INTRODUCTION

• Complement activation products in blood have been used to understand the pathophysiology of diseases and assess treatment responses to complement therapies. Yet the use of urinary complement proteins as biomarkers of glomerular disease has not been investigated.

• Urinary complement activation products can be derived from the circulation as a result of damaged glomerular basement membranes, or from locally activated complement cascades within the glomerulus.

• Here, we report our study of urinary complement activation products in C3 glomerulopathy (C3G), a rare kidney disease of complement alternative pathway dysregulation.

• Systematic evaluation was conducted with urine samples from C3G patients enrolled in a 14-day proof-of-mechanism study of danicopan (ACH-4471), an orally small-molecule inhibitor of complement factor D (FD).

• Results from four patients have been presented previously; results for six patients are presented here.

• Following baseline analysis of all activation fragments in pre-dose urine samples, urinary Ba, C3c, and sC5b-9 were selected for systematic evaluation in C3G patients in the danicopan clinical study.

OBJECTIVES

• Assessment of the potential utility of urinary complement activation fragments as biomarkers for C3G patients at baseline and during treatment, using samples collected during a 14-day study of danicopan in C3G patients.

METHODS

• Samples: Urine and plasma samples were collected from patients at protocol-specified timepoints during a 14-day study of danicopan. The study design is described in Figures 1 and 2 and patient characteristics are in Table 1.

• Assays and Analysis: Plasma and urinary levels of the complement alternative pathway (AP) activation product Ba, and the activation products C3c and sC5b-9, were measured using commercial ELISA kits. Albumin levels were determined by clinical laboratories using standard methods.

• Urinary protein concentrations were normalized where indicated to urinary creatinine and albumin levels. Detection methods and ranges for urinary complement proteins were established using samples from healthy volunteers and patients with chronic kidney disease (CKD).

• Urinary complement protein concentrations were measured for exploratory purposes and were not evaluated in full accordance with good laboratory practice (GLP).

RESULTS

Phase 2 14-Day Proof-of-Mechanism Trial of Danicopan in Patients with C3G or IC-MPGN

Figure 1: Danicopan C3G Clinical Studies

Figure 2: 14-Day Proof-of-Mechanism Study Design

Figure 3: Urinary Protein Concentrations (Absolute)

Figure 4: Urinary Protein Concentrations (Normalized to Creatinine)

Table 2: Systemic and Urinary Protein Concentrations (Without and With Creatinine Normalization)

CONCLUSIONS

• We established methods for detection of the urinary complement activation products Ba, C3c, and sC5b-9 and showed that these products are elevated at baseline in C3G patients and are reduced upon treatment.

• Our findings suggest that complement activation products in urine may serve as additional biomarkers for understanding C3G pathophysiology and predicting clinical responsiveness to danicopan.

REFERENCES