Levels of VEGF but not VEGF165b are Increased in the Vitreous of Patients With Retinal Vein Occlusion

Christoph Ehlken, Emma S. Rennel, Daniel Michels, Bastian Grundel, Amelie Pielen, Bernd Junker, Andreas Stahl, Lutz L. Hansen, Nicolas Feltgen, Hansjürgen T. Agostini, And Gottfried Martin


Study was done to determine the concentration of the proangiogenic vascular endothelial growth factor VEGF165 (VEGF) and the anti-angiogenic VEGF165b in vitreous samples of patients with branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO) in comparison to patients without retinal occlusive disease. It was an experimental laboratory investigation. Vitreous samples were collected from patients undergoing surgery for arteriovenous dissection after BRVO, radial optic neurotomy after CRVO in the occlusion group, or macular pucker or macular hole in the control group. Concentrations of VEGF and VEGF165b were determined by ELISA and an ELISA type antibody microarray. Average vitreal concentration of VEGF was 8.6 ng/mL in the CRVO group and 2.0 ng/mL in the BRVO group as compared to 0.26 ng/mL in the control group. Average vitreal concentration of VEGF165b was 27 pg/mL in the CRVO group, 42 pg/mL in the BRVO group, and 49 pg/mL in the control group. In patients with CRVO and BRVO, the angiogenic balance was shifted towards angiogenic stimulation. The authors concluded that the pro-angiogenic shift of the ratio of VEGF165b/VEGF in favour of VEGF seems to be a mechanism underlying retinal ischemic disease not only in patients with proliferative diabetic retinopathy but also in patients with retinal vein occlusion. The possible effects of lowering the anti-angiogenic VEGF165b by non selective anti-VEGF treatment should be taken into consideration for future treatment. Altering the ratio of VEGF165b/VEGF in favour of the anti-angiogenic splice variant VEGF165b might be a promising alternative or additional approach to treat vision loss and reduce complications caused by overabundance of VEGF.

Preoperative Intravitreal Bevacizumab Use as an Adjuvant to Diabetic Vitrectomy: Histopathologic Findings and Clinical Implications

Hazem A. El-Sabagh, Walid Abdelghaffar Ahmad M. Labib, et al,
Ophthalmology Volume 118, Number 4, April 2011

Purpose was to evaluate the effects of intervals between preoperative intravitreal injection of bevacizumab (IVB) and surgery on the components of removed diabetic fibrovascular proliferative membranes. It was an interventional, consecutive, prospective, comparative case series. A total of 52 eyes of 49 patients with active diabetic fibrovascular proliferation with complications necessitating vitrectomy were included. Participant eyes that had IVB were divided into 8 groups in which vitreoretinal surgery was performed at days 1, 3, 5, 7, 10, 15, 20, and 30 post injections. A group of eyes with the same diagnosis and surgical intervention without IVB injection was used for comparison. In all eyes, proliferative membrane specimens obtained during vitrectomy were sent for histopathologic examination using hematoxylin–eosin stain, immunohistochemistry (CD34 and smooth muscle actin), and Masson’s trichrome stain. Comparative analysis of different components of the fibrovascular proliferation (CD34, smooth muscle actin, and collagen) among the study groups. Pan-endothelial marker CD34 expression levels starting from day 5 post injection were significantly less than in the control group (P < 0.001), with minimum expression in all specimens removed at or after day 30 post injection. Positive staining for smooth muscle actin was barely detected in the control eyes at day 1, and consistently intense at day 15 and beyond (P 0.001). The expression level of trichrome staining was significantly high at day 10, compared with control eyes (P <0.001), and continued to increase at subsequent surgical time points. The study concludes thus that the histologic findings of ERM surgically removed after preoperative adjunctive use of IVB demonstrated a profibrotic switch, with significant reduction
in the neovascular component and marked increase in the contractile elements of the proliferative membranes over time. The results suggest that retinal neovascularization is markedly reduced at approximately day 10 after injection, whereas contractile elements (smooth muscle actin and collagen) are not yet abundant. However, in the presence of dense fibrovascular proliferation, it is advisable to closely monitor patients for the untoward progression of TRD after IVB. The histologic findings are also in accordance with many published clinical findings and might be predictive of an optimal time interval for the preoperative use of adjunctive IVB, which makes surgery more successful with less intraoperative bleeding and complications, consequently leading to a better visual outcome; however, such favourable outcomes require larger-scale clinical trials to be proven.

The Functional Significance of Foveal Abnormalities in Albinism Measured Using Spectral-Domain Optical Coherence Tomography

Sarim Mohammad, Irene Gottlob, Anil Kumar, Mervyn Thomas, Christophe Degg, Viral Sheth, Frank Antony Proudlock

Ophthalmology Volume 118, Number 8, August 2011

The relationship between foveal abnormalities in albinism and best-corrected visual acuity (BCVA) is unclear. High-resolution spectral-domain optical coherence tomography (SD OCT) was used to quantify foveal retinal layer thicknesses and to assess the functional significance of foveal morphologic features in patients with albinism. It was a cross-sectional study. Forty-seven patients with albinism and 20 healthy control volunteers were recruited to the study. Using high-resolution SD OCT, 7X7X2-mm volumetric scans of the fovea were acquired (3 micron axial resolution). The B scan nearest the center of the fovea was identified using signs of foveal development. The thickness of each retinal layer at the fovea and foveal pit depth were quantified manually using ImageJ software and were compared with BCVA. Total retinal thickness, foveal pit depth, photoreceptor layer thickness, and processing layer thickness in relation to BCVA. Total photoreceptor layer thickness at the fovea was correlated highly to BCVA (P = 0.0008; r = -0.501). Of the photoreceptor layers, the outer segment length was correlated most strongly to BCVA (P < 0.0001; r = -0.641). In contrast, there was no significant correlation between either total retinal thickness or pit depth and BCVA (P > 0.05). This was because of an inverse correlation between total photoreceptor layer thickness and total processing layer thickness (P < 0.0001; r = -0.696). The results of this study provide quantitative evidence for the functional significance of foveal photoreceptors in the retina of patients with albinism. Photoreceptor outer segment length was found to be the strongest predictor of visual acuity. In contrast, there was no significant relationship between either total retinal thickness or foveal pit depth and visual acuity. This lack of correlation was the result of the relationship between the total thickness of photoreceptor layers and the total thickness of processing layers, where increasing total thickness of photoreceptor layers was associated with decreasing total thickness of processing layers. This meant that the degree of deviation away from normal foveal morphologic features was not related to overall retinal thickness. Since nystagmus associated with albinism also leads to deterioration in vision because of motion blur, these findings indicate that OCT has a clinical use in recognizing patients who have potential for visual improvement as a result of treatments to reduce nystagmus intensity, such as pharmacologic interventions. With the rapid development of OCT technology, it is likely that high-resolution hand-held OCT devices soon will be available clinically. These may allow the visualization of photoreceptor morphologic features in neonates, possibly enabling us to assess the future potential for vision and the need for early intervention.

Flucinolone Acetonide Intravitreal Implant for Diabetic Macular Edema: A 3-Year Multicenter, Randomized, Controlled Clinical Trial

P. Andrew Pearson, Timothy L. Comstock, Michael Ip, David Callanan, Lawrence S. Morse, Paul Ashton, Brian Levy, Eric S. Mann, Dean Elliott

Ophthalmology Volume 118, Number 8, August 2011

This trial studied the 3-year efficacy and safety results of a 4-year study evaluating flucinolone acetonide (FA) intravitreal implants in eyes with persistent or recurrent diabetic macular edema (DME). It was a prospective, evaluator-masked, controlled, multicenter clinical trial. 196 eyes with refractory DME were included. Patients were randomized 2:1 to receive 0.59-mg FA implant (n = 127) or standard of care (SOC additional laser or observation; n = 69). The implant was inserted through a pars plana incision. Visit were scheduled on day 2, weeks 1, 3, 6, 12, and 26, and thereafter every 13 weeks through 3 years post implantation. The primary efficacy outcome was 15-letter improvement in visual acuity (VA) at 6 months. Secondary outcomes included resolution of macular retinal thickening and Diabetic Retinopathy Severity Score (DRSS). Safety measures included incidence of adverse events (AEs). Overall, VA improved 3 lines in 16.8% of implanted eyes at 6 months (P = 0.0012; SOC, 1.4%); in 16.4% at 1 year (P = 0.1191; SOC, 8.1%); in 31.8% at 2 years (P = 0.0016; SOC, 9.3%); and in 31.1% at 3 years (P = 0.1566; SOC, 20.0%). The number of implanted eyes with no evidence of retinal thickening at the center of the macula was higher.
than SOC eyes at 6 months (P<0.0001), 1 year (P<0.0001; 72% vs. 22%), 2 years (P<0.016), and 3 years (P<0.861). A higher rate of improvement and lower rate of decline in DRSS occurred in the implanted group versus the SOC group at 6 months (P<0.0006), 1 year (P<0.0016), 2 years (P<0.012), and 3 years (P<0.0207). Intraocular pressure (IOP) 30 mmHg was recorded in 61.4% of implanted eyes (SOC, 5.8%) at any time and 33.8% required surgery for ocular hypertension by 4 years. Of implanted phakic eyes, 91% (SOC, 20%) had cataract extraction by 4 years. The FA intravitreal implant met the primary and secondary outcomes, with significantly improved VA and DRSS and reduced DME. The most common AEs included cataract progression and elevated IOP. The 0.59-mg FA intravitreal implant may be an effective treatment for eyes with persistent or recurrent DME. This is the first study to demonstrate that sustained (>6 months) drug delivery to the posterior segment is efficacious in the treatment of diabetic retinal disease. Specifically, improvements of 3 lines of VA in the FA group were significant at 6 (primary endpoint), 9, 18, and 24 months compared with SOC. The results also indicate that sustained drug delivery is beneficial for DME, because effects of treatments such as IVTA do not persist in the long term and need to be repeated. This study also demonstrates that sustained delivery of steroids can result in resolution of DME and improvement in DRSS. With careful monitoring of IOP and lens clarity, the 0.59-mg FA intravitreal implant may be an effective treatment for eyes with persistent or recurrent DME. There is no evidence from this study that long-term exposure of the retina to low concentrations of steroids has any deleterious effect; in fact, the opposite may be true, as demonstrated by the improvement in DRSS. In clinical practice, when the implant is depleted of drug (30 months), the stimulus responsible for the development of DME may persist or may have significantly lessened, and close follow-up is therefore indicated.