PBI-4425, A NOVEL ANTI-INFLAMMATORY/FIBROTIC COMPOUND, IMPROVES KIDNEY FUNCTION AND GLOMERULAR INTEGRITY IN THE DIABETIC DB/db MOUSE MODEL

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Introduction and Aims: PBI-4425, a novel first-in-class treatment for fibrotic diseases, possesses a pleiotropic mechanism of action with anti-inflammatory, antioxidant and antifibrotic properties. The aim of this study was to investigate the protective effect of PBI-4425 on kidney function and structure in uninephrectomized (NX) diabetic (db/db) mice.

Methods: Total nephrectomy of the right kidney was performed on day 0 and animals were treated with vehicle or PBI-4425 (100 mg/kg, oral once a day) from day 1 through 105. Kidney function (GFR), kidney mesangium lesions, modulation of gene expression, and serum cytokines were investigated.

Results: Kidney function assessed by GFR (inulin clearance) was significantly reduced in NX-db/db mice compared to NX-C57BL/6 negative control mice and significantly improved with PBI-4425 treatment. At the histological level, NX-db/db mice had larger glomeruli with increased mesangial matrix, while mesangial lesions scores were significantly reduced in NX-db/db mice treated with PBI-4425. To further characterize the activity of PBI-4425 on the fibrotic process, gene expression of inflammation, fibrosis, oxidative stress, and extracellular matrix remodeling markers was assessed. Kidney MCP-1, IL-6, collagen I, iNOS, MMP2, and TIMP1 mRNA expression was markedly increased in NX-db/db mice, and PBI-4425 treatment induced a significant decrease of these markers. Glomerular response to injury is accompanied by activation of kidney development-related genes, such as glomerular epithelial protein 1 (GLEPP1); expression of GLEPP1 was significantly increased in NX-db/db mice, and restored to the negative control level following treatment with PBI-4425. Moreover, PBI-4425 significantly reduced serum pro-inflammatory cytokines IL-1β, IL-6, IL-12 (p70), as well as TH9-type pro-inflammatory cytokine IL-9.

Conclusions: These results suggest that PBI-4425 offers the potential as a novel therapy for diabetic nephropathy by improving kidney function and integrity, and reducing pro-inflammatory and pro-fibrotic markers.