Proteinuria and Disease Progression in the RaDaR IgAN Cohort

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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 PCR at diagnosis was 172 mg/mmol (1.5 g/g) and median 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 KF/death during follow-up (**Table 1**)
- Mean eGFR slope was −3.6 mL/min/1.73 m^2/year (**Table 1**)

Elevated TA-PU was associated with KF/death

- Time to KF/death was significantly shorter with higher levels of TA-PU (**Figure 1**)
- Approximately 1 in 4 patients with 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 TA-PU was associated with more rapid loss of eGFR

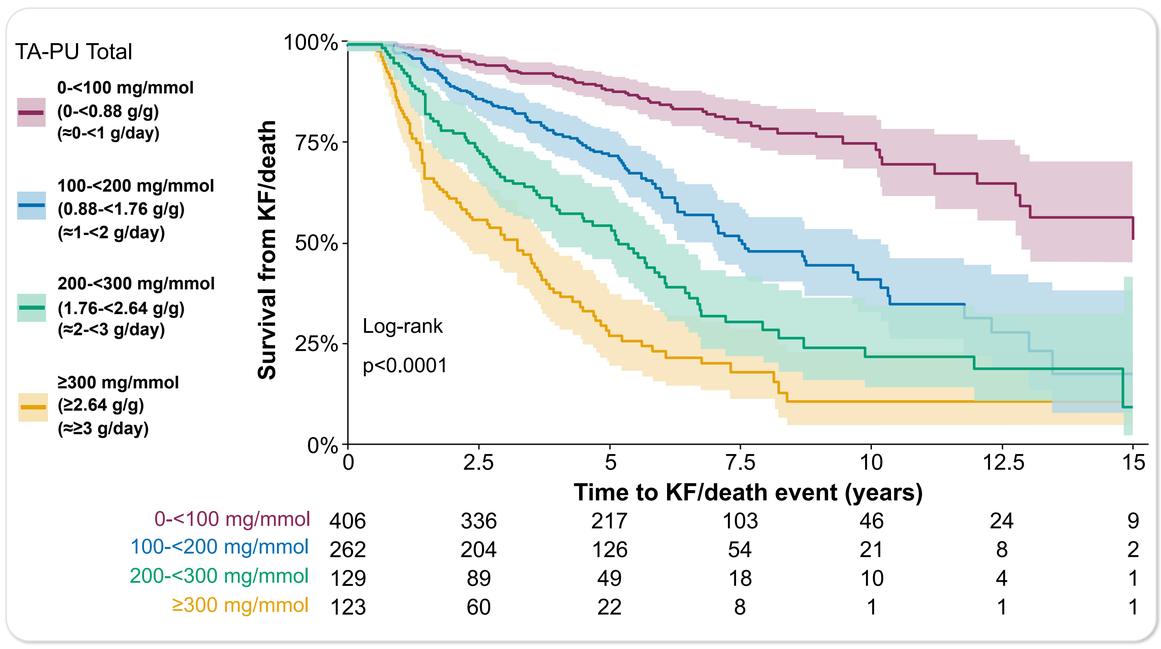
- Higher grades of TA-PU were associated with a higher rate of eGFR loss (p<0.001) (**Table 2**)
- The rate of eGFR loss escalated from an eGFR slope of −0.35 mL/min/1.73 m^2/year for TA-PU <100 mg/mmol to −12.41 mL/min/1.73 m^2/year with TA-PU ≥300 mg/mmol (**Table 2**)

Table 1. Characteristics at diagnosis and clinical outcomes

	N	%
Age	**923**	**100**
Median (IQR), years	41.7 (30.3-53.3)	
Pediatric, n (%)	36	4
Sex, n (%)	**923**	**100**
Female	294	32
Male	629	68
PCR* at baseline, n (%)	**515**	**56**
Median (IQR), mg/mmol	172 (73-356)	
Median (IQR), g/g	1.5 (0.6-3.1)	
eGFR at baseline, n (%)	**565**	**61**
Median, mL/min/1.73 m^2	50	
IQR, mL/min/1.73 m^2	33-78	
Duration of follow-up, n (%)	**923**	**100**
Median, years	4.5	
IQR, years	2.5-6.8	
KF/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, mL/min/1.73 m^2/year	9.4	

eGFR, estimated glomerular filtration rate; IQR, interquartile range; KF, kidney failure; PCR, protein-creatinine ratio; SD, standard deviation.
* PCR of 1 mg/mmol is equivalent to 0.0088 g/g.

Figure 1. Kaplan-Meier survival curves for patients categorized by TA-PU



KF, kidney failure; TA-PU, time-averaged proteinuria.

Table 2. Clinical outcomes for patients categorized by TA-PU

	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	Reference	Reference
100-<200 mg/mmol	247	-3.32	10.09	264	2.83	2.09-3.82
200-<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

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

CONCLUSIONS

- Elevated PU over time was significantly associated with rapid loss of eGFR and greater risk of progression to KF/death in IgAN
- Although TA-PU <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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INTRODUCTION

- Primary immunoglobulin A 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 patients with IgAN 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 rate (eGFR) <60 mL/min/1.73 m^2 or PU >0.5 g/day have been enrolled into the RaDaR IgAN cohort
- RaDaR contains data on patients with IgAN 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 was 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 (KRT), 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 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/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 was evaluated using Cox regression

DISCUSSION

- Adults represented >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 were significantly associated with shorter time to KF/death and increased KF/death risk
- Higher grades of TA-PU were also significantly associated with more rapid loss of eGFR
- PU <1 g/day is commonly perceived as defining patients at low risk; however, in this cohort, approximately 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 lead to enrollment of patients with progressive disease, who represent a high-risk IgAN population
- Reporting of PU 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

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