ANTI-INFLAMMATORY EFFECTS OF THE PlGF NEUTRALIZING ANTIBODY THR-317 IN PATIENTS WITH DIABETIC MACULAR EDEMA

AUTHORS

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PURPOSE

Evaluate the effect of anti-placental growth factor (PlGF) neutralizing antibody, THR-317, on inflammatory cytokine, chemokine and growth factor levels in the aqueous humor of diabetic macular edema (DME) patients.

SETTING

THR-317 (ThromboGenics NV) is a monoclonal antibody targeting placental growth factor (PlGF), which is under phase II clinical evaluation for the treatment of DME. In addition to inhibiting vascular leakage, preclinical animal models have shown that anti-PlGF reduces inflammation and fibrosis, without triggering a neurodegenerative response in retinal ganglion cells.

METHODS

Aqueous humor was collected from patients participating in a clinical trial evaluating the safety and efficacy of three monthly intravitreal injections of THR-317 (ClinicalTrials.gov Identifier NCT03071068). Informed consent was obtained from all participants before entering into the study and all investigations adhered to the principles of the Declaration of Helsinki. Twelve aqueous humor samples were collected from six study participants. Aqueous humor was sampled just prior to the injection of THR-317 (Baseline, Day 0) as well as 30 days after the second injection of THR-317 (Day 60). Cytokines, chemokines, and growth factors were assayed using two highly sensitive multiplex analysis platforms: the OLINK inflammation platform, which allows parallel measurement of 92 inflammation-related analytes (full analyte list at www.olink.com, OLINK Proteomics, Uppsala Sweden), as well as the AYOXXA Lunaris™ Ophthalmology platform, which allows parallel measurement of 11 ophthalmology-related analytes (Ang-2, VEGF-A, MCP1, IP-10, CXCL12, CXCL13, IL-6, IL-8, PlGF and PDGF-BB, AYOXXA Biosystems, Cologne Germany). Data analysis and statistical follow-up were performed in Graphpad Prism using the Mann-Whitney U test for statistical analyses.

RESULTS

On the OLINK inflammation platform, analysis of DME aqueous yielded 718 data points (65%) above LLOQ. On day 60, (30 days after the second injection of THR-317), the levels of 50 inflammatory proteins were decreased versus 17 increased as compared to baseline. Given the limited sample size and inter-patient

heterogeneity, no individual analyte was significantly up-or downregulated at day 60 as compared to baseline. However, the chemokine family of inflammatory proteins was found to be significantly downregulated at day 60 as compared to baseline ($p=5.17 \times 10^{-5}$). The strongest downregulated analyte at day 60 was chemokine CCL20 (2.02-fold decrease, uncorrected p-value=0.056). The strongest upregulated analyte at day 60 was TNFSF14 (1.20-fold increase, uncorrected p-value=0.355).

On the AYOXXA ophthalmology platform, analysis of DME aqueous yielded 120 data points (91%) above LLOQ. On day 60, levels of 9 analytes were decreased versus 2 increased as compared to baseline. Although no individual analytes were found to be significantly up-or downregulated at day 60 as compared to baseline, the clearest downward trends occurred for IL-8, IP10 and PlGF (decreased 1.35, 1.95 and 1.89-fold, with uncorrected p-values 0.180, 0.149 and 0.261, respectively). Data from OLINK and AYOXXA platforms correlated well.

CONCLUSIONS

Analysis of aqueous humor sampled from DME patients indicated an overall reduction of inflammatory proteins after treatment with THR-317. Despite the limited sample number, a statistically significant reduction of chemokine family proteins was observed after treatment with THR-317. Taken together, these data collected in clinical DME samples confirm observations made in preclinical animal models, pointing towards an anti-inflammatory action of THR-317. Additional analyses will be required to confirm the observations made in this study and to correlate with clinical outcomes. Broad multiplex profiling of aqueous humor was found to be feasible using both OLINK and AYOXXA technologies, yielding information on >100 analytes from as little as 10 µL ocular fluid, and with data from both methods correlating well.

THEME

New drug treatment and technology

FINANCIAL DISCLOSURE

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