Intravenous UNI-494 Slows the Progression or Halts/Reverses Acute Kidney Injury When Administered After Ischemia/Reperfusion in Rats

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BACKGROUND

- Currently, there are no effective treatments for acute kidney injury (AKI) approved by the US Food and Drug Administration or the European Medicines Agency (EMA); management of the condition is primarily supportive[1, 2]
- Inflammation and reactive oxygen species driven mitochondrial permeability transition pore (mPTP) opening causes mitochondrial dysfunction/swelling and cell death[3-7]
- This is implicated in acute diseases originating from ischemia-reperfusion (I/R) injury or delayed graft function (DGF)[3-7]
- Furthermore, unresolved inflammation exacerbates sustained mPTP opening, evident in chronic kidney diseases (CKD)[8, 9]
- UNI-494, a selective mitochondrial ATP-sensitive potassium channel activator, reverses mitochondrial dysfunction by closing the mPTP

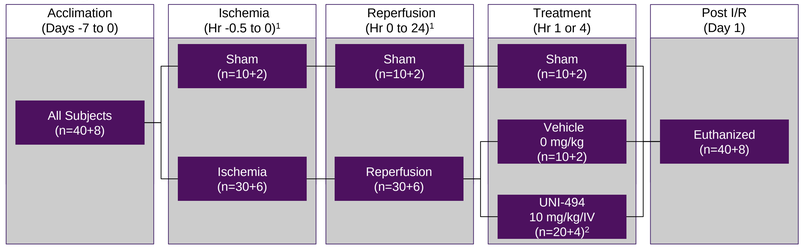
OBJECTIVE

We present results from a study evaluating the in vivo efficacy of intravenous (IV) UNI-494 when administered therapeutically after unilateral renal ischemia-reperfusion (I/R) in a rat model of AKI, which is a well-established model of delayed graft function (DGF) (Cavaille-Coll, 2013)

METHODS

- Rats were anesthetized, right kidney removed, ischemia induced injury by clamping renal vessels in left kidney (30 minutes)
- After 1 or 4 hours of reperfusion with established renal injury confirmed by elevated serum creatinine (sCr), 10 mg/kg of UNI-494 was administered IV **(Figure 1)**
- After 24 hours reperfusion in metabolic cages, blood samples were collected for sCr and blood urea nitrogen (sBUN) levels, and urinary samples collected for albumin-creatinine ratio (uACR) and neutrophil gelatinase-associated lipocalin (uNGAL)
- At necropsy, clamped left kidney was collected and processed for histology for tubular injury scores

Figure 1. UNI-494 I/R Study Design – Therapeutic Dosing (IV)

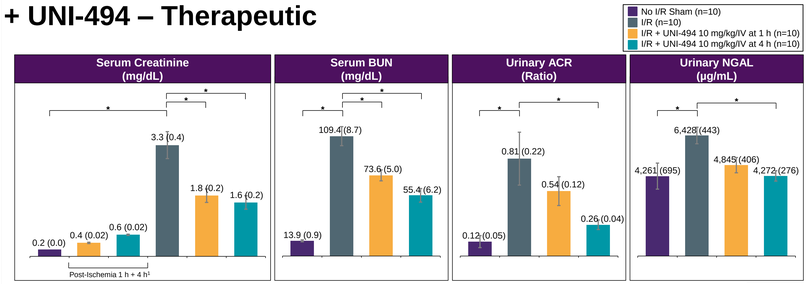


Abbreviations: IV=intravenous
Note: n number consists of experimental + spare animals
1 Hr 0 is defined as the start of reperfusion
2 UNI-494 dosed at 1 hour after ischemia (12+2); and UNI-494 dosed at 4 hours after ischemia (12+2)

RESULTS

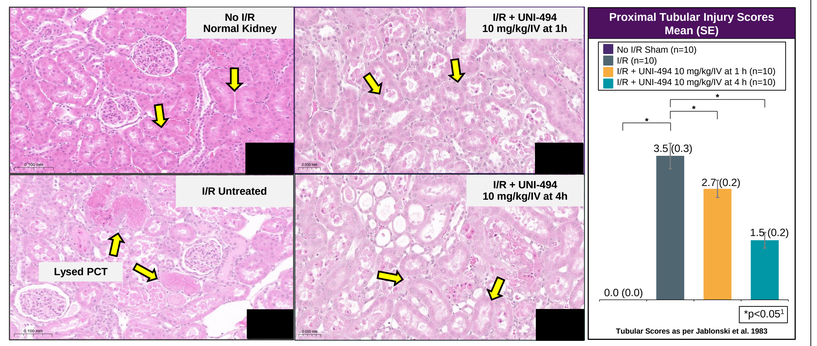
- I/R induced significant increases of sCr, sBUN, uACR, uNGAL, and proximal tubular injury scores in the vehicle treated I/R group when compared to no I/R sham group ($p<0.05$ – as per one-way ANOVA with Dunnett's comparison test)
- A single IV dose of 10 mg/kg of UNI-494 improved kidney functional markers sCr, sBUN, uACR, the tubular injury marker uNGAL **(Figure 2)**, and proximal tubular injury scores **(Figure 3)**

Figure 2. Mean (SE) Serum Creatinine, Serum BUN, Urinary ACR, and Urinary NGAL – No I/R Sham vs. I/R vs. I/R + UNI-494 – Therapeutic



Abbreviations: BUN = Blood Urea Nitrogen; ACR = Albumin: Creatinine Ratio; NGAL = Neutrophil Gelatinase-Associated Lipocalin; I/R = Ischemia-Reperfusion; IV = Intravenous
1 All other data points depict data 24 h after reperfusion
2 Statistical comparisons were conducted using one-way ANOVA with Dunnett's Multiple Comparison Test

Figure 3. Histological Image Where Nature of the Proximal Tubular Injury Is Pointed with Arrows – Therapeutic



Abbreviations: I/R = Ischemia-Reperfusion; IV = Intravenous
1 Statistical comparisons were conducted using one-way ANOVA with Dunnett's Multiple Comparison Test

CONCLUSIONS

- Single IV doses of 10 mg/kg of UNI-494 administered after I/R significantly reduced serum and urinary AKI markers and improved proximal tubular injury scores
- These data indicate therapeutic administration of UNI-494 slows down, or even halts/reverses, AKI progression

DISCUSSION

- UNI-494 is a potential candidate for prevention of DGF and other AKI clinical conditions
- The mechanism of this potential therapeutic effect should be further investigated
- Studies evaluating this promising treatment in the target population of patients with AKI should be conducted

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