ANG-3777 Treatment Attenuates Ischemia-Reperfusion-Induced Renal Injury in Rat and Dog Models

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Background

HGF is an endogenous protein that is released in response to organ injury. It is the natural ligand for the c-Met receptor, which is also upregulated after injury. HGF has significant cytoprotective and anti-apoptotic effects in renal epithelial cells[1,2]. In preclinical models of acute kidney injury (AKI) secondary to ischemia, treatment with HGF decreased renal epithelial apoptosis and tubular necrosis, and augmented renal regeneration, improving renal function[3,4]. ANG-3777 is a small molecule mimetic of hepatocyte growth factor (HGF). The objective of these studies were to determine the effect of ANG-3777 treatment in ischemia-reperfusion-induced renal dysfunction [measured by blood urea nitrogen (BUN) and serum creatinine (SCr) levels], urine output, and overall mortality in rats and dogs subjected to normothermic renal ischemia and reperfusion (nRIR).

Methods

Studies were conducted following an approved Institutional Animal Care and Use Committee (IACUC) protocol.

Animals. Study 1 and 2: Adult male and female Sprague-Dawley (SD) rats; Study 3: Adult Male Beagle Dogs.

Study 1: 32 male and 20 female SD rats were subjected to 60-min renal ischemia and 24-hr reperfusion. ANG-3777 (2 mg/kg, intravenous [IV]; N=26) or vehicle (N=26) was given pre-ischemia and 18 hours post-reperfusion. At the onset of reperfusion, the contralateral (right) kidney was excised. BUN and SCr levels, key markers of renal function, were assessed at 24 hrs pre-sacrifice.

Study 2: 136 SD rats were subjected to 60-min renal ischemia and 96-hr reperfusion. Animals were dosed with ANG-3777 IV (0.2, N=48; or 2 mg/kg, N=15) or vehicle (N=70) at 24-hr post-onset of reperfusion, then once daily for the next four days. Blood and urine were collected daily (24, 48, 72, and 96 hours); mortality was recorded. Normal rats (n=3) not subjected to ischemia and reperfusion, and not treated with ANG-3777 nor vehicle, were included as additional controls.

Study 3: 13 Beagle dogs were subjected to 120-min left kidney renal ischemia and 7 days of reperfusion. At the onset of reperfusion, the contralateral (right) kidney was excised. Dogs were randomized to one of the following groups: 1) vehicle (IV, QD, n=4), 2), ANG-3777 (10 mg/kg, IV, QD, n=4), both started at the onset of reperfusion (Day 1), or 3) ANG-3777 delayed treatment (10 mg/kg, IV, QD, n=5) started 1 day post ischemia-reperfusion (Day 2). Dogs were dosed QD until and including Day 4. Blood was collected every 24 hours from an indwelling catheter for a total of 8 days that included a day prior to ischemia-reperfusion (Day 0) and SCr and BUN was measured.

Results

Study 1: ANG-3777 treatment immediately prior to ischemic injury and 18 hours post-reperfusion significantly reduced BUN levels in male rats (Figure 1) and SCr levels in both male and female rats (Figure 2) subjected to nRIR

Figure 1: BUN Levels after 24 hours of Reperfusion in Rats Treated with ANG-3777

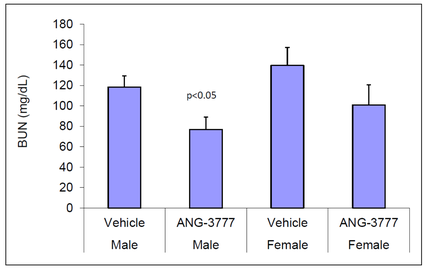
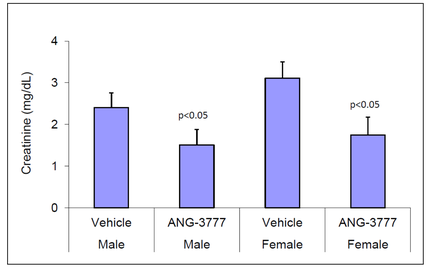


Figure 2: SCr Levels after 24 hours of Reperfusion in Rats Treated with ANG-3777



The data is presented as mean ± SEM (male, n=16 and female, n=10)

Study 2: QD treatment with ANG-3777 starting 24-hours post-ischemic injury for 4 days significantly reduced BUN (Figure 3) and SCr (Figure 4) levels, increased urine output (Figure 5), and improved survival (Figure 6) in male rats subjected to nRIR

Figure 3: BUN Levels in Rats Treated QD with ANG-3777 Initiated 24-Hours Post-reperfusion

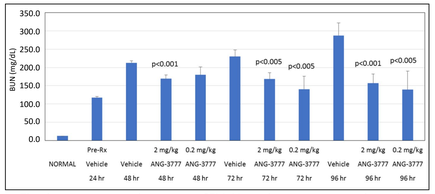
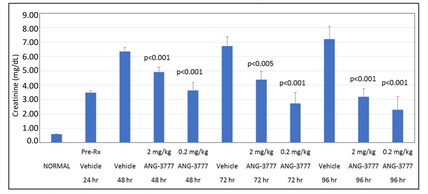
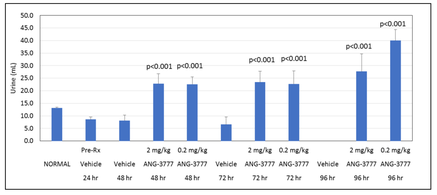


Figure 4: SCr Levels in Rats Treated QD with ANG-3777 Initiated 24-Hours Post-reperfusion



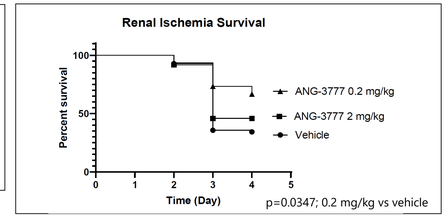
The data are presented as mean ± SEM. Normal rats are untreated rats that were not subjected to renal ischemia-reperfusion

Figure 5: Urine Output in Rats Treated QD with ANG-3777 Initiated 24-Hours Post-reperfusion



The data are presented as mean ± SEM. Normal rats are untreated rats that were not subjected to renal ischemia-reperfusion

Figure 6: Survival of Rats Treated QD with ANG-3777 Initiated 24-Hours Post-reperfusion



Results (2)

Study 3: Initiating QD treatment of ANG-3777 at the onset of reperfusion or 1-day post-reperfusion significantly improved BUN and SCr levels in dogs subjected to nRIR

Figure 7: BUN Levels in Dogs Treated QD with ANG-3777 Initiated at Onset of Reperfusion or 1-day Post-Reperfusion (delayed)

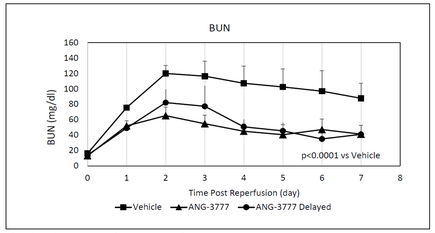
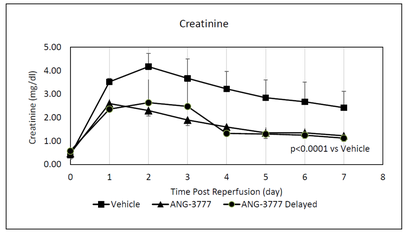


Figure 8: SCr Levels in Dogs Treated QD with ANG-3777 Initiated at Onset of Reperfusion or 1-day Post-Reperfusion (delayed)



The data is presented as mean ± SEM

Conclusion

In nRIR animal models, immediate or delayed treatment with ANG-3777 resulted in a statistically significant improvement in:

1. Markers of renal function (SCr and BUN levels) in SD rats and Beagle Dogs
2. Urine output and survival in SD rats

These results provide evidence that ANG-3777 can improve kidney function after ischemia reperfusion injury. Research is currently ongoing to evaluate if these effects translate into significant treatment effects in humans experiencing AKI.

References

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