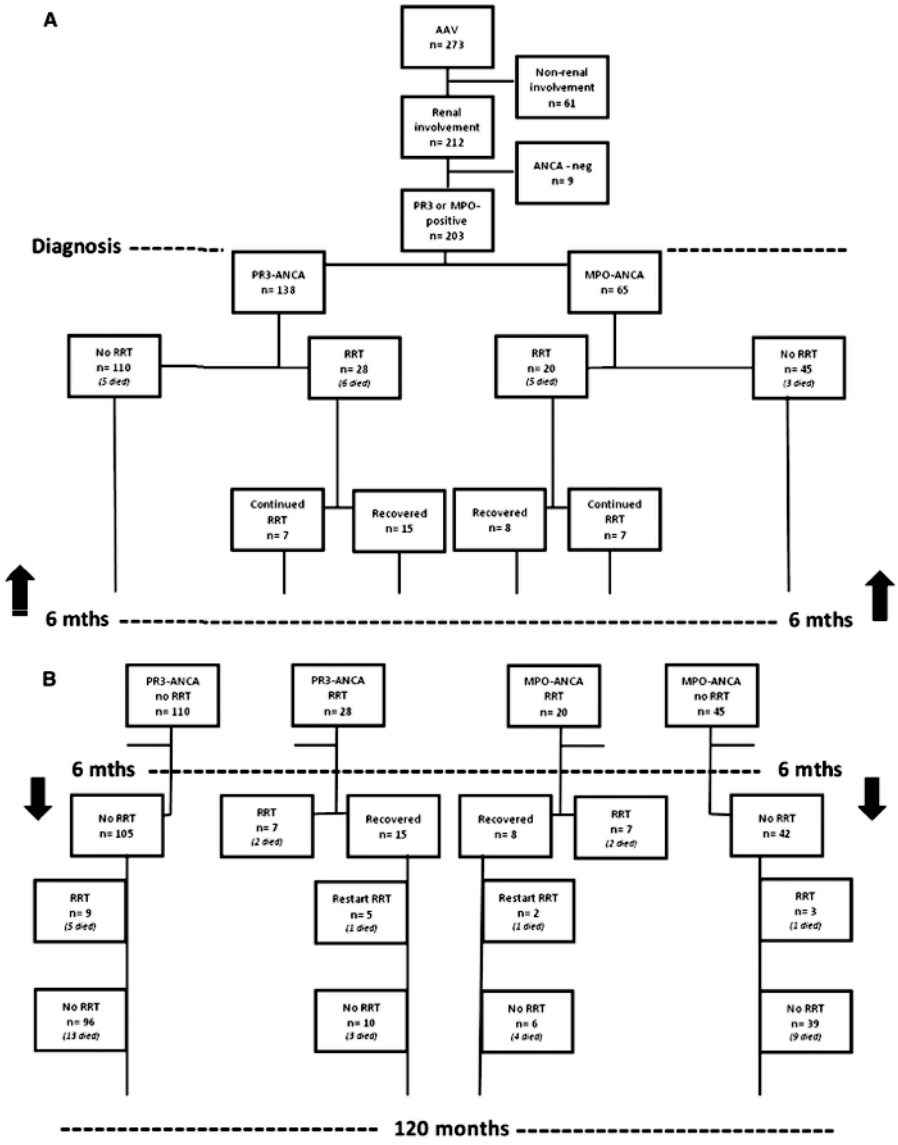


Figure 5A/B Flowchart of renal survival before and after six months of treatment in patients with PR3- and MPO-ANCA-associated vasculitis with renal involvement.

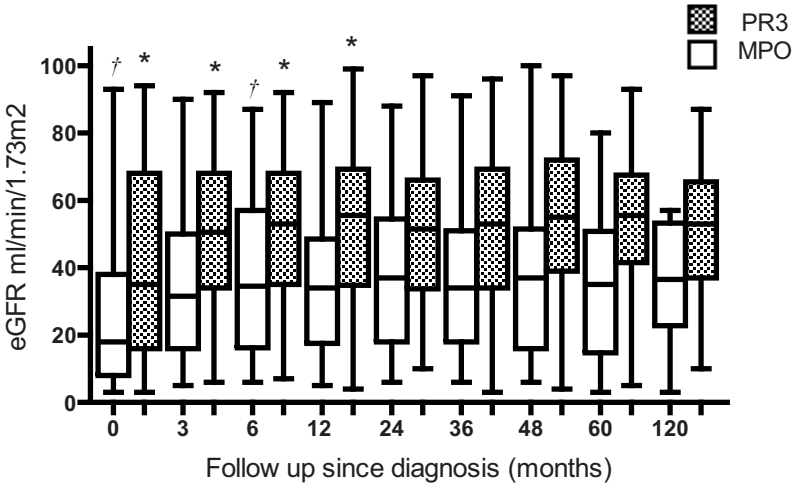


Figure 6 Course in eGFR (ml/min/1.73m2) during long term follow up of patients with PR3- and MPO-ANCA-associated vasculitis with renal involvement at diagnosis.

Relapses

During a follow up period from 6 months after diagnosis to 120 months, 223 relapses occurred, 105 of which were renal relapses (47%). Of 249 patients alive after the first 6 months of treatment, 124 patients (50%) did not experience a relapse and 60 (24%) patients experienced at least two relapse. Overall frequency of relapses per patient-years was 0.10; this frequency was 0.051 during the first year after diagnosis, 0.17 from 1 year to 5 years, and 0.056 after 5 years.

PR3-ANCA-positive patients experienced more relapses than MPO-ANCA-positive patients (P< 0.001, Supplemental Figures 4 and 5). We analysed the influence of these renal relapses on renal function by comparing renal function 1 year before and 1 year after relapse. We found that renal relapse caused a significant loss of eGFR of 8 ± 4 ml/min, (P< 0.001, Supplemental Figures). In addition, a difference in eGFR was found comparing those patients with renal relapses and those without at 120 months after diagnosis (P=0.01) (Supplemental Figure 7).

PR3- ANCA-negative and MPO-ANCA- negative patients

Nine PR3-ANCA-negative patients and MPO-ANCA-negative patients were diagnosed with vasculitis with renal involvement. Four patients died during follow-up, three of them within 6 months after diagnosis. One patient needed for RRT at diagnosis. His kidney function recovered during the first months of treatment but he died due to a severe infection. Of all

six patients who were alive > 6 months after diagnosis, no other patient developed ESRD despite five relapses (three of which were renal relapses) in three patients. During long-term follow- up, the slope of decline in kidney function was comparable with the ANCA-positive patients with renal involvement (data not shown).

DISCUSSION

Although induction therapy for AAV has become standardized currently, questions remain regarding possible individualized treatment strategies for AAV with and without renal involvement and potential differences between PR3-ANCA- positive patients and MPO-ANCA- positive patients (6). In this retrospective study, we evaluated both patient and renal survival in patients with AAV and aimed to report differences between the aforementioned groups.

Overall cumulative survival rates in our cohort were similar to previous studies, with 1-year patient survival of 90% and 10 year survival of 74% (1,2,4). Patients with renal involvement at diagnosis had worse survival outcomes. In addition, severity of renal involvement at diagnosis affected both patient and renal survival. In multivariate analysis a low eGFR at 6 months and renal relapses were associated with reaching ESRD. However, traditional risk factors like hypertension and proteinuria at diagnosis and 6 months had no significant prognostic value.

Patients who needed RRT had worse survival rates, were prone for remaining dependent of RRT and showed a 30% risk for loss of renal function and becoming RRT-dependent if renal function improved after initial treatment. Renal survival was 100% in patients without renal involvement at diagnosis.

In our cohort renal relapse was associated with a median decline of 8 ml/min in renal function, comparable with previously reported data of Slot el al (3). This decline in renal function involves patients with PR3-AAV, in particular because these patients are especially at risk for relapse of disease (2,4,5). However, during long-term follow-up only a small percentage of patients (3%) moved downwards in CKD stage. The fact that almost all PR3-ANCA- positive patients (13 of 14) who became dialysis dependent during follow- up had a relapse before reaching ESRD highlights our finding that relapse is a significant predictor for renal function during follow up.

MPO-ANCA- positive patients presented with worse renal function and higher levels of proteinuria, probably due to advanced chronic damage at presentation. Those patients who presented with CKD stage 4 or 5 also showed less recovery of renal function. Renal survival was thus significantly worse (HR 2.1, 95% CI 1.11-3.8, p=0.01), compared with PR3-ANCA- positive patients. The majority of MPO-positive patients had a marginal decline in renal function during follow up (slope -0.06 ml/min, SD 3,13); however patients who

became dialysis dependent had somewhat steeper slopes (especially a mean eGFR of only 14.5 ml/min per 1.73m^2 at 6 months after diagnosis). Because MPO-ANCA- positive patients seldom experience relapses, this underscores our finding that renal survival is also predicted by a marginal or low eGFR at 6 months after diagnosis.

Our study has several limitations. First, this is a retrospective analysis of a single centre cohort, encompassing > 2 decades of clinical observation. Renal biopsies were not undertaken in all patients and information on comorbidities prior to presentation is scarce. Although induction therapy was standardized, maintenance regimes and treatment of traditional risk factors like proteinuria and hypertension at baseline and at 6 months were not. Our population consists mainly of Caucasians and geographically, it includes more PR3-postive than MPO-positive patients. However, to our knowledge, this is one of the largest series of long-term follow- up in AAV especially focused on differences between PR3-ANCA-positive patients and MPO-ANCA- positive patients.

CONCLUSION

PR3-AAV and MPO-AAV present as different entities at diagnosis because MPO-ANCA-positive patients are older and have higher serum creatinine at baseline. Both factors are of prognostic value for patient survival as well as renal survival in AAV (12). During follow up, PR3-ANCA- positive patients show a good recovery in renal function during the first 6 months and although relapses occur frequently, they seldom reach ESRD. In contrast, MPO-ANCA- positive patients present with worse renal function and have less recovery of renal function, independent of hypertension or proteinuria. Therefore, although relapses are scarce, they still result in ESRD.

Thus, although presentation and disease course are different, renal function at diagnosis and especially the regained renal function after initial treatment at 6 months are major predictors for renal survival in both groups, next to renal relapses. In particular traditional risk factors as hypertension or proteinuria at 6 months seemed not to be associated with reaching ESRD and becoming dialysis dependent.

On the basis of our observations, it seems to be important to regain as much renal function as possible after diagnosis has been made. Therefore, one could argue to expand treatment options when response to standard initial treatment is limited, for instance by adding plasmapheresis.

Supplementary material provided, showing

- Table 4: Causes of death during long term follow up in ANCA-associated vasculitis patients without renal involvement (NR) versus renal involvement (R) and in renal involvement with renal replacement therapy (RRT) versus without (no RRT).
- Figure 7: Differences in development of proteinuria between PR3- and MPO-ANCA associated vasculitis patients during long term follow up.
- Figure 8: course in eGFR (ml/min/1.73m2) in first six months after treatment of patients with PR3- and MPO-ANCA-associated vasculitis with renal involvement at diagnosis.
- Figure 9. Number and characteristics of relapses
- Figure 10: Relapse free survival according to ANCA specificity
- Figure 11: Delta eGFR (ml/min/1.73m^2) per patient per renal relapse
- Figure 12: Delta eGFR (ml/min/1.73m^2) during long-term follow up: difference between renal relapse versus no renal relapse.
- Figure 13: Recovery in eGFR (ml/min/1.73m2) in first six months of follow up: difference between MPO and PR3 for CKD stage IV and V.

REFERENCES

1. Falk RJF, Jennette JC. ANCA small-vessel vasculitis. *Journal of American Society of Nephrology* 8(2): 314-322, 1997
2. Franssen CFM, Stegeman CA, Kallenberg CGM, Gans ROB, de Jong PE, Hoorntje SJ, Cogen Tervaert JW. Antiproteinase 3- and antimyeloperoxidase-associated vasculitis. *Kidney International* 57: 2195-2206, 2000.
3. Slot MC, Cohen Tervaert JW, Franssen CFM, Stegeman CA. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal survival. *Kidney International* 63: 670-677, 2003.
4. Westman KWA, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse rate, renal survival and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement. *Journal of American Society of Nephrology* 9(5): 842-852, 1998.
5. Booth AD, Almond MKA, Burns A, Ellis P, Gaskin G, Neild GH, Plaisance M, Pusey CD, Jayne DRW for the Pan-Thames Renal Research Group. Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. American *Journal of kidney diseases* 41(4): 776-784, 2003.
6. Lyons PA, Rayner TF, Trivedi S, Phil M, Holle JU, Watts RA, Jayne DRW, Baslund B, Brenchley P, Bruchfeld A, Chaudhry AN, Cohen Tervaert JW, Deloukas P, Feighery C, Gross WL, Guillevin L, Gunnarsson I, Harper L, Hruskova Z, Little MA, Martorana D, Neumann T, Ohlsson S, Padmanabhan S, Pusey CD, Salama AD, Sanders JSF, Savage CO, Segelmark M, Stegeman CA, Tesar V, Vaglio A, Wieczorek S, Wilde B, Zwerina J, Rees AJ, Clayton DG Smith KGC. Genetically distinct subsets within ANCA-associated vasculitis. *NEJM* 367(3): 214-223, 2012.
7. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CGM, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzenkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman CA, Ytterberg SR, Specks U for the RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *New England Journal of Medicine* 363: 221-232, 2010.
8. Hauer HA, Bajema IM, v. Houwelingen HC, Ferrario F, Noel LH, Waldherr R, Jayne DRW, Rasmussen N, Bruijn JA, Hagen EC for the European Vasculitis Study Group. Determinants of outcome in ANCA-associated glomerulonephritis: a prospective clinico-histopathological analysis of 96 patients. *Kidney International* 62: 1732-1742, 2002.
9. Rihova Z, Jancova E, Merta M, Rysava R, Reiterova J, Zabka J, Tesar V. Longterm outcome of patients with antineutrophil cytoplasmic anto-antibody-associated vasculitis with renal involvement. *Kidney and Blood Pressure Research* 28: 144-152, 2005.
10. Luqmani RA, Bacon PA, Moots RJ, Janssen BA, Pall A, Emery P, Savage C, Adu D. Birmingham Vasculitis Activiy Score (BVAS) in systemic necrotizing vasculitis. *QJM* 87(11): 671-678, 1994.
11. Exley AR, Bacon PA, Luqmani RA, Kitas GD, Carruthers DM, Moots RJ. Examination of disease severity in systemic vasculitis from the novel perspective of damage using the vasculitis damage index (VDI). *British Journal of Rheumatism* 37: 57-63, 1998.

12. Franssen CFM, Stegeman CA, Oost-Kort WW, Kallenberg CGM, Limburg PC, Tiebosch A, de Jong PE, Tervaert. Determinants of renal outcome in anti-myeloperoxidase-associated necrotizing crescentic glomerolunephritis. *J Am Soc Nephrol* 9: 1915-1923, 1998.

SUPPLEMENTARY MATERIAL

Table 4 Causes of death during long term follow up in ANCA-associated vasculitis patients without renal involvement (NR) versus renal involvement (R) and in renal involvement with renal replacement therapy (RRT) versus without (no RRT).

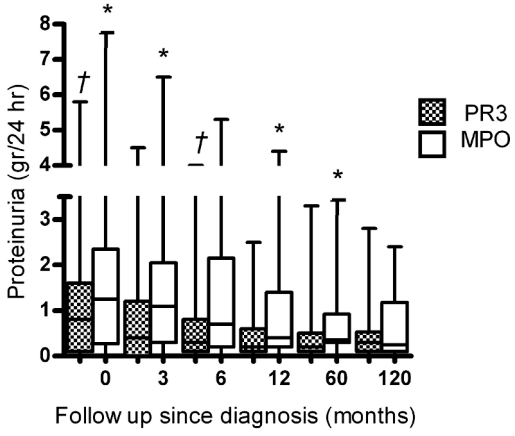
	Non renal	Renal	RRT	no RRT
Number	61	212	61	151
Number of death	11	76	34	42
Active vasculitis	0	4	2	2
Infectious	2	27*	13	14**
Cardiovascular	1	11	5	6
Malignancy	2	6	4	2
Others (incl ESRD)	1	10	5	5
Unknown	5	18	5	13

* p=0.05

** p= 0.04

Abbreviations:
ESRD=end stage renal disease.

Figure 7 Differences in development of proteinuria between PR3- and MPO-ANCA associated vasculitis patients during long term follow up.



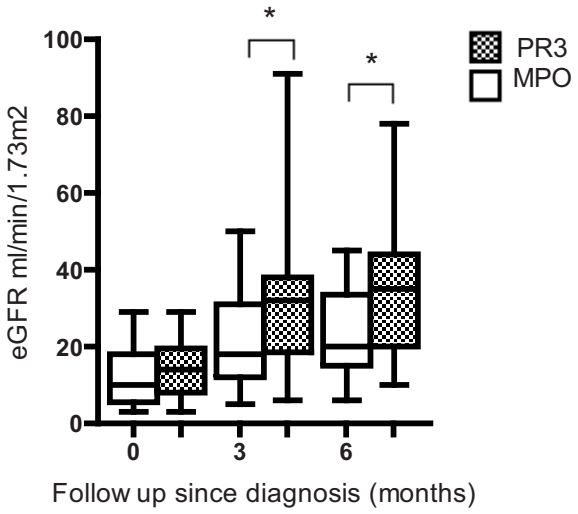


Figure 8 Course in eGFR (ml/min/1.73m2) in first six months after treatment of patients with PR3- and MPO-ANCA-associated vasculitis with renal involvement at diagnosis.

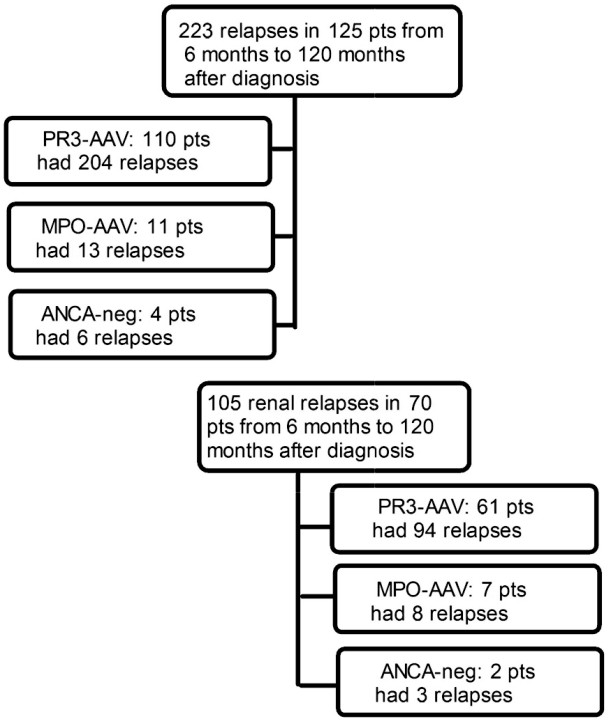
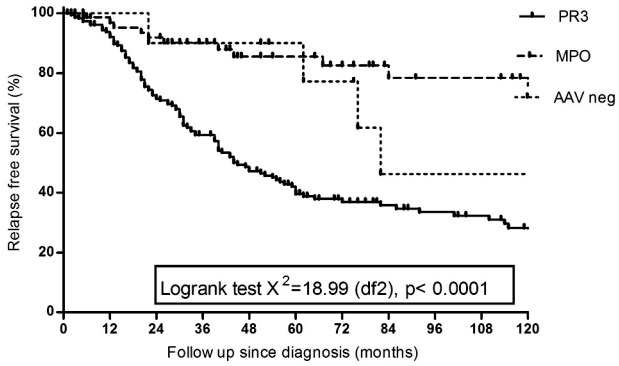


Figure 9 Number and characteristics of relapses.



No at risk 0	6	12	60	96	120	
PR3	138	123	114	36	20	13
MPO	65	56	53	31	18	15
ANCA neg 48	37	34	16	8	3	

Figure 10 Relapse free survival according to ANCA specificity

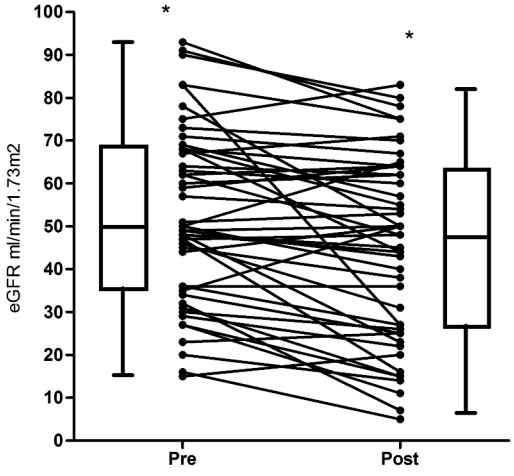


Figure 11 Delta eGFR per patient per renal relapse

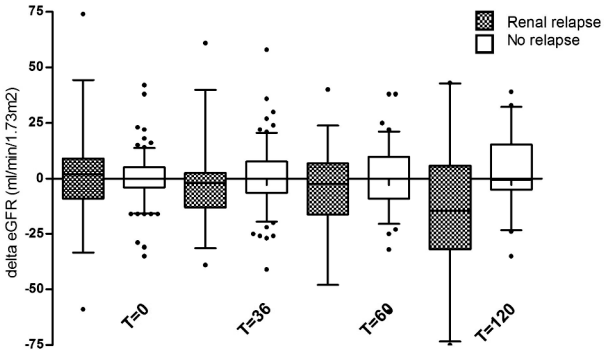


Figure 12 Delta eGFR (ml/min/1.73m^2) during long term follow up: difference between renal relapse versus no renal relapse.

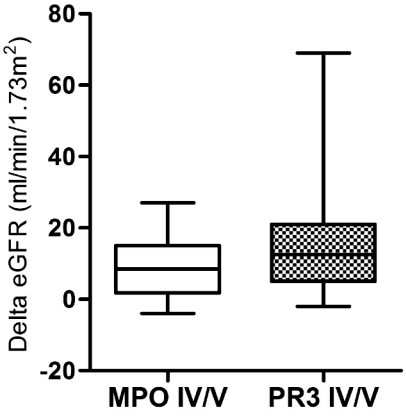


Figure 13 Recovery in eGFR (ml/min/1.73m2) in first six months of follow up: difference between MPO and PR3 for CKD stage IV and V.