Therapeutic efficacy of PlGF-inhibition on inflammation and fibrosis in a CNV mouse model

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PURPOSE (max 100 words). The current standard of care in clinical practice for diabetic retinopathy (DR), anti-vascular endothelial growth factor (VEGF) therapy, has shown a significant improvement in visual acuity. However, treatment response can be variable and might be associated with potential side effects, such as the formation of fibrovascular membranes and neurotoxicity. The goal of this study is to investigate the effect of 5D11D4, an antibody against murine placental growth factor (PlGF), on leukocyte infiltration, on fibrosis and on the survival of retinal ganglion cells (RGC). Previous studies already showed inhibition of angiogenesis, leakage and inflammation of this anti-PlGF-antibody.

SETTINGS (max 50 words). Alternative therapeutic strategies for anti-VEGF therapies are needed to reduce the risk of treatment-related complications, such as scar formation and irreversible neurodegeneration.

METHODS (max 200 words). The efficacy of 5D11D4 was investigated *in vivo* in a laser-induced choroidal neovascularization (CNV) mouse model. Intravitreal injections (1 µL) were given after laser treatment on day 0, 4, 10 and 20 with 5D11D4 (dose range of 0.77, 1.5 or 3.1 µg/eye), murine anti-VEGF-R2 antibody (DC101; 3.2 µg/eye), aflibercept (dose range of 2.4 and 20 µg/eye) or irrelevant IgG (3.1 µg/eye) (10 mice per group). Treatment outcome was blindly assessed by analysis of leukocyte infiltration (CD45; day 5) and collagen deposition (collagen I; day 30). The effect on RGC survival after repeated administration of the different compounds was investigated as well in naïve mice by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining (n=6 mice per group).

RESULTS (max 200 words). Intravitreal injections of 5D11D4 (0.77-3.1µg) dose-dependently reduced inflammation and fibrosis, as compared to irrelevant IgG ($p<0.05$). Administration of 3.1 µg 5D11D4 and 2.4 µg aflibercept (equimolar concentrations) both reduced leukocyte infiltration with 49% ($p<0.05$), whereas DC101 (3.1 µg) had no effect. Administration of 3.1 µg 5D11D4 induced a reduction of 41% in collagen deposition ($p<0.05$), while no effect could be observed after DC101 (3.1 µg) or aflibercept (2.4 and 20 µg) administration. Naïve mice treated with the VEGF-R2 inhibitor exhibited reduced RGC density of 32% ($p<0.05$) and an increased number of apoptotic RGC cells with 33% ($p<0.001$), as compared to control-treated mice. In contrast, PlGF inhibition did not induce any alteration in RGC density or apoptotic rate.

CONCLUSIONS (max 200 words). It can be concluded that the antibody against PlGF is able to reduce inflammation and fibrosis, without affecting RGC survival. As such, the anti-PlGF-antibody might differentiate itself from VEGF inhibitors which are currently the gold standard

therapies for DR. Clinical trials will be initiated to test the efficacy of an anti-PlGF antibody in DR patients.

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