A Possible Mechanism of Long-Term Intraocular Pressure Increase After Repeated Anti-VEGF Injections

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Purpose:
To test the hypothesis whether long-term intraocular pressure increase after repeated injections of anti-VEGF is due to cell death at trabecular meshwork and Schlemm's canal via activation of the complement system.

Methods:
Surgical trabeculectomy specimens were obtained from 8 patients, 2 of whom had been receiving repeated (>6) anti-VEGF (aflibercept and/or bevacizumab) injections for the treatment of exudative macular degeneration for more than a year. Tissue sections were co-immunostained for complement activation markers (c3b, c4d, c5b-9, C3a) along with von Willebrand factor and neuron-specific enolase to identify Schlemm’s canal endothelial cells and trabecular meshwork cells targeted by complement activation. TUNEL staining was also used to detect cells that are undergoing apoptosis. Ratio of Schlemm’s canal endothelial cells and trabecular meshwork cells revealing complement activation and apoptotic cell death was determined by counting cells under 400x magnification. Data obtained from patients receiving anti-VEGF drugs and the ones that had never received anti-VEGF injections were compared.

Results:
A low-grade complement activation (6.1±2.4%) was detected in the trabecular meshwork of patients with open angle glaucoma undergoing filtering surgery. Complement activation significantly increased (15.7±6.4%, p<0.05) after repeated intravitreal anti-VEGF injections and involve both trabecular meshwork cells and Schlemm's canal endothelial cells. Comparable low-grade staining of tissue samples for c4d suggest the alternate pathway involvement in complement activation. Anti-VEGF treated eyes also reveal upregulation of C3a receptor (6.3±5.7% vs 3.0±2.7%, p<0.05). No difference was found in TUNEL (+) cells between groups (2.8±1.1% vs 2.2 ±2.1%, p>0.05) suggesting that increase complement activation with anti-VEGF injection is not a part of physiological scavenging task of the complement system.

Conclusions:
Patients receiving anti-VEGF injection reveal increased complement activation in the trabecular meshwork and Schlemm’s canal. Increased activation of the complement system induces cell death through the formation of membrane attack complex (MAC) and may incite an inappropriate and damaging inflammatory response through C3a receptor upregulation. The most possible cause of complement activation is the formation of immune complexes through the interaction of the anti-VEGF drugs with VEGF in the aqueous and subsequent binding to either Fc or VEGF receptors on the cell membrane.