

ALT-711, an “AGE cross-link breaker”, Ameliorates Diabetic Renal Injury in db/db Mice

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Background: Advanced glycation end-products (AGE) play an independent pathogenic role in the development and progression of diabetic nephropathy. ALT-711, 3-(2-oxo-2-phenyl)ethyl-4,5-dimethylthiazolium chloride, was introduced as an AGE cross-link breaker and has been shown to reduce vascular and renal tubular AGE accumulation, TGF- β 1 expression, and epithelial-mesenchymal transition in streptozotocin-induced diabetic rat, a model for type 1 diabetes. In this study, we examined the effects of ALT-711 on renal injury in db/db mice, a model of type 2 diabetes.

Method: ALT-711 (2 mg/kg/day) or saline was administered intraperitoneally to 8-week-old diabetic db/db mice with stable hyperglycemia and control db/m mice for 12 weeks. In a separate group of 16-week-old db/db mice ALT-711 was administered for 4 weeks in order to evaluate the effect of delayed treatment. Urinary albumin was measured by ELISA and plasma creatinine by Jaffe method. Glomerular volume (VG) and relative mesangial area (RMA) were quantitated using a computer-assisted color image analyzer. Fibronectin (FN), vascular endothelial growth factor (VEGF), pentosidine, and N ϵ -(carboxyethyl)lysine (CEL) protein expression in isolated glomeruli were analyzed by Western blot analysis and immunohistochemistry.

Results: Untreated diabetic db/db mice at 20 weeks of age had significantly increased body and kidney weight, VG, RMA, plasma creatinine, and urinary albumin excretion (UAE) compared to db/m mice of the same age. Glomerular FN increased 8-fold in db/db mice compared to db/m mice, VEGF by 1.6-fold, pentosidine by 1.6-fold, and CEL by 1.3-fold. Both early and delayed treatment with ALT-711 effectively ameliorated UAE and RMA without an effect on plasma glucose level. VG and FN and pentosidine (a cross-linking AGE) in db/db mice glomeruli were significantly reduced by early treatment with ALT-711. The level of VEGF and CEL (a non cross-linking AGE) did not change with ALT-711.

Conclusion: ALT-711 effectively reduced VG, RMA, glomerular pentosidine and FN accumulation, and UAE in db/m mice and may prove to be a novel therapeutic agent in type 2 diabetes.