Urine and blood biomarkers correlate with rate of eGFR decline in Alport syndrome: The ATHENA study

Michelle N. Rheault[1], Oliver Gross[2], Bertrand Knebelmann[3], James F. Simon[4], Jale Guner[5], Mark Deeg[5], Clifford E. Kashtan[1]

[1]University of Minnesota, Minneapolis, MN, [2]University Medicine Goettingen, Goettingen, Germany, [3]Necker Hopsital, Paris, France, [4]Cleveland Clinic, Cleveland, OH, [5]Regulus Therapeutics, San Diego, CA

BACKGROUND

Alport syndrome (AS) is a genetic kidney disorder caused by mutations in the collagen IV genes (*COL4A3, COL4A4, and COL4A5*) resulting in defects to the structure and function of the glomerular basement membrane. AS is characterized by progressive renal fibrosis and matrix accumulation, leading to end stage kidney disease (ESKD), often by early adulthood. There are currently no approved therapies for AS, although angiotensin-converting enzyme (ACE) inhibitors may delay the onset of ESKD. To date, the natural rate of progression of chronic kidney disease (CKD) in AS has not been studied in detail. In addition, biomarkers to accurately predict progression of CKD are lacking. *A better understanding of the decline of kidney function in Alport syndrome is necessary to design clinical trials to enable the development of new therapeutics.*

ATHENA NATURAL HISTORY STUDY

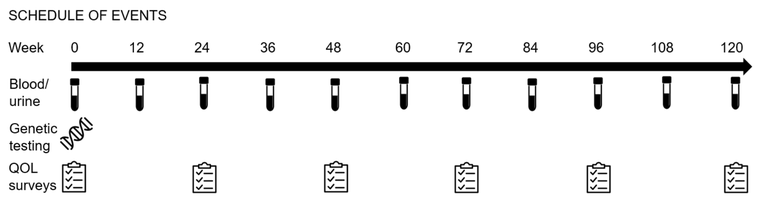
Primary Objective: To characterize the natural decline of renal function (eGFR) in patients with AS over the course of up to 120 weeks

Study design: Observational, global, multicenter natural history study (NCT02136862)

Inclusion:

- Age ≥ 16 years (after 4/2015, age 12-65 years)
- mGFR between 30-75ml/min/1.73m^2 (after 4/2015, eGFR 45-90)
- Confirmed clinical, histopathologic, and/or genetic diagnosis of Alport syndrome

SCHEDULE OF EVENTS



Enrollment start 9/2014. Final follow up 12/2017.

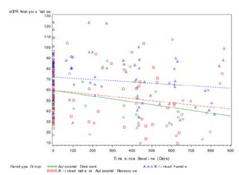
DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Table 1: Baseline Demographics and Clinical Information (N=165)	
Age, years (mean, SD)	44.8 (14.4)
Male, N (%)	56 (33.9%)
Race/ethnicity, N (%)	
White	137 (83%)
Asian	7 (4.2%)
Black	1 (0.6%)
Other/Not reported	20 (12.1%)
Genetics, N (%)	
X-linked	104 (63%)
Autosomal recessive	1 (0.6%)
Autosomal dominant	31 (18.8%)
Negative/unable to characterize	29 (17.6%)
eGFR CKD-EPI ml/min/1.73m^2, mean (SD)	63.9 (21.6)
24 hour urine protein, mg mean, (SD)	1844 (2608)
24 hour urine albumin, mg mean (SD)	1293 (1866)
Systolic blood pressure mmHg, mean (SD)	125.6 (17.3)
Diastolic blood pressure mgHg, mean (SD)	74.7 (10.7)
ACE inhibitor (N, %)	81 (49.1%)
ARB (N, %)	71 (43.0%)
Either ACE inhibitor or ARB (N, %)	136 (82.4)

eGFR DECLINE

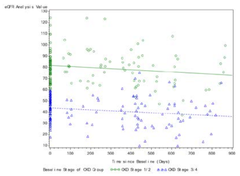
Median slope decline in eGFR$_{CKD-EPI}$ was -2.33 ml/min/year for the entire cohort

Change in eGFR by Alport genetics and sex



- X-linked males/AR = -1.63 ml/min/yr
- X-linked females = -1.51 ml/min/yr
- Autosomal dominant = -2.35 ml/min/yr

Change in eGFR by baseline eGFR ≥60 vs. < 60



- Baseline eGFR ≥60 = -1.96 ml/min/yr
- Baseline eGFR ≤60 = -2.21 ml/min/yr

CORRELATION WITH eGFR DECLINE

Methods: Pearson correlations of the GFR slope with each baseline biomarker were derived. Statistical significance was based on FDR adjusted p-value <0.02

- Positive correlation: increase in biomarker correlates with a less negative slope decline in eGFR
- Negative correlation: increase in biomarker correlates with a more negative slope decline in eGFR

Table 2: Correlation between baseline biomarker and slope eGFR		
Biomarker	**Correlation estimate**	**FDR p-value (NS =not significant)**
Serum Albumin	0.38	<0.001
U MICROALB/Cr ratio	-0.43	<0.001
U PROT/Cr ratio	-0.32	0.001
Serum NGAL	-0.27	0.004
LDL Cholesterol	-0.27	0.004
Total Cholesterol	-0.25	0.008
Urine Clusterin/Cr ratio	-0.28	0.004
Urine KIM-1/CR ratio	-0.31	0.001
eGFR Baseline	0.14	NS
HDL Cholesterol	0.16	NS
CO2	0.09	NS
Hemoglobin	-0.05	NS
Serum ADMA	0.01	NS
SerumTGF β1	-0.11	NS
Urine β2-microglobulin	-0.29	NS

- Higher serum albumin correlated with slower decline in eGFR
- Higher urine albumin, protein, clusterin, and KIM-1 and serum NGAL, LDL cholesterol, and total cholesterol correlated with more rapid decline in eGFR

CONCLUSIONS

- Enrollment of patients with Alport syndrome into prospective clinical trials is feasible
- Males with XLAS and males/females with autosomal dominant AS had the most rapidly progressive kidney disease in this cohort
- A number of biomarkers correlate with rate of eGFR decline and could be used in future clinical trials to enrich for a more rapidly progressive cohort