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MD Research News

Issue 1 Monday November 1, 2010

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Drug Treatment

1. Mol Vis. 2010 Sep 12;16:1848-53.

Bevacizumab neutralizes the protective effect of vascular endothelial growth factor on retinal ganglion cells.

Brar VS, Sharma RK, Murthy RK, Chalam KV.

University of Florida College of Medicine, Department of Ophthalmology Jacksonville, FL.

Abstract

PURPOSE: Vascular endothelial growth factor (VEGF) is well known for its role in pathologic neovascularization, including wet age-related macular degeneration. However, a growing body of evidence indicates that VEGF is also neuroprotective of non-vascular cells in various animal models through reduction of oxidative stress. In light of the widespread use of intraocular anti-VEGF therapies for age-related macular degeneration (AMD), we evaluated the impact of anti-VEGF agents on the neuroprotective effect of VEGF on retinal ganglion cells.

METHODS: Staurosporine differentiated retinal ganglion cells were treated with increasing doses of VEGF in the presence of hydrogen peroxide. After optimization, an increasing concentration of bevacizumab was added to neutralize VEGF-mediated protection. The degree of oxidative damage was measured at various time points using buthionine sulfoxime (BSO), a glutathione reductase inhibitor. Cell viability was assessed using WST-1 and Crystal violet assays.

RESULTS: VEGF (200 ng/ml) protected differentiated retinal ganglion cells (RGC)-5 against H(2)0(2)-mediated oxidative stress. This effect was eliminated by co-treatment with bevacizumab (2.0 mg/ml), which by itself was not cytotoxic.

CONCLUSIONS: These results indicate an important role for VEGF in the maintenance of retinal ganglion cells.

PMID: 21031022 [PubMed - in process]

2. Diabetes Care. 2010 Nov;33(11):2399-405.

Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study): A 12-month, randomized, controlled, double-masked, multicenter phase II study.

Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, Mitchell P, Sharp D, Wolf-Schnurrbusch UE, Gekkieva M, Weichselberger A, Wolf S.

Corresponding author: Sebastian Wolf, sebastian.wolf@insel.ch.

Abstract

OBJECTIVE The expression of vascular endothelial growth factor (VEGF) is elevated in diabetic macular edema (DME). Ranibizumab binds to and inhibits multiple VEGF variants. We investigated the safety and efficacy of ranibizumab in DME involving the foveal center. RESEARCH DESIGN AND METHODS This was a 12-month, multicenter, sham-controlled, double-masked study with eyes (age >18 years, type 1 or 2 diabetes, central retinal thickness [CRT] ≥300 μm, and best corrected visual acuity [BCVA] of 73-39 ETDRS letters [Early Treatment Diabetic Retinopathy Study]) randomly assigned to intravitreal ranibizumab (0.3 or 0.5 mg; n = 51 each) or sham (n = 49). The treatment schedule comprised three monthly injections, after which treatment could be stopped/reinitiated with an opportunity for rescue laser photocoagulation (protocol -defined criteria). After month 1, dose-doubling was permitted (protocol-defined criteria, injection volume increased from 0.05 to 0.1 ml and remained at 0.1 ml thereafter). Efficacy (BCVA and CRT) and safety were compared between pooled ranibizumab and sham arms using the full analysis set (n = 151, patients receiving ≥1 injection). RESULTS At month 12, mean ± SD BCVA improved from baseline by 10.3 ± 9.1 letters with ranibizumab and declined by 1.4 ± 14.2 letters with sham (P < 0.0001). Mean CRT reduction was 194.2 ± 135.1 μm with ranibizumab and 48.4 ± 153.4 μm with sham (P < 0.0001). Gain of ≥10 letters BCVA from baseline occurred in 60.8% of ranibizumab and 18.4% of sham eyes (P < 0.0001). Safety data were consistent with previous studies of intravitreal ranibizumab. CONCLUSIONS Ranibizumab is effective in improving BCVA and is well tolerated in DME. Future clinical trials are required to confirm its long-term efficacy and safety.

PMID: 20980427 [PubMed - in process]

3. Br J Ophthalmol. 2010 Oct 22. [Epub ahead of print]

Intravitreal bevacizumab (Avastin) versus ranibizumab (Lucentis) for the treatment of age-related macular degeneration: a safety review.

Schmucker C, Loke YK, Ehlken C, Agostini HT, Hansen LL, Antes G, Lelgemann M.

University Medical Centre Freiburg, Freiburg, Germany.

Abstract

Aim To conduct a systematic review in order to compare adverse effects (AE) and the reporting of harm in randomised controlled trials (RCTs) and non-RCTs evaluating intravitreal ranibizumab and bevacizumab in age-related macular degeneration. Methods Medline, Embase and the Cochrane Library were searched with no limitations of language and year of publication. Studies which compared bevacizumab or ranibizumab as monotherapy with any other control group were included. Case series were included if they met predefined quality standards. Results The 2 year results of phase III trials evaluating ranibizumab show that the rates of serious ocular AE were low (≤2.1%) but indicate major safety concerns (RR 3.13, 95% CI 1.10 to 8.92). A possible signal with regard to thromboembolic events (RR 1.35, 95% CI 0.66 to 2.77) and a significant increase in non-ocular haemorrhage (RR 1.62, 95% CI 1.03 to 2.55) were also noted. In contrast to ranibizumab trials, the RCTs evaluating bevacizumab are of limited value. The main shortcomings are small sample sizes and an apparent lack of rigorous monitoring for AE. A critical assessment of the large number of published case series evaluating bevacizumab also shows that no reliable conclusions on safety can be drawn using this study design. Therefore, any perception that intravitreal bevacizumab injections are not associated with major ocular or systemic AE are not supported by reliable data. Conclusion The bevacizumab studies show too many methodological limitations to rule out any major safety concerns. Higher evidence from ranibizumab trials suggests signals for an increased ocular and systemic vascular and haemorrhagic risk which warrants further investigation.

PMID: 20971791 [PubMed - as supplied by publisher]

Genetics

4. Mol Vis. 2010 Oct 5;16:1958-81.

LOC387715/HTRA1 gene polymorphisms and susceptibility to age-related macular degeneration: A HuGE review and meta-analysis.

Tong Y, Liao J, Zhang Y, Zhou J, Zhang H, Mao M.

Abstract

PURPOSE: To examine the association of age-related macular degeneration (AMD) with HtrA serine peptidase 1 (HTRA1) gene rs11200638 G→A polymorphism and LOC387715/ ARMS2 gene rs10490924 G→T polymorphisms, and to evaluate the magnitude of the gene effect and the possible genetic mode of action.

METHODS: We searched the US National Library of Medicine's PubMed, Embase, OMIM, ISI Web of Science, and CNKI databases in a systematic manner to retrieve all genetic association studies on the HTRA1 (rs11200638) and LOC387715/ ARMS2 (rs10490924) gene polymorphisms and AMD. We performed a meta-analysis conducted with Stata software, version 9.0.

RESULTS: Individuals who carried the AA and AG genotypes of HTRA1 gene rs11200638 G→A polymorphism had 2.243 and 8.669 times the risk of developing AMD, respectively, when compared with those who carry the GG genotype. Individuals carrying the TT and TG genotypes of LOC387715/ ARMS2 gene rs10490924 G→T polymorphism had 7.512 and 2.353 times the risk of developing AMD, respectively, compared with those who carry GG genotype. These results suggested a "moderate" codominant, multiplicative genetic mode; that is, both HTRA1 rs11200638 G→A polymorphism and LOC387715/ARMS2 rs10490924 G→T polymorphism play important roles in the pathogenesis of AMD. We found no evidence of publication bias. Between-study heterogeneity was found in both allele-based analysis and genotype-based analysis.

CONCLUSIONS: HTRA1 rs11200638 G→A polymorphism and LOC387715/ARMS2 rs10490924 G→T polymorphism play important roles in AMD. Gene-gene and gene-environmental interactions, as well as precise mechanisms underlying common variants in the HTRA1 gene and LOC387715/ ARMS2 gene, potentially increase the risk of AMD and need further exploration.

PMID: 21031019 [PubMed - in process]

5. Hum Genet. 2010 Oct 28. [Epub ahead of print]

Genome-wide analysis of copy number variants in age-related macular degeneration.

Meyer KJ, Davis LK, Schindler EI, Beck JS, Rudd DS, Grundstad AJ, Scheetz TE, Braun TA, Fingert JH, Alward WL, Kwon YH, Folk JC, Russell SR, Wassink TH, Stone EM, Sheffield VC.

Interdisciplinary Genetics Program, University of Iowa, Iowa City, IA, USA.

Abstract

Age-related macular degeneration (AMD) is a complex genetic disease, with many loci demonstrating appreciable attributable disease risk. Despite significant progress toward understanding the genetic and environmental etiology of AMD, identification of additional risk factors is necessary to fully appreciate and treat AMD pathology. In this study, we investigated copy number variants (CNVs) as potential AMD risk variants in a cohort of 400 AMD patients and 500 AMD-free controls ascertained at the University of Iowa. We used three publicly available copy number programs to analyze signal intensity data from Affymetrix(®) GeneChip SNP Microarrays. CNVs were ranked based on prevalence in the disease cohort and absence from the control group; high interest CNVs were subsequently confirmed by qPCR. While we did not observe a single-locus "risk CNV" that could account for a major fraction of AMD, we identified several rare and overlapping CNVs containing or flanking compelling candidate genes such as NPHP1 and EFEMP1. These and other candidate genes highlighted by this study deserve further scrutiny as sources of genetic risk for AMD.

PMID: 20981449 [PubMed - as supplied by publisher]

Other Management

6. Br J Ophthalmol. 2010 Oct 24. [Epub ahead of print]

Short wavelength fundus autofluorescence versus near-infrared fundus autofluorescence, with microperimetric correspondence, in patients with geographic atrophy due to age-related macular degeneration.

Pilotto E, Vujosevic S, Melis R, Convento E, Sportiello P, Alemany-Rubio E, Segalina S, Midena E.

University of Padua, Padua, Italy.

Abstract

Aim To compare standard short-wavelength fundus autofluorescence (SW-FAF) and near infrared-wavelength fundus autofluorescence (NIR-FAF) in detecting geographic atrophy (GA) secondary to age-related macular degeneration, and its retinal sensitivity impairment. Methods Twenty-five consecutive patients (36 eyes) affected by GA were studied by means of fundus autofluorescence imaging, using both SW -FAF (excitation: 488 nm, emission >500 nm) and NIR-FAF (excitation: 787 nm, emission >800 nm). All patients underwent microperimetry to assess fixation characteristics and retinal sensitivity. Results In the extrafoveal region, the total hypoautofluorescent (hypo-FAF) area was significantly wider with NIR-FAF than with SW-FAF (8.03±6.68 mm(2) vs 7.37±6.34 mm(2) respectively; p=0.005). In the foveal area, the total hypo-FAF area was smaller with NIR-FAF than with SW-FAF (0.19±0.03 mm(2) versus 0.42±0.12 mm(2) respectively; p=0.008). Foveal sparing was larger at NIR-FAF compared with SW-FAF (p=0.021). In nine cases (25%) the site of fixation was hypoautofluorescent on SW-FAF, but normal on NIR-FAF with preserved retinal sensitivity. Conclusions Standard SW-FAF may overestimate GA in the foveal area, correctly detected by NIR-FAF. In the extrafoveal area, SW-FAF may underestimate GA. Standard SW-FAF should be integrated with NIR FAF when detecting and following GA to avoid inconsistent results and misinterpretation, from both a morphological and functional perspective. Microperimetry helps to quantify retinal sensitivity in GA.

PMID: 20974627 [PubMed - as supplied by publisher]

7. Contemp Clin Trials. 2010 Oct 22. [Epub ahead of print]

Improving function in age-related macular degeneration: Design and methods of a randomized clinical trial.

Rovner BW, Casten RJ, Hegel MT, Massof RW, Leiby BE, Tasman WS.

Departments of Psychiatry and Neurology, Jefferson Medical College, Jefferson Hospital for Neuroscience, 900 Walnut Street, Philadelphia, Pa 19107.

Abstract

Age-Related Macular Degeneration (AMD) is the leading cause of severe vision loss in older adults and impairs the ability to read, drive, and live independently and increases the risk for depression, falls, and earlier mortality. Although new medical treatments have improved AMD's prognosis, vision-related disability remains a major public health problem. Improving Function in AMD (IF-AMD) is a two-group randomized, parallel design, controlled clinical trial that compares the efficacy of Problem-Solving Therapy (PST) with Supportive Therapy (ST) (an attention control treatment) to improve vision function in 240 patients with AMD. PST and ST therapists deliver 6 one-hour respective treatment sessions to subjects in their homes over 2months. Outcomes are assessed masked to treatment assignment at 3months (main trial endpoint) and 6months (maintenance effects). The primary outcome is targeted vision function (TVF), which refers to specific vision-dependent functional goals that subjects highly value but find difficult to achieve. TVF is an innovative outcome measure in that it is targeted and tailored to individual subjects yet is measured in a standardized way. This paper describes the research methods, theoretical and clinical aspects of the study

treatments, and the measures used to evaluate functional and psychiatric outcomes in this population.

PMID: 20974293 [PubMed - as supplied by publisher]

8. Am J Ophthalmol. 2010 Oct 21. [Epub ahead of print]

Clinicopathologic Correlation of Choroidal and Retinal Neovascular Lesions in Age-Related Macular Degeneration.

Klein ML, Wilson DJ.

Abstract

PURPOSE: To describe histopathologic findings in donor eyes of 3 individuals with neovascular age-related macular degeneration and to correlate with results of clinical and fluorescein angiographic studies performed before death.

DESIGN: Retrospective, observational case series.

METHODS: Three eyes of 3 individuals with neovascular age-related macular degeneration were obtained after death and were prepared for histopathologic examination at a tertiary care referral center. Serial sections through the macula and optic nerve were evaluated with light microscopy. Findings were correlated with results of clinical evaluation, including findings of fluorescein angiography performed from 1 week to 5 months before death.

RESULTS: In Case 1, histopathologic examination revealed a thin choroidal neovascular membrane beneath a relatively intact retinal pigment epithelium (type 1 neovascularization). This correlated with an occult choroidal neovascular membrane on fluorescein angiography characterized by a stippled appearance with minimal late leakage, representing possibly the earliest clinically detectable neovascular membrane for which histopathologic correlation is available. In Case 2, histopathologic examination demonstrated subfoveal choroidal neovascularization with distinctly separate subretinal pigment epithelial (type 1) and subretinal (type 2) components, correlating to fluorescein angiographic appearance of a mixed neovascular membrane with corresponding occult and classic features. The histopathologic findings in Case 3 revealed a plexus of blood vessels in the outer retina surrounded by an abundant eosinophiolic extracellular matrix and associated with a pigment epithelial detachment. There was no communication with the choroid. This correlated with clinical findings of retinal angiomatous proliferation.

CONCLUSIONS: These 3 in situ clinicopathologic correlative studies add new knowledge of the broad clinical spectrum of neovascular age-related macular degeneration.

PMID: 20970772 [PubMed - as supplied by publisher]

Pre-Clinical

9. Mol Vis. 2010 Sep 12;16:1864-73.

Subtoxic levels hydrogen peroxide-induced production of interleukin-6 by retinal pigment epithelial cells.

Wu WC, Hu DN, Gao HX, Chen M, Wang D, Rosen R, McCormick SA.

Abstract

PURPOSE: To study the effect of subtoxic levels of hydrogen peroxide (H(2)O(2)) on the expression and release of interleukin-6 (IL-6) by cultured retinal pigment epithelial (RPE) cells and to explore the relevant signal pathways.

METHODS: Cultured human RPE cells were stimulated with various subtoxic concentrations of H(2)O(2) for different periods. Conditioned medium and cells were collected. IL-6 in the medium and IL-6 mRNA in

the collected cells were measured using an IL-6 enzyme-linked immunosorbent assay kit and reverse transcriptase polymerase chain reaction, respectively. Nuclear factor-kappaB (NF-κB) in nuclear extracts and phosphorylated p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinases (JNK) in cells cultured with and without H(2)O(2) were measured by NF-κB and MAPK enzyme-linked immunosorbent assay kits. Inhibitors of p38 (SB203580), ERK (UO1026), JNK (SP600125), and NF-κB (BAY11-7082) were added to the cultures before the addition of H(2)O(2) to test their effects(.)

RESULTS: Subtoxic levels of H(2)O(2) (100 μM and less) increased the IL-6 mRNA level and the release of IL-6 protein by the cultured human RPE cells in a dose- and time-dependent manner. This was accompanied by an increase of NF-κB in nuclear extracts and phosphorylated p38 MAPK, ERK, and JNK in cell lysates, particularly in the p38 and NF-κB. The NF-κB inhibitor decreased the H(2)O(2)-induced expression of IL-6. The p38 inhibitor, but not the ERK or JNK inhibitor, completely abolished H(2)O(2)-induced expression of IL-6 by RPE cells. The p38 inhibitor also abolished the increase of NF-κB in nuclear extracts in cells treated with H(2)O(2).

CONCLUSIONS: H(2)O(2) stimulated the production of IL-6, a key factor in the modulation of immune responses, inflammatory processes, and the occurrence of autoimmune diseases, which recently has been documented to be increased in age-related macular degeneration (AMD). This may be a molecular linkage for the oxidative stress and inflammatory/autoimmune reactions in AMD and may provide a novel target for the treatment of AMD.

PMID: 21031020 [PubMed - in process]

10. Diabetologia. 2010 Oct 27. [Epub ahead of print]

The role of lipid peroxidation products and oxidative stress in activation of the canonical wingless-type MMTV integration site (WNT) pathway in a rat model of diabetic retinopathy.

Zhou T, Zhou KK, Lee K, Gao G, Lyons TJ, Kowluru R, Ma JX.

Department of Biochemistry, Zhongshan Medical School, Sun Yat-sen University, Guangzhou, China.

Abstract

AIMS/HYPOTHESIS: Our recent studies suggest that activation of the wingless-type MMTV integration site (WNT) pathway plays pathogenic roles in diabetic retinopathy and age-related macular degeneration. Here we investigated the causative role of oxidative stress in retinal WNT pathway activation in an experimental model of diabetes.

METHODS: Cultured retinal pigment epithelial cells and retinal capillary endothelial cells were treated with a lipid peroxidation product, 4-hydroxynonenal (HNE), and an antioxidant, N-acetyl-cysteine (NAC). In vivo, rats with streptozotocin-induced diabetes were treated by NAC for 8 weeks. Activation of the canonical WNT pathway was measured by TOPFLASH assay and by western blot analysis of WNT pathway components and a WNT target gene, Ctgf. Oxidative stress in the retina was evaluated by immunostaining of HNE and 3-nitrotyrosine.

RESULTS: Levels of phosphorylated and total LDL receptor-related protein (LRP)6, and cytosolic β-catenin, as well as transcriptional activity of T cell factor (TCF)/β-catenin were significantly increased by HNE. The production of connective tissue growth factor (CTGF) was also upregulated by HNE. NAC blocked the WNT pathway activation induced by HNE. Furthermore, LRP6 stability was increased by HNE and decreased by NAC. Retinal levels of HNE and 3-nitrotyrosine were significantly increased in diabetic rats, compared with those in non-diabetic rats. In the same diabetic rat retinas, levels of LRP6, cytosolic β-catenin and CTGF were significantly increased. NAC treatment reduced HNE and 3-nitrotyrosine levels and attenuated the upregulation of LRP6, β-catenin and CTGF in diabetic rat retina.

CONCLUSIONS/INTERPRETATION: Lipid peroxidation products activate the canonical WNT pathway through oxidative stress, which plays an important role in the development of retinal diseases.

PMID: 20978740 [PubMed - as supplied by publisher]

11. Mol Ther. 2010 Oct 26. [Epub ahead of print]

Inhibition of Choroidal Neovascularization in a Nonhuman Primate Model by Intravitreal Administration of an AAV2 Vector Expressing a Novel Anti-VEGF Molecule.

Lukason M, Dufresne E, Rubin H, Pechan P, Li Q, Kim I, Kiss S, Flaxel C, Collins M, Miller J, Hauswirth W, Maclachlan T, Wadsworth S, Scaria A.

Genzyme Corporation, Framingham, Massachusetts, USA.

Abstract

Inhibition of vascular endothelial growth factor (VEGF) for the management of the pathological ocular neovascularization associated with diseases such as neovascular age-related macular degeneration is a proven paradigm; however, monthly intravitreal injections are required for optimal treatment. We have previously shown that a novel, secreted anti-VEGF molecule sFLT01 delivered by intravitreal injection of an AAV2 vector (AAV2-sFLT01) gives persistent expression and is efficacious in a murine model of retinal neovascularization. In the present study, we investigate transduction and efficacy of an intravitreally administered AAV2-sFLT01 in a nonhuman primate (NHP) model of choroidal neovascularization (CNV). A dose-dependent and persistent expression of sFLT01 was observed by collecting samples of aqueous humor at different time points over 5 months. The location of transduction as elucidated by in situ hybridization was in the transitional epithelial cells of the pars plana and in retinal ganglion cells. AAV2-sFLT01 was able to effectively inhibit laser-induced CNV in a dose-dependent manner as determined by comparing the number of leaking CNV lesions in the treated versus control eyes using fluorescein angiography. Our data suggest that intravitreal delivery of AAV2-sFLT01 may be an effective long-term treatment for diseases caused by ocular neovascularization.

PMID: 20978476 [PubMed - as supplied by publisher]

12. PLoS One. 2010 Oct 15;5(10):e13403.

Novel rodent models for macular research.

Huber G, Heynen S, Imsand C, vom Hagen F, Muehlfriedel R, Tanimoto N, Feng Y, Hammes HP, Grimm C, Peichl L, Seeliger MW, Beck SC.

Division of Ocular Neurodegeneration, Centre for Ophthalmology, Institute for Ophthalmic Research, University of Tuebingen, Tuebingen, Germany.

Abstract

BACKGROUND: Many disabling human retinal disorders involve the central retina, particularly the macula. However, the commonly used rodent models in research, mouse and rat, do not possess a macula. The purpose of this study was to identify small laboratory rodents with a significant central region as potential new models for macular research.

METHODOLOGY/PRINCIPAL FINDINGS: Gerbillus perpallidus, Meriones unguiculatus and Phodopus campbelli, laboratory rodents less commonly used in retinal research, were subjected to confocal scanning laser ophthalmoscopy (cSLO), fluorescein and indocyanine green angiography, and spectral-domain optical coherence tomography (SD-OCT) using standard equipment (Heidelberg Engineering HRA1 and Spectralis™) adapted to small rodent eyes. The existence of a visual streak-like pattern was assessed on the basis of vascular topography, retinal thickness, and the topography of retinal ganglion cells and cone photoreceptors. All three species examined showed evidence of a significant horizontal streak-like specialization. cSLO angiography and retinal wholemounts revealed that superficial retinal blood vessels typically ramify and narrow into a sparse capillary net at the border of the respective area located dorsal to the optic nerve.

Similar to the macular region, there was an absence of larger blood vessels in the streak region. Furthermore, the thickness of the photoreceptor layer and the population density of neurons in the ganglion cell layer were markedly increased in the visual streak region.

CONCLUSIONS/SIGNIFICANCE: The retinal specializations of Gerbillus perpallidus, Meriones unguiculatus and Phodopus campbelli resemble features of the primate macula. Hence, the rodents reported here may serve to study aspects of macular development and diseases like age-related macular degeneration and diabetic macular edema, and the preclinical assessment of therapeutic strategies.

PMID: 20976212 [PubMed - in process]PMCID: PMC2955520Free PMC Article