Proteinuria and its association with disease progression in IgA nephropathy: Analysis of the UK National RaDaR IgA nephropathy cohort

David Pitcher[1], Fiona Braddon[1], Bruce Hendry[2], Alex Mercer[3], Kate Osmaston[1], Moin A. Saleem[4], Retha Steenkamp[1], Neil Turner[5], Kaijun Wang[2], Jonathan Barratt[6], Daniel P. Gale[7]

[1]UK Kidney Association; [2]Travere Therapeutics, Inc., San Diego, CA; [3]JAMCO Pharma Consulting, Sweden; [4]University of Bristol & Bristol Royal Hospital for Children, UK; [5]University of Edinburgh, UK; [6]University of Leicester & Leicester General Hospital, UK; [7]Department of Renal Medicine, University College London, UK

RESULTS

Characteristics at diagnosis and clinical outcomes

- The cohort included 923 patients (68% male and 96% adult) with a median age at diagnosis of 41.7 years (Table 1)
- Among patients with available data, the median urinary protein-creatinine ratio (PCR) at diagnosis was 172 mg/mmol (1.5 g/g) and median estimated glomerular filtration rate (eGFR) was 50 mL/min/1.73 m^2 (Table 1)
- Median duration of follow-up was 4.5 years and 38% of patients progressed to kidney failure (KF)/death during follow-up (Table 1)
- Mean eGFR slope was -3.6 mL/min/1.73 m^2/year (Table 1)

Elevated time-averaged proteinuria is associated with kidney failure/death

- Time to KF/death was significantly shorter with higher levels of time-averaged proteinuria (TA-PU) (Figure 1)
- Approx. 1 in 4 patients with time-averaged proteinuria (TA-PU) <100 mg/mmol (<0.88 g/g; approximately <1 g/day) progressed to KF/death within 10 years (Figure 1)
- TA-PU 100–<200 mg/mmol (0.88–<1.76 g/g; approximately 1.0–<2.0 g/day) was associated with an almost 3-fold increase in risk of KF/death compared with TA-PU <100 mg/mmol (Table 2)
- The risk of KF/death was increased almost 5-fold at TA-PU 200–<300 mg/mmol (1.76–<2.64 g/g; approximately 2.0–<3.0 g/day) compared with TA-PU <100 mg/mmol (Table 2)
- TA-PU ≥300 mg/mmol (≥2.64 g/g; ≥3.0 g/day) was associated with a 9-fold increase in the risk of KF/death compared with TA-PU <100 mg/mmol (Table 2)

Elevated time-averaged proteinuria is associated with more rapid loss of eGFR

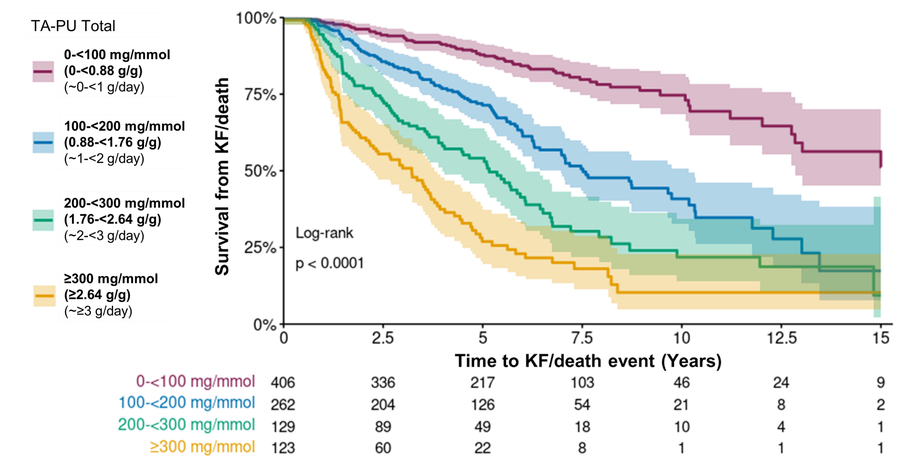
- Higher grades of TA-PU were associated with a higher rate of eGFR loss (p<0.001) (Table 2)
- The rate of eGFR loss escalated from an eGFR slope of -0.35 mL/min/1.73 m^2/year for TA-PU <100 mg/mmol to -12.41 mL/min/1.73 m^2/year with TA-PU ≥300 mg/mmol (Table 2)

Table 1. Characteristics at diagnosis and clinical outcomes

		N	%
Age (years)		**923**	**100**
Median (IQR)		41.7 (30.3–53.3)	
Pediatric		36	4
Sex		**923**	**100**
Female		294	32
Male		629	68
PCR at baseline, n (%)		**515**	**56**
mg/mmol	Median (IQR)	172 (73–356)	
g/g	Median (IQR)	1.5 (0.6–3.1)	
eGFR at baseline, n (%)		**565**	**61**
Median, mL/min/1.73 m^2		49.8	
IQR		33.0–78.2	
Duration of follow-up, n (%)		**923**	**100**
Median, years		4.5	
IQR		2.5–6.8	
KF or death event, n (%)		**923**	**100**
Yes		355	38
No		568	62
eGFR slope, n (%)		**856**	**93**
Mean, mL/min/1.73 m^2/year		-3.6	
SD		9.4	

Abbreviations: eGFR, estimated glomerular filtration rate; **KF,** kidney failure; **IQR,** interquartile range; **SD**, standard deviation
Note: PCR of 1 mg/mmol is equivalent to 0.0088 g/g

Figure 1. Kaplan Meier survival curves for patients categorized by time-averaged proteinuria



Abbreviation: KF, kidney failure; **TA-PU**, time-averaged proteinuria

Table 2. Clinical outcomes for patients categorized by time-averaged proteinuria

	eGFR slope (mL/min/1.73 m^2/year)			KF/death risk		
TA-PU	**N**	**Mean**	**SD**	**N**	**HR**	**95% CI**
<100 mg/mmol	385	-0.35	7.15	405	Ref	Ref
100 to <200 mg/mmol	247	-3.32	10.09	264	2.83	2.09-3.82
200 to <300 mg/mmol	113	-6.67	5.73	128	4.82	3.49-6.66
≥300 mg/mmol	111	-12.41	11.28	126	9.00	6.56-12.34

Abbreviations: CI, confidence interval; **eGFR,** estimated glomerular filtration rate; **HR**, hazard ratio; **KF,** kidney failure; **Ref**, reference; **SD**, standard deviation; **TA-PU**, time-averaged proteinuria
Note: PCR of 100 mg/mmol (0.88 g/g) is approximately equivalent to 24-hour urinary protein excretion of 1.0 g/day

INTRODUCTION

- Primary IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide and a major cause of kidney failure (KF)[1,2]
- Rate of progression to KF varies widely and can span over decades[3]
- Time-averaged proteinuria (TA-PU) over long-term follow-up is an important predictor of disease progression and KF risk in patients with IgAN[3,4]

Objective

- To investigate the relationship between proteinuria (PU) measured over follow-up (TA-PU) and rate of kidney function loss and kidney survival in UK IgAN patients within the UK National Registry of Rare Kidney Diseases (RaDaR)

METHODS

Data Source

- This study uses data from the RaDaR database
- Since 2013, patients with biopsy-proven IgAN and estimated glomerular filtration (eGFR) <60 mL/min/1.73 m^2 or PU >0.5 g/day have been enrolled into (RaDaR) IgAN Cohort
- RaDaR contains data on IgAN patients from 87 kidney units across the UK, with automated collection of retrospective and prospective laboratory data

Definitions and Clinical Measures

- Diagnosis was the earliest of either primary kidney diagnosis date or date of biopsy recorded in RaDaR
- eGFR calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[5] (adults) and the modified Schwartz formula[6] (pediatric)
- KF was defined as the first occurrence of either chronic kidney replacement therapy, a confirmed eGFR <15 mL/min/1.73 m^2, or KF/CKD stage 5 recorded in RaDaR
- TA-PU was defined as the time-weighted averages for urinary protein-creatinine ratio (PCR), calculated from the area under the curve of serial measurements divided by the length of follow-up

Eligibility Criteria

- Patients were included if they had a biopsy/primary renal diagnosis date recorded in RaDaR and PU measurements in follow-up (within 2 years from diagnosis and ≥2 values if follow-up >3 years)
- Patients were excluded if they had a KF event (CKD stage 5 or kidney replacement therapy [KRT]) or death within 6 months from diagnosis or prior to first PU value

Statistical Analyses

- TA-PU and rate of eGFR loss (eGFR slope) were calculated over the full duration of follow-up or until KF or death. A linear mixed model was used to estimate each patient's intercept and slope of eGFR
- Kaplan-Meier estimates for kidney survival, from diagnosis to KF/death, were calculated for each TA-PU group. The log-rank test was used for differences between pairwise and all groups
- Association of TA-PU and survival from KF/death evaluated using Cox regression

DISCUSSION

- Adults represent >90% of the cohort with a median baseline age of 41.7 years reflecting a disease with onset at a stage when patients should have a long life-expectancy remaining
- Higher grades of TA-PU are significantly associated with shorter time to KF/death and increased KF/death risk
- Higher grades of TA-PU are also significantly associated with more rapid loss of eGFR
- Proteinuria <1 g/day is commonly perceived as defining patients at low risk, however, in this cohort, approx. 1 in 4 patients progressed to KF/death within 10 years, despite a TA-PU of <100 mg/mmol (approximately <1 g/day)

Limitations

- The inclusion criteria for RaDaR-IgAN leads to enrollment of patients with progressive disease who represent a high risk IgAN population
- Reporting of proteinuria and eGFR data at disease onset is incomplete and may not be representative of the full cohort, however data are likely to be missing at random with limited bias

CONCLUSIONS

- Elevated proteinuria over time is significantly associated with rapid loss of eGFR and greater risk of progression to KF/death in IgAN
- Although TA-PU below 100 mg/mmol (~1 g/day) is strongly associated with lower risk of KF/death, 25% of patients in this treated, monitored group reached KF/death within 10 years

DISCLOSURES

DP and FB have nothing to disclose; **BH** is an employee and stockholder of Travere Therapeutics, Inc.; **AM** received consultancy fees from Travere Therapeutics, Inc.; **KO** has nothing to disclose; **MAS** received consultancy fees from Travere Therapeutics, Inc. and Purespring Therapeutics; **RS** has nothing to disclose; **NT** has nothing to disclose; **KW** is an employee and stockholder of Travere Therapeutics, Inc.; **JB** received consultancy fees from Travere Therapeutics, Inc.; **DPG** received consultancy fees from Travere Therapeutics, Inc.

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Contact information: David Pitcher, david.pitcher@renalregistry.nhs.uk

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