

FT011, a Novel Synthetic Anti-Fibrotic Drug Attenuates the progression of Experimental Diabetic Nephropathy

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Objective: Pathological fibrosis is a key feature of diabetic nephropathy (DN) that correlates closely with renal dysfunction and that can be partially attenuated with agents that block the renin-angiotensin system. However, the effects of a more direct approach that specifically targets fibrosis has not been studied in detail, mostly due to a lack of suitable agents. Accordingly, we synthesized a novel anti-fibrotic drug based on a cinnamoyl core structure, FT011 (Fibrotech Therapeutics Pty Ltd, Melbourne, Australia), to test the hypothesis that preventing pathological fibrosis will attenuate renal injury in advanced experimental model of DN.

Aims: The aims of the present study were to determine the effects of FT011 on TGF- β stimulated matrix synthesis on cultured mesangial cells, and to test the efficacy of FT011 *in vivo* on the structural and functional manifestation of experimental DN.

Methods: Mesangial cells (1097 clone) were studied *in vitro* to determine the effects of FT011 on TGF- β induced collagen synthesis by measuring ³H-proline incorporation. Forty, six-week old female, heterozygous (mRen-2)27 rats, were assigned to receive either 55 mg/kg of STZ or citrate buffer alone (non-diabetic) by tail vein injection following an overnight fast. Control and diabetic groups were then each randomised into 2 groups (n=10), receiving either treatment with FT011 (100mg/kg bid gavage) or without treatment for 16 weeks.

Results: In response to TGF- β stimulation, mesangial cells demonstrated a dose-dependent inhibition of proline incorporation in response to FT011. Without affecting blood pressure or hyperglycaemia, diabetic Ren-2 rats treated with FT011 had less albuminuria (10.10 \times/\div 1.11 vs 1.97 \times/\div 1.46, mg/day, $P < 0.01$), tubulointerstitial fibrosis (2.28 \pm 0.46 vs 0.64 \pm 0.07, %/area, $P < 0.01$), glomerulosclerosis (1.05 \pm 0.05 Vs 0.63 \pm 0.04, glomerulosclerotic index $P < 0.05$), macrophage infiltration (62 \pm 16 vs 26 \pm 5, number/area $P < 0.05$) and glomerular endothelial cell loss (1.04 \pm 0.5 vs 4.1 \pm 0.9, %/gcs $P < 0.05$) when compared with untreated diabetic rats. Non-diabetic rats were unaffected by FT011 and no adverse effects of FT011 were observed in either diabetic or non-diabetic groups.

Conclusion: FT011 is a novel anti-fibrotic drug that attenuates the functional and structural manifestations of experimental model diabetic nephropathy, providing a novel therapeutic strategy for the treatment of progressive kidney disease.