Evaluating Renal Disease in Pediatric Anti-Neutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis in the First 24-Months

Kiran Toor[1,2], Audrea Chen[1], David Cabral[1,3], Cherry Mammen[1,3], Else Bosman[3], Ye Shen[2], Jeffrey Bone[2] , Kelly Brown[1,2] and Kimberly Morishita[1,3]
on behalf of the PedVas Investigator Network
[1]Department of Pediatrics, The University of British Columbia, [2]BC Children's Hospital Research Institute, [3]BC Children's Hospital, Vancouver, BC

INTRODUCTION

What is ANCA-associated vasculitis?
ANCA-associated vasculitis is a rare systemic disease characterized by inflammation and damage to small and/or medium blood vessels. Renal disease is the most common manifestation of pediatric ANCA associated vasculitis (AAV). Our previous research demonstrated high rates of significantly reduced renal function at diagnosis and evidence of early renal damage, despite aggressive treatment (Morishita, *Arthritis and Rheumatology*, 2017). Recommended treatment of major organ involvement in children is based on adult data and involves aggressive treatment with steroids and immunosuppressive agents. This is despite a lack of data about pediatric specific disease course, outcomes and treatment related toxicity that may be unique to children. Due to disease rarity in childhood, renal outcomes and predictors of outcome in pediatric-AAV have not been well studied.

Overarching Research Question: What is the course of renal disease and outcomes for children with AAV in the first 24-months and are there predictors of these outcomes?

OBJECTIVES

- Describe renal disease course and outcomes in the first 24-months of disease
- Evaluate the utility of estimated glomerular filtration rate (eGFR) as a predictor of renal outcome at 12-months

METHODS

PedVas Initiative:
- Multi-centre, international study
- Clinical and biological data collection from patients with systemic vasculitis
- 35 international sites; >400 AAV patients enrolled

Inclusion Criteria:
- GPA, MPA, or ANCA-positive immune glomerulonephritis diagnosis
- <18 years of age at time of diagnosis (TOD)
- Follow-up data at 12-months and/or 24-months
- Biopsy confirmed glomerulonephritis OR dialysis dependence at TOD

Table 1: Patients classified according to eGFR. Classifications based on Chronic Kidney Disease Staging System

KDIGO Category	Kidney dys(function)	eGFR (ml/min/1.73m²)
1	Normal	>90
2	Mildly Reduced (MildR)	60-89
3a	Mild-Moderately Reduced (Mild-ModR)	45-59
3b	Moderately-Severely Reduced (Mod-SevR)	30-44
4	Severely Reduced (SevR)	15-29
5	Renal Failure (RF)	<15

- Disease activity was assessed using the pediatric vasculitis activity score (PVAS) (Dolezalova, *Annals of the Rheumatic Diseases*, 2013)
- Damage was assessed using the pediatric vasculitis damage index (pVDI) (Dolezalova, *Annals of the Rheumatic Diseases*, 2014)

Statistical Analysis:
- Proportional odds logistic regression model used to assess the association between eGFR at diagnosis and eGFR at 12-months
- Linear regression model on subset of patients with eGFR values at diagnosis and 12-months. A cutpoint analysis that maximized the sum of specificity and sensitivity determined a threshold value at which the outcome (12-month eGFR) is highly likely to be 'bad' (Category 3b-5)

RESULTS

1. Baseline characteristics at diagnosis

Table 2: Baseline demographics and renal characteristics

Overall Characteristics	
Age at diagnosis, median (IQR) years	13.8 (10.7-15.7)
Sex, Female N (%)	98 (68)
Ethnicity, Caucasian N (%)	64 (55)
Diagnosis, N (%)	
Granulomatosis with polyangiitis	113 (78)
Microscopic polyangiitis	32 (22)
Renal Characteristics	
Haematuria	133 (92)
Proteinuria	133 (92)
Hypertension	41 (28)
Dialysis	36 (25)
Disease activity (renal PVAS), median (IQR)	12 (10-12)

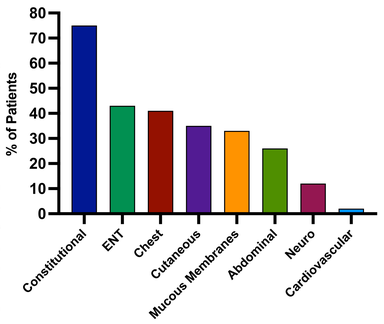

Figure 1: Extra-renal manifestations at diagnosis

2. Despite high renal disease activity at onset, most AAV patients attain inactive renal disease within two years of diagnosis; however, not without permanent renal damage

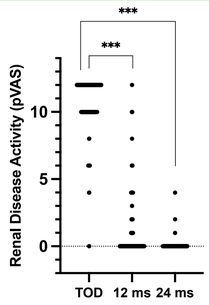

Figure 2: Renal-specific disease activity at 12- and 24-months post diagnosis. Inactive renal disease indicated by renal PVAS=0 or 1. Active renal disease is indicated by PVAS ≥2. ***$P < 0.001$

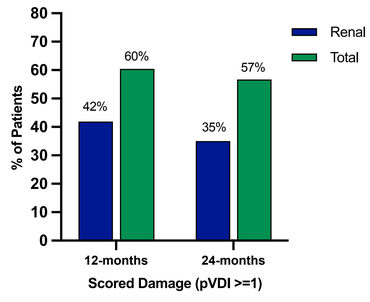

Figure 3: Overall and renal-specific damage at 12- and 24-months post diagnosis, as measured by the pVDI. Renal damage is indicated by pVDI >=1.

3. Change in eGFR categories over 24-months

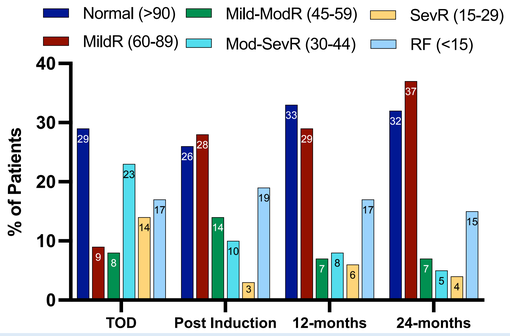

Figure 4: eGFR trajectories across 24-months. Percent of pediatric-onset AAV cases (%, y-axis) with eGFR values corresponding to KDIGO category of renal function at (x-axis) diagnosis, post induction, 12-months and 24-months

4. Patients that present with renal failure at diagnosis are unlikely to recover normal renal function

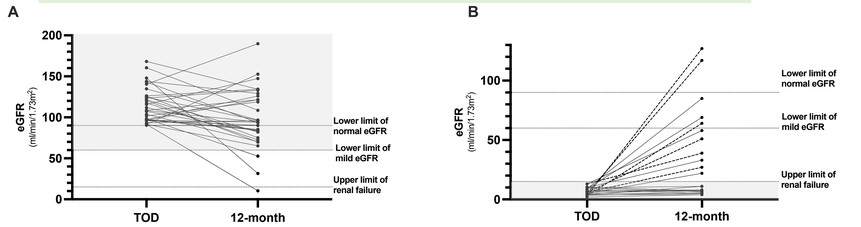

Figure 5: Extreme renal function (normal and renal failure eGFR) trajectories at TOD, 12-months and 24-months. *Dotted line represents patients who have received a renal transplant.* eGFR (y-axis; ml/min/1.73m²) in the AAV cohort grouped based on patients at diagnosis with **A)** 'normal' renal function (eGFR>90) (n=33) and renal failure (eGFR<15) (n=23) followed across 12-months.

5. eGFR at diagnosis is predictive of renal function 12-months after diagnosis

Table 3: Odds ratio for KDIGO categories at 12-months

Characteristic	OR[1]	95% CI[1]	p-value
KDIGO Diagnosis			
Normal	-	-	-
MildR	1.36	0.31, 5.87	0.680
Mild-ModR	1.02	0.24, 4.36	0.981
Mod-SevR	4.77	1.60, 14.2	0.005
SevR	8.62	2.31, 32.1	0.002
RF	26.3	6.32, 109	<0.001

[1] OR= Odds Ratio, CI= Confidence Interval Adjusted for diagnosis (GPA or MPA), ANCA (specificity for PR3 or MPO), PVAS at baseline, and induction treatment

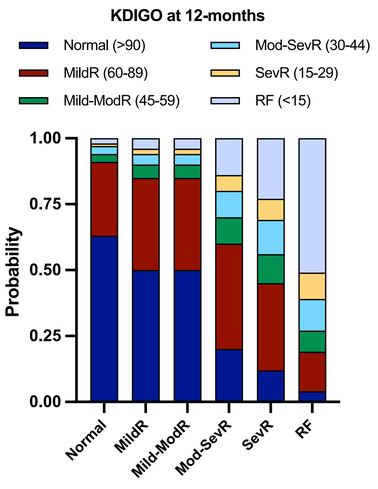

Figure 6: Predicted probability of KDIGO stage at 12-months post-diagnosis based on KDIGO stage at the time of diagnosis.

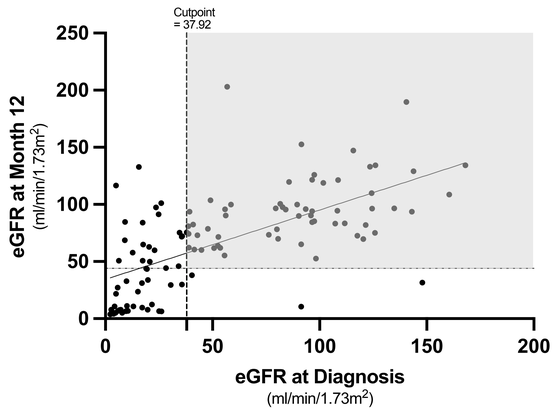

Figure 7: eGFR in pediatric AAV at diagnosis and 12-months with identified cutpoint (n=113). The vertical dotted line at the x-axis represents the cutpoint eGFR value of 38. The horizontal line on the y-axis represents the eGFR value of 44.0, the upper limit of the moderately reduced renal function (KDIGO category).

CONCLUSIONS

- 54% of children with AAV-associated renal disease have moderately-reduced renal function or worse at diagnosis
- At 12- and 24- month follow-up, two-thirds of patients continue to have reduced renal function
- Most patients achieve inactive renal disease by 12-months; however, 42% have evidence of renal damage
- An eGFR at diagnosis that is greater than/equal to 37.92 is predictive of renal function at 12-months that is mildly reduced or normal

SIGNIFICANCE

- This project comprises the largest outcome study of renal disease in pediatric-onset AAV to date
- Elucidation of AAV-associated renal disease trajectories will contribute to improved pediatric-specific counseling around anticipated disease course and outcome
- Outcome prediction could lead to a more individualized approach, thereby guiding treatment decisions
- Identified predictive eGFR value has potential as a clinical tool

ACKNOWLEDGEMENTS

Brown Lab
BC Children's Hospital Rheumatology Team
PedVas Investigators Network

FUNDING SUPPORT

Childhood Arthritis and Rheumatology Alliance (CARRA)
Centre for Blood Research
BC Children's Hospital Research Institute