Change in Glomerular Filtration Rate and Renal Biomarkers in Patients With Chronic Kidney Disease Due to Alport Syndrome: Interim Results from the ATHENA Study, a Prospectively-Designed Natural History Study

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Introduction

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

Methods

Primary Objective

Characterize the natural decline in renal function (based on glomerular filtration rate [GFR] and creatinine) in patients with Alport syndrome over the course of 120 weeks.

Study Design

- Observational, global, multicenter study
- Estimated GFR (eGFR), clinical chemistry, urinalysis, and urine and plasma renal biomarkers were assessed every 12 weeks
- Measured GFR (mGFR) by iohexol clearance was assessed every 24 weeks
- See clinicaltrials.gov for more detail: NCT02136862

Patient Population: Inclusion/Exclusion Criteria

- ≥16 years of age
- Confirmed clinical, histopathologic and/or genetic diagnosis of Alport syndrome
- mGFR between 30 and 75mL/min/1.73m^2
- Patients undergoing dialysis treatment and previous renal transplant recipients were excluded

Results

Recruitment of subjects began in September 2014 and an interim data cut was performed in April 2016 at which time 113 patients had been enrolled and had variable lengths of follow-up as presented in Table 1.

Table 1. Extent of Follow-up through April 2016

	Baseline	Week 12	Week 24	Week 36	Week 48
No. of Subjects	113	89	75	66	35

Table 2. Demographics and Baseline Characteristics

Characteristic	Statistic	All Subjects (N=113)
Age (y)	Mean (SD)	44.8 (15.2)
Male / Female	%	35 / 65
White / Asian / Black / Other / Not Reported	%	81 / 4 / 1 / 4 / 11
Weight (kg)	Mean (SD)	77 (20)
Baseline mGFR, n =104	Mean (SD)	55.2 (16.0)
	Median	51.6
	Min, Max	30.8, 95.6
Baseline eGFR, MDRD, n =106	Mean (SD)	58.5 (19.2)
	Median	56.3
	Min, Max	18.9, 107.0
Baseline eGFR, CKD-EPI creatinine, n =106	Mean (SD)	60.8 (21.1)
	Median	57.9
	Min, Max	17.8, 117.7

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

Table 3. Genetic Analysis

Likely Genetic Inheritance	N=100 n (%)
X-linked	65 (65)
Autosomal Recessive or Dominant	31 (31)
Unknown/None	4 (4)

Genotype	N=100 n (%)
COL4A5	65 (65)
COL4A4	15 (15)
COL4A3	16 (16)
Unknown/None	4 (4)

Type of Mutation	N=100 n (%)
Missense	60 (60)
Splicesite	13 (13)
Frameshift	8 (8)
Unknown/None	7 (7)
Inframe Deletion	4 (4)
Nonsense	4 (4)
Silent	2 (2)
Intronic Deletion	1 (1)
Non-Frameshift Deletion	1 (1)

Table 4. Adverse Events During the Observational Study

Overview of Adverse Events		All Subjects (N=113) n (%)
Subjects with:		
Any Adverse Event		29 (25.7)
Adverse Event Leading to Study Termination		1 (0.9)
Serious Adverse Event[1]		3 (2.7)
By Severity	Mild	14 (12.4)
	Moderate	6 (5.3)
	Severe	5 (4.4)
	Life-Threatening	2 (1.8)
By Causal Relationship	Alport Syndrome	5 (4.4)
	Another Medical Condition	10 (8.8)
	Other	22 (19.5)
	Study-Related Procedure	0 (0)
All Adverse Events Occurring in >1 Subject		**n (%)**
Ear infection		2 (1.8)
Nasopharyngitis		2 (1.8)
Upper respiratory tract infection		2 (1.8)
Urinary tract infection		2 (1.8)
Leukopenia		2 (1.8)
Nausea		2 (1.8)
Fatigue		2 (1.8)

[1]Serious adverse events were 1 subject with acute renal failure and major depression, 1 subject with perforated appendicitis, and 1 subject with suicide attempt.

Results

Figure 1. Glomerular Filtration Rate – Overall Population

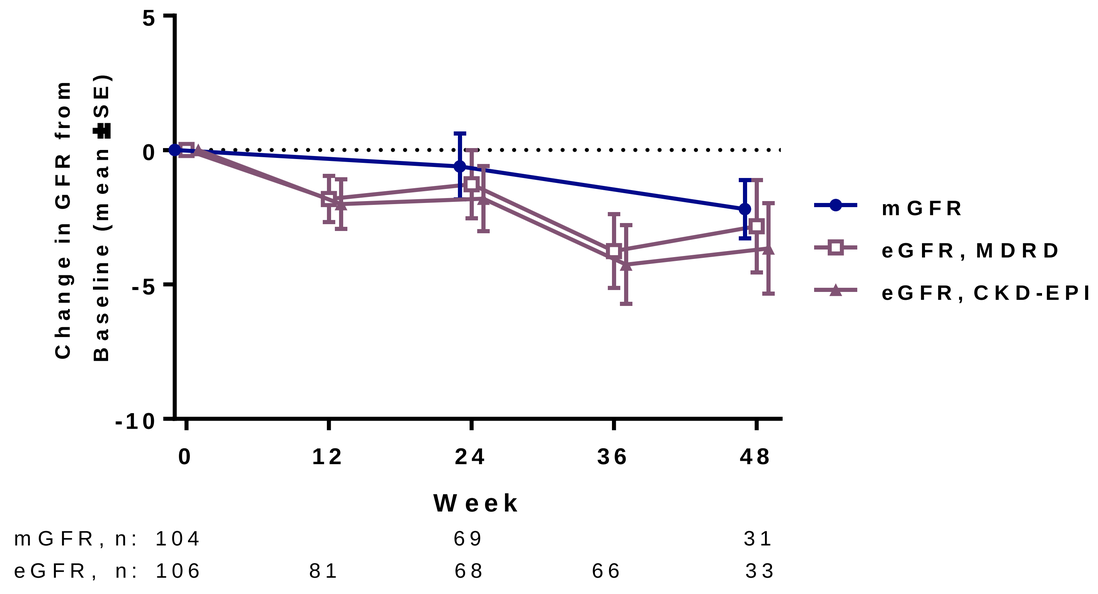
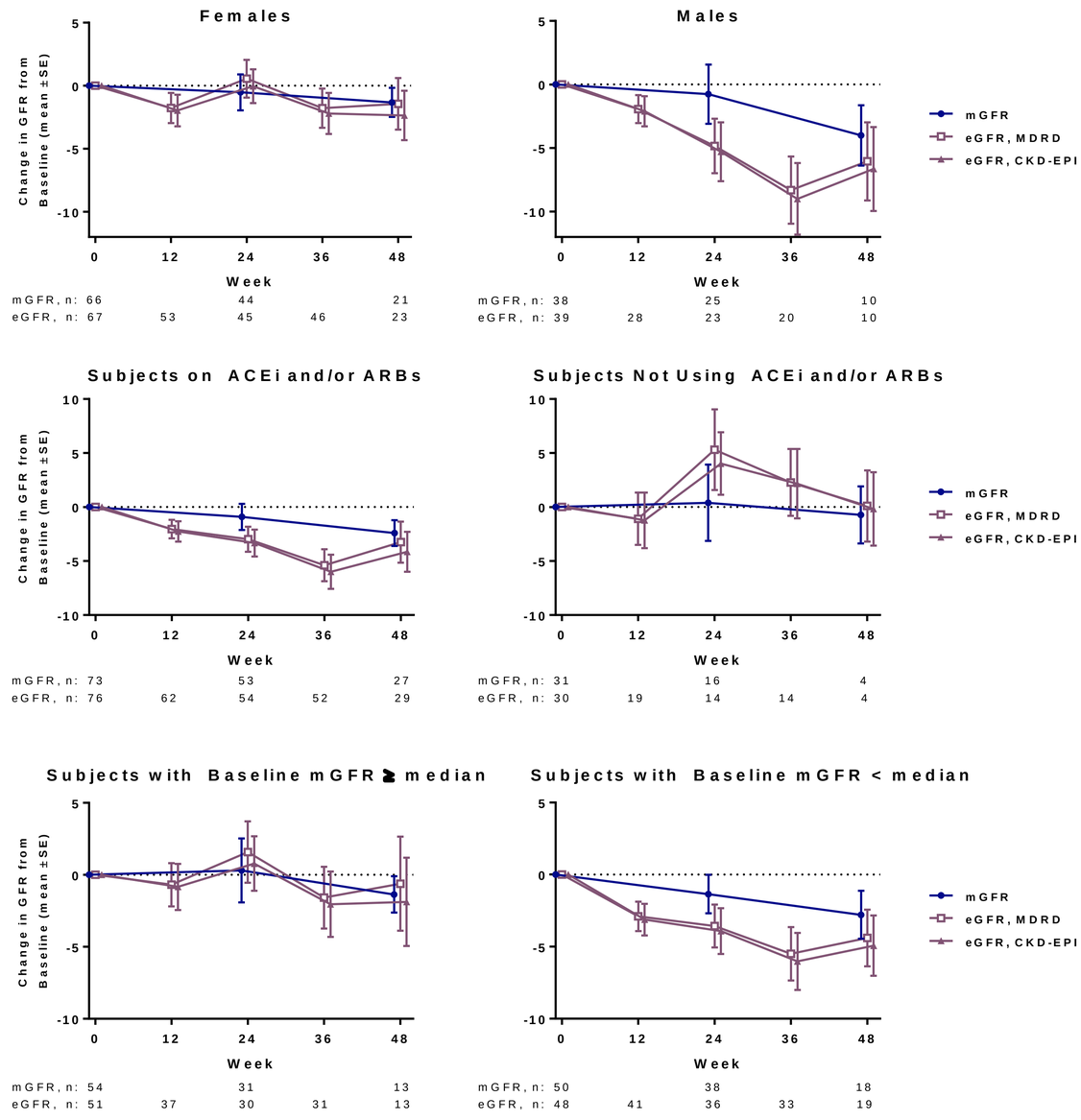


Figure 2. Glomerular Filtration Rate – Subgroup Analyses



Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mGFR, measured glomerular filtration rate.

Table 5. Change Over Time in Creatinine and Other Biomarkers

Biomarker, Mean (SD)	**Baseline**	**Δ Week 24**	**Δ Week 48**
Serum Creatinine (mg/dL)	1.35 (0.54), n=106	+0.11 (0.32), n=68	+0.17 (0.36), n=33
Other Serum Biomarkers	n=97	n=63	n=17
ADMA (µmol/L)	0.765 (0.801)	-0.124 (0.970)	-0.372 (1.826)
NGAL (ng/mL)	174.5 (77.0)	+5.8 (56.3)	-8.7 (42.4)
TGF-β1 (pg/mL)	10808.0 (3687.2)	+243.7 (4381.8)	-495.2 (3577.9)
Urine Biomarkers	n=97	n=60	n=17
β-2-microglobulin (ng/mL)	274.8 (452.2)	+21.8 (248.46)	-28.5 (173.7)
Clusterin (ng/mL)	617.8 (732.2)	+234.9 (832.0)	+141.4 (754.7)
Cystatin-C (ng/mL)	111.1 (163.7)	+33.4 (133.6)	+22.3 (123.6)
KIM-1 (pg/mL)	1315.8 (1245.2)	+261.4 (1086.6)	-12.0 (1027.3)
NGAL (ng/mL)	31.8 (40.3)	+14.6 (46.0)	+30.4 (77.0)

ADMA, asymmetric dimethylarginine; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; TGF, transforming growth factor.

Conclusions

To our knowledge, this is the first prospectively-designed natural history study conducted in patients with Alport syndrome. These interim data indicate that a measurable decline in mGFR and eGFR may be observed in patients with Alport syndrome within 48 weeks of follow-up. Trends were observed for numerically greater declines in mGFR and eGFR in male subjects, subjects using ACE inhibitors and/or ARBs, and subjects with baseline mGFR < median. With no currently approved therapies, these data have important implications for the design of future Alport syndrome clinical trials and the assessment of clinical benefit of future therapeutic agents. Enrollment in the ATHENA study is ongoing and an interventional study in patients with Alport syndrome is being planned to evaluate the clinical benefit of RG-012, an oligonucleotide that binds to and inhibits the activity of miRNA 21, a micro RNA upregulated in a number of CKD states.

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