Evaluation of Urinary Complement Biomarkers in C3 Glomerulopathy Following Oral Administration of ACH-4471, an Investigational Complement Factor D Inhibitor

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BACKGROUND

- C3 glomerulopathy (C3G) is a rare disease of complement alternative pathway (AP) dysregulation that is characterized by glomerular C3 fragment accumulation, progressive kidney damage, and proteinuria.
- Preliminary data from an ongoing 14-day proof-of-mechanism clinical trial have provided evidence that ACH-4471, an oral AP-specific inhibitor that blocks complement factor D (fD) function, can temper the systemic AP hyperactivation and reduce the proteinuria in C3G patients[1].
- Although complement biomarkers in blood are valuable for assessing systemic AP activation, their levels in urine may provide additional information about AP activation in the kidney.
- Here, we extend our analysis of the first four C3G study patients with a comparative evaluation of systemic and urinary AP biomarkers in response to 14-day ACH-4471 treatment.

Figure 1. Complement Pathways

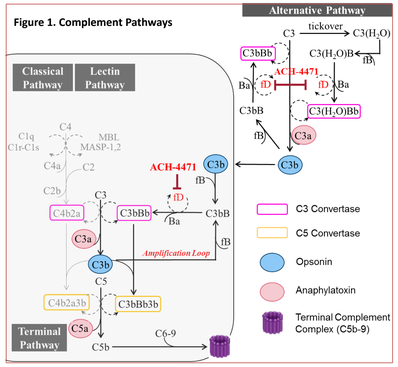


Figure 1 AP activation, directly or in amplification of the classical and lectin pathways, initiates a series of proteolytic events that result in the fD-dependent formation of fluid and membrane-bound C3 convertases, C3(H_2O)Bb and C3bBb. The C3 convertases catalyze C3 cleavage and promote downstream events which lead to C3 fragment deposition, inflammatory activation, and assembly of lytic terminal complement complexes (C5b-9). AP activity is tightly regulated by soluble and membrane regulatory proteins that protect against complement-mediated tissue injury. C3G is associated with hereditary or acquired AP dysregulation, the latter mediated by stabilizing or inactivating autoantibodies against complement components and regulators. ACH-4471 inhibits fD proteolytic activity, prevents complement factor B (fB) cleavage at multiple steps of the cascade, prevents AP convertase formation, and thereby effectively blocks AP activity.

METHODS

Samples: Urine and blood samples were collected from patients at protocol-specified timepoints prior to, during, and after dosing with ACH-4471. Samples from non-study healthy volunteers served as controls.

Assays and Analysis: Complement biomarkers including the proximal and terminal complement activation products, Ba and sC5b-9, were measured in serum or plasma and in urine samples by ELISA or multiplex assay. Ex vivo Ba production was measured in a functional assay following incubation of serum supplemented with exogenous C3 at 37°C for 30 mins. Urinary levels of complement products were normalized where indicated to urinary creatinine and albumin levels. Note, ex vivo Ba production and urine biomarkers were not conducted in accordance with GLP and were for exploratory purposes only.

RESULTS

Figure 2. Phase 2 Proof-of-Mechanism Trial of ACH-4471 in C3G or IC-MPGN

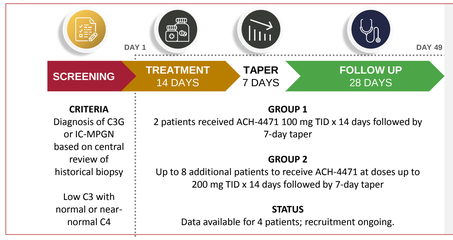


Table 1. Key Baseline Patient Characteristics

Group	Patient	Age (Y)	Sex	Weight (kg)	Urine dipstick for protein	ACR Day 1 Pre-dose (mg/mmol) *	BP (mm Hg)	Renal Biopsy Diagnosis
1	A	30	M	67	3+	259	126 / 72	C3GN
	B	19	M	68	3+	580	123 / 80	IC-MPGN †
2	C	27	M	90	Trace	57.7	129 / 83	C3GN
	D	22	M	39	3+	224	119 / 74	C3GN

*ACR (albumin-to-creatinine ratio) normal range = 0 – 2.5 mg/mmol; † Final review by central pathologist confirmed that the historical biopsy met criteria for IC-MPGN

Concomitant medication doses stable ≥1 mo prior to first dose ACH-4471: mycophenolate mofetil (n=2), prednisone (n=2), ACE/ARB (n=4), atorvastatin (n=2), spironolactone (n = 3)

eGFR > 60 mL / min / (1.73 m^2) in all patients

Figure 3. Reduction in ACR with 14-Day ACH-4471 Treatment

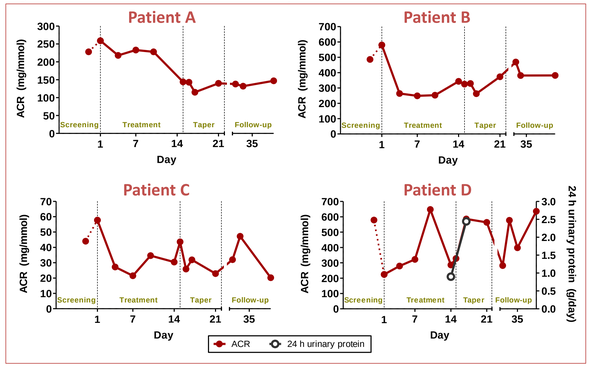


Figure 3

- Patients A, B, and C showed approximately 50% reductions in ACR during a two-week treatment with ACH-4471.
- Patient D showed highly variable ACR values; accordingly 24 h urinary proteins were collected on days 14 and 17.

Figure 4. Systemic Complement Proteins: Trends with 14-Day ACH-4471 Treatment

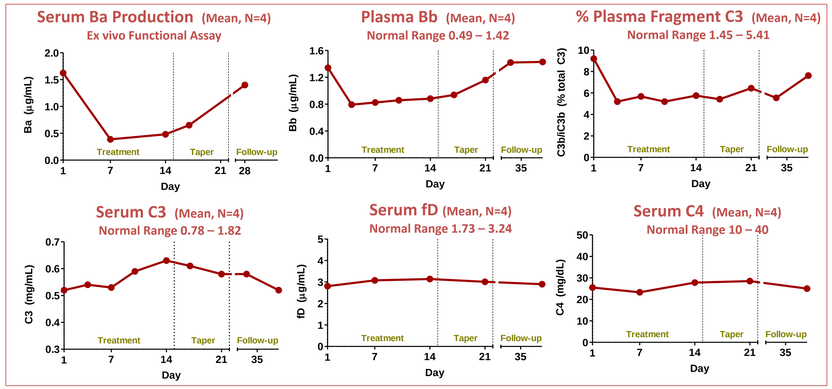
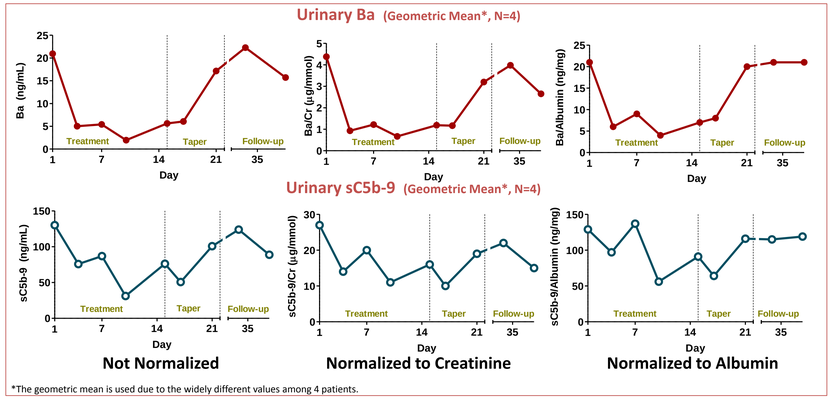


Figure 4

- Ex vivo serum Ba production, a functional biomarker for AP C3 convertase formation, was inhibited with ACH-4471 treatment.
- Plasma Bb, an in vivo biomarker for AP C3 convertase level, was reduced with ACH-4471 treatment.
- Serum C3 was increased accompanied with reduced % fragment C3 with ACH-4471 treatment, indicating lower C3 consumption in vivo.
- Serum C4 and fD remained unchanged during ACH-4471 treatment.
- The overall trend indicates that ACH-4471 tempered the AP hyperactivity in these patients .

Figure 5. Urinary Complement Proteins: Trends with 14-Day ACH-4471 Treatment



*The geometric mean is used due to the widely different values among 4 patients.

Figure 5

- Urinary Ba and sC5b-9 concentrations were elevated above normal at baseline.
- Absolute urinary Ba and sC5b-9 levels were reduced during a two-week treatment with ACH-4471.
- Urinary Ba and sC5b-9 levels normalized to urinary creatinine or albumin levels also were reduced during a two-week treatment with ACH-4471.

Figure 6. Urinary Complement Proteins: Selected Individual Patients

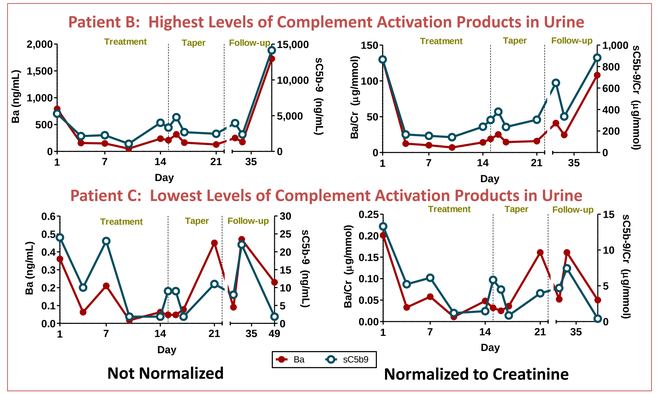


Figure 6

- Absolute, creatinine-normalized, and albumin-normalized (not shown) urinary Ba and sC5b-9 levels varied widely at baseline among patients.
- Patient B had the highest degree of proteinuria and also the highest absolute and normalized urinary Ba and sC5b-9 levels at baseline.
- Regardless of baseline levels, urinary Ba and sC5b-9 levels were reduced in all patients during a two-week treatment with ACH-4471.

CONCLUSIONS

- A two-week treatment with ACH-4471 was associated with approximately 50% reduction in ACR.
- In parallel, serum and plasma complement biomarkers showed evidence of inhibition of AP activity.
- In addition, significant observed changes in urinary complement biomarkers further indicated a tempering of AP hyperactivation during ACH-4471 treatment.
- Urinary complement proteins may serve as additional biomarkers for understanding C3G pathology and predicting responsiveness to ACH-4471.

REFERENCE

[1] Abstract SaO018, Presented at 55th Congress of the European-Renal-Association (ERA) and European-Dialysis-and-Transplantation-Association (EDTA). Publisher: Nephrology Dialysis Transplantation, Volume 33, Issue suppl_1, 1 May 2018, Pages i322.

ACH-4471 is an investigational drug product under clinical development. It has not been approved for commercial marketing by any regulatory health authority.