Neutralization of placental growth factor as a novel treatment option in diabetic retinopathy

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PURPOSE. Anti-vascular endothelial growth factor (VEGF) therapy has shown a significant improvement in visual acuity in patients with diabetic retinopathy (DR). Treatment response can be variable and might be associated with potential side effects. Therefore, there is clear need for alternative therapies with potential to reduce the risk of treatment-related complications. In this study, the effect of placental growth factor (PlGF) inhibition on different hallmarks of diabetic retinopathy (DR) was investigated in experimental murine models.

METHODS. The *in vivo* efficacy of the anti-PlGF antibody (5D11D4; 0.77 – 5.4 µg/eye) was tested in diabetic streptozotocin (STZ; n=15/group) and Akimba mouse models (n≥20/group) and in the laser-induced mouse model of choroidal neovascularization (CNV; n=10/group). Intravitreal (IVT) administration of the anti-PlGF antibody was compared to anti-VEGFR-2 antibody (DC101; 3.1 - 6.2µg/eye), VEGF-Trap (aflibercept; 2.4 -20 µg/eye) and triamcinolone acetonide (TAAC; 40 µg/eye). Vascular leakage was investigated by fluorescein isothiocyanate labelled bovine serum albumin perfusion or by fluorescein

angiography. Immunohistological stainings were performed to check for neurodegeneration (Brn3a), inflammation (CD45, F4/80) and fibrosis (collagen type 1a).

RESULTS. In the diabetic STZ and Akimba model, repeated IVT administration of 5D11D4 reduced vascular leakage with 32 and 22%, respectively ($P<0.05$). This effect was equally efficacious as DC101 treatment in STZ mice ($P=0.43$). 5D11D4 treatment did not alter retinal ganglion cell (RGC) density, whereas DC101 significantly reduced the RGC number with 20% ($P=0.04$). In the CNV model, D11D4 injection dose-dependently reduced inflammation and fibrosis, as compared to PBS treatment ($P<0.05$). Equimolar administration of 5D11D4, aflibercept and TAAC decreased leukocyte and macrophage infiltration with 50% ($P<0.05$), whereas DC101 had no effect on the inflammatory response ($P=0.96$). Administration of 5D11D4 and TAAC similarly reduced fibrosis with 40% ($P<0.05$), while no effect was observed after equimolar DC101 ($P=0.82$) nor aflibercept administration ($P=0.66$).

CONCLUSIONS. The neutralization of -PlGF showed equal efficacy compared to VEGF-inhibitors on the process of vascular leakage, but differentiates itself by also reducing inflammation and fibrosis, without triggering a neurodegenerative response.