Intravenous Administration of UNI-494 Ameliorates Acute Kidney Injury in Rat Model of Delayed Graft Function

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BACKGROUND

- There are no FDA approved drugs for the treatment of acute kidney injury (AKI), which affects 10-15% of hospitalized patients and often results in renal transplantation or lifelong dialysis
- UNI-494 is a novel nicotinamide ester derivative and selective mitochondrial ATP-sensitive potassium channel activator that may be beneficial for several disease states, including AKI

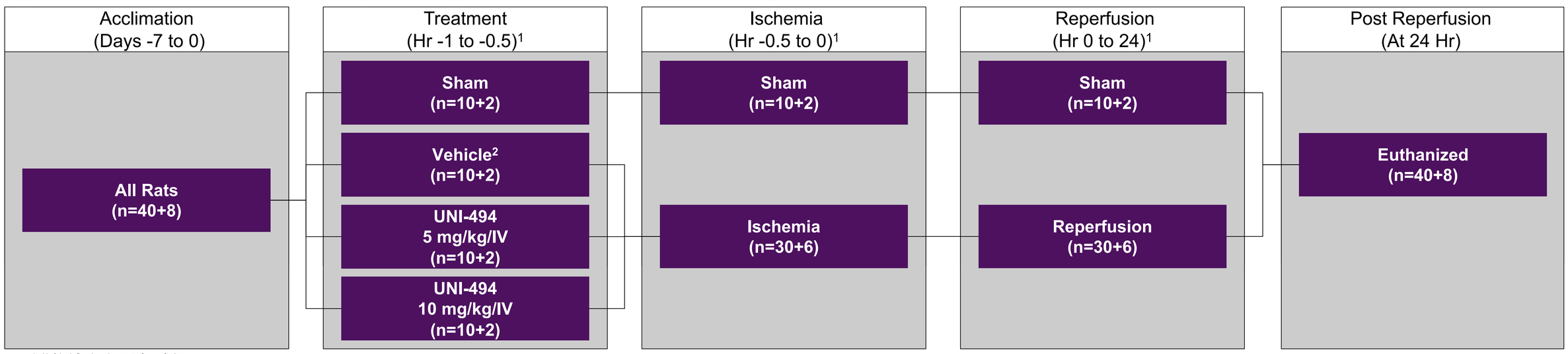
OBJECTIVE

We present results from a study evaluating the in vivo efficacy of intravenous (IV) UNI-494 in the unilateral renal ischemia-reperfusion (I/R) rat model of AKI, which is a well-established model of delayed graft function (DGF)[1]

METHODS

- Rats were anesthetized, the right kidney was removed, and I/R was induced by clamping the renal vessels in the left kidney for 30 minutes **(Figure 1)**
- UNI-494 was administered IV 30 minutes prior to I/R **(Figure 1)**
- After 24 hours of reperfusion in metabolic cages, blood samples were collected for serum creatinine (sCr) and BUN levels, and urinary samples were collected for ACR and NGAL
- The clamped left kidney was collected and processed for histology for tubular injury scores

Figure 1. UNI-494 I/R Study Design – Preventive Dosing

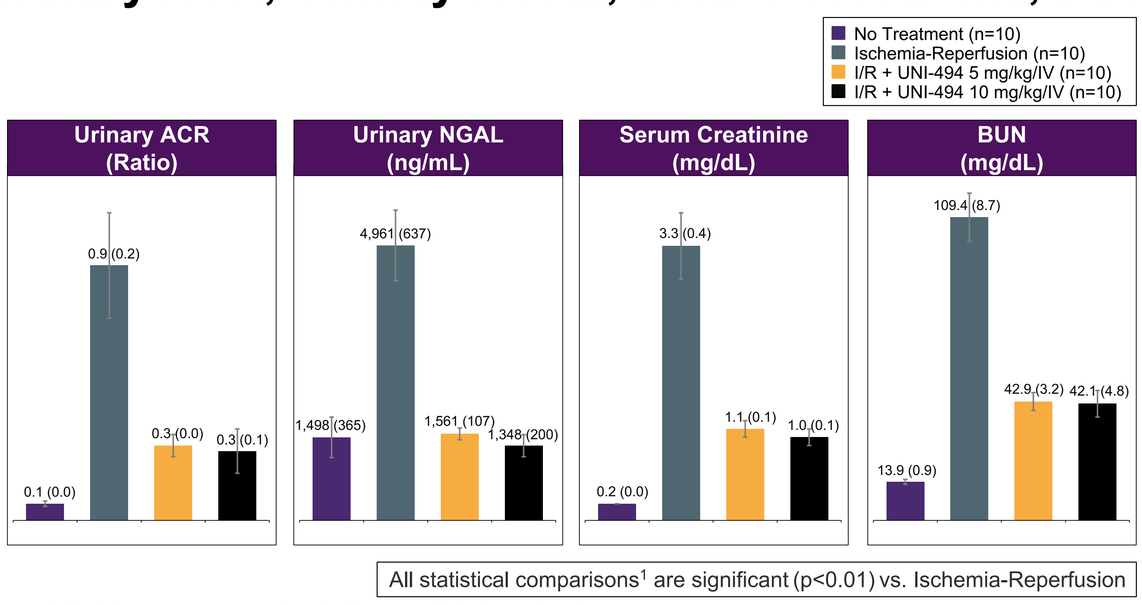


1 Hr 0 is defined as the start of reperfusion
2 Vehicle = 0 mg/kg/Intraperitoneal
Abbreviations: IV=intravenous
Note: Jablonski P, Howden BO, Rae DA, Birrell CS, Marshall VC, Tange J. An experimental model for assessment of renal recovery from warm ischemia. Transplantation 1983; 35: 198-204

RESULTS

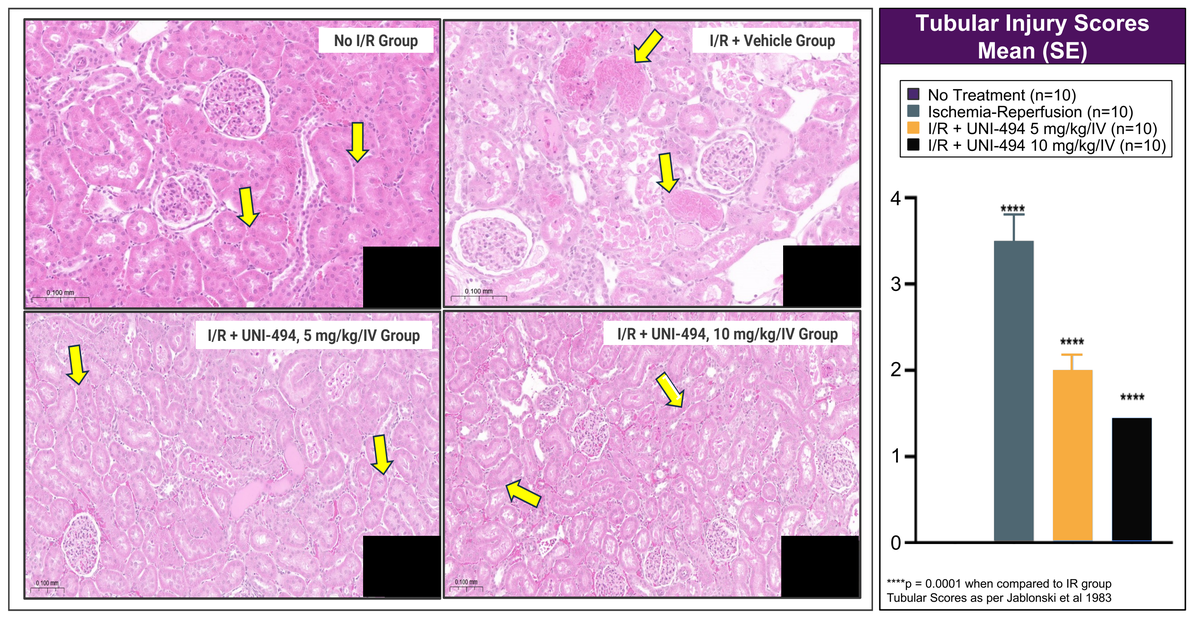
- In this study, I/R induced significant increases of sCr, BUN, uACR, and uNGAL in the vehicle treated I/R group vs No I/R sham group **(Figure 2, 3)**
- A single IV dose of UNI-494 at 5 mg/kg/IV or 10 mg/kg/IV reduced the kidney functional markers sCr, BUN, uACR, and tubular injury marker (uNGAL) (all p<0.01) **(Figure 2, 3)**

Figure 2. Mean (SE) UNI-494 + I/R vs I/R vs Sham – Urinary ACR, Urinary NGAL, Serum Creatinine, BUN



1 All statistical comparisons were conducted using two-tailed nonpaired t-test vs. the ischemia-reperfusion group
Abbreviations: ACR = Albumin: Creatinine Ratio; NGAL = Neutrophil Gelatinase-Associated Lipocalin; BUN = Blood Urea Nitrogen; I/R = Ischemia-Reperfusion

Figure 3. Histological Image Where the Nature of the Proximal Tubule Injury Is Pointed with Arrows



CONCLUSIONS/IMPLICATIONS

- UNI-494 prevented serum and urinary markers of AKI at 5 mg/kg
- Proximal tubular injury scores improved in a dose-dependent manner
- UNI-494 is a potential candidate for prevention of DGF and other AKI clinical conditions
- Further studies are ongoing

References:
1. Cavaillé-Coll M. et al., *Am J Transplant*. 2013. May.

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