Targeting plasma kallikrein with a novel bicyclic peptide inhibitor (THR-149) reduces retinal thickening in a diabetic rat model

Tine Van Bergen, Isabelle Etienne, Tjing-Tjing Hu, Jean H.M. Feyen

Oxurion NV, Gaston Geenslaan 1, 3001 Heverlee, Belgium

DESIGN OF THE STUDY. To investigate the therapeutic effect of plasma kallikrein (PKal) inhibition on retinal thickening in a diabetic rat model.

PURPOSE. The aim of this study was to test the efficacy of intravitreal (IVT) administration of THR-149 on leakage-associated retinal thickening in the diabetic streptozotocin (STZ)-induced rat model. THR-149 is a novel potent and highly specific peptide inhibitor for PKal.

METHODS. One non-diabetic control group of rats was included (group 1), together with 4 groups of diabetic rats (n=8-10 rats/group), in which treatment was started immediately after diabetes onset. Group 2 and 3 received 3 consecutive IVT injections (with 1-week interval) of THR-149 (12.5 µg/eye) or vehicle, respectively. Anti-VEGF (2 mg/kg) and its vehicle were administered 3x/week via intraperitoneal injection for 3 weeks in group 4 and 5, respectively. Retinal thickness was quantified in all groups at 4 weeks after diabetes onset, by measuring the thickness of the total retina or of the individual retinal layers on FITC-BSA perfused histological tissue sections.

RESULTS. Total retinal thickness was significantly increased at 4 weeks after diabetes onset in vehicle-treated diabetic rats compared to non-diabetic control rats (by approximately 20 µm; $p<0.001$). Administration of 12.5 µg/eye of THR-149 significantly reduced retinal thickness with 12 µm ($p<0.001$) *versus* vehicle-treated eyes. Administration of anti-VEGF treatment significantly reduced total retinal thickness with 15 µm, as compared to its vehicle ($p<0.001$). Analysis of the individual retinal layers showed that the thickness of the inner plexiform layer (IPL), inner nuclear layer (INL), outer nuclear layer (ONL) and photoreceptor layer (PR) was significantly increased in vehicle-treated diabetic rats, which was significantly reduced in the THR-149 and anti-VEGF treated rats ($p<0.05$). Moreover, THR-149 additionally reduced the ONL thickness with 16%, as compared to anti-VEGF administration ($p<0.001$).

CONCLUSIONS. In this study, it was shown that repeated administration of THR-149, a novel bicyclic peptide, significantly reduced retinal thickening in the diabetic rat STZ model, compared to vehicle-treated eyes. These positive results further strengthen the perspective to use THR-149 as a treatment option for diabetic macular edema (DME).