

Attenuation of renal injury by administration of TK-850, a dual inhibitor of TGF β R1/MAP4K4

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Objectives/Goals: Renal fibrosis is an outcome of chronic kidney disease that affects approximately one-tenth of the global community. Its pathogenesis and progression are highly multi-factorial, likely demanding a need to target various mechanisms for providing better treatment. Using an animal model of renal fibrosis, we sought to test the therapeutic response of TK-850, an experimental drug that acts as a dual-inhibitor of transforming growth factor beta receptor 1 (TGF β R1) and mitogen-activated protein kinase kinase kinase 4 (MAP4K4). Both serine/threonine kinases are associated with inducing pro-inflammatory and pro-fibrotic responses.

Methods/Study Population: To assess the possible renal anti-fibrotic effects of TK-850, we performed a preclinical study using 8-10-week-old male and female C57BL/6 mice, who underwent unilateral ureteral obstruction (UUO) surgery for inducing renal fibrosis. Rodents either had UUO only (control), were administered TK-850 prior to and following UUO (UUO-P, 20 mpk/d/ip), or administered TK-850 following UUO (UUO-I, 20 mpk/d/ip). In either case, the kidneys and blood were collected ten days post-UUO for histopathological evaluation and biochemical analysis. Fibrosis of the kidneys was evaluated from renal hydroxyproline estimation and Picrosirius red stain for assessing collagen deposition.

Results/Anticipated Results (700-character limit): As a result of UUO, both male and female mice showed similar renal hydroxyproline levels, $5.4 \pm 0.41 \mu\text{g}/10\text{mg}$, $n = 5$ and $5.5 \pm 0.50 \mu\text{g}/10\text{mg}$, $n = 5$, respectively, in comparison to the contralateral (control) kidney, $2.9 \pm 0.14 \mu\text{g}/10\text{mg}$, $n = 10$. Prophylactic and interventional administration of TK-850 significantly reduced hydroxyproline levels (UUO-P: $3.4 \pm 0.24 \mu\text{g}/10\text{mg}$, $n = 10$; UUO-I: $4.30 \pm 0.20 \mu\text{g}/10\text{mg}$, $n = 10$). Histological assessment of kidney injury (UUO) revealed increased collagen deposition ($17.1 \pm 0.43\%$ collagen positive area, $n = 10$) in comparison to the non-injured, control kidney ($2.0 \pm 0.23\%$, $n = 10$). TK-850 treatment was also shown to significantly reduce collagen deposition in UUO-P ($10.5 \pm 0.38\%$, $n = 10$) and UUO-I ($13.1 \pm 0.25\%$, $n = 10$) mice. Both biochemical and histological responses with and without drug treatment were gender neutral.

Discussion/Significance of Impact (300-character limit): In summary, our results show a positive effect of TK-850 administration to reduce kidney injury, supporting the notion of its use as a potential therapeutic compound. The results herein could also affirm the idea of having a concerted pharmacotherapeutic approach to treat such complex diseases.

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