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Attenuation of renal injury by administration of TK-850, a dual inhibitor of TGFβR1/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 (TGFβR1) and mitogen-activated protein kinase 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 ± 0.41 μg/10mg, n = 5 and 5.5 ± 0.50 μg/10mg, n = 5, respectively, in comparison to the contralateral (control) kidney, 2.9 ± 0.14 μg/10mg, n = 10. Prophylactic and interventional administration of TK-850 significantly reduced hydroxyproline levels (UUO-P: 3.4 ± 0.24 μg/10mg, n = 10; UUO-I: 4.30 ± 0.20 μg/10mg, n = 10). Histological assessment of kidney injury (UUO) revealed increased collagen deposition (17.1 ± 0.43% collagen positive area, n = 10) in comparison to the non-injured, control kidney (2.0 ± 0.23%, n = 10). TK-850 treatment was also shown to significantly reduce collagen deposition in UUO-P (10.5 ± 0.38%, n = 10) and UUO-I (13.1 ± 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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