Suppression of Murine Choroidal and Retinal Neovascularization by Risuteganib and the Accompanying Transcriptome Changes in the OIR Retina

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Abstract

Purpose: Wet age-related macular degeneration and diabetic retinopathy are leading causes of blindness with characteristic neovascularization (NV) of the choroid (CNV) or retina (RNV), respectively. This preclinical study explores effects of the investigational drug, risuteganib (RSG), in cell culture and three murine disease models using histology and transcriptomics.

Methods: In photocoagulation-induced CNV model, 1-50 µg RSG or control peptides were intravitreally injected, followed by measurement of NV area on day 14 (n=4). The rhoNEGF model of subretinal NV was used to examine: i) injection of vehicle, 25 µg RSG, 10 µg ranibizumab, or combination of two drugs, followed by NV area measurement on day 7 (n=5), and ii) vascular leakage 1 day after PBS or 25 µg RSG injection (n=8). In oxygen-induced retinopathy (OIR) RNV model, 0.1-50 µg of RSG or PBS were injected and NV area was measured on day 5 (n=8). Student's t-test was used except with ANOVA in the rhoNEGF study of NV. Transcriptome changes associated with RNV and 10 µg RSG injection was measured by RNA-seq. Changes in gene levels were determined by edgaf and enrichment of biological processes/pathways by goseq. RT-CRISPR-based MRCS cell adhesion and migration assays were used to test effect of 43-1393 µM RSG on surfaces coated with vitronectin (VN) or fibronectin (FN) (n=2), statistical test by ANOVA.

Results: In the photocoagulation model, 10 and 25 µg RSG reduced the area of CNV (p<0.0453, 0.0498). In the rhoNEGF model, RSG (p=0.001) and ranibizumab (p=0.001) both reduced the NV area, while combination showed further reduction (p=0.05). RSG reduced vascular leakage by 24% (p<0.017). In OIR, 12.5, 25, and 50 µg RSG (p<0.027), 0.0414, 0.0403) reduced NV area. Transcriptome data showed biological processes and pathways related to angiogenesis, inflammation, integrin, cell adhesion and migration were enriched in genes elevated in OIR retina and reduced with RSG. Cell migration on FN was inhibited at low RSG dose (p<0.01), while migration on VN (p<0.01), adhesion on VN (p<0.05) and FN (p<0.01) were inhibited at high RSG dose.

Conclusions: RSG demonstrated anti-NV property, reduced retinal vascular leakage, and inhibited cell adhesion and migration. Transcriptome data suggest important pathological cellular responses are modulated by RSG, with possible therapeutic implication for treatment of human retinal diseases.

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