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MD Research News

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Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2013 Nov 7. [Epub ahead of print]

Aqueous vascular endothelial growth factor and ranibizumab concentrations after monthly and bimonthly intravitreal injections of ranibizumab for age-related macular degeneration.

Wang X, Sawada T, Kakinoki M, Miyake T, Kawamura H, Saishin Y, Liu P, Ohji M.

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PURPOSE: To evaluate vascular endothelial growth factor (VEGF) and ranibizumab concentrations in eyes with age-related macular degeneration (AMD) after monthly and bimonthly intravitreal ranibizumab (IVR) injections.

METHODS: Aqueous humor samples were obtained from 26 eyes with AMD before and after IVR injections. Nine eyes received three monthly injections and 17 eyes received two bimonthly injections. The VEGF and ranibizumab concentrations were measured by enzyme-linked immunosorbent assay.

RESULTS: The aqueous VEGF concentrations in the monthly injection group decreased below the lowest detectable limit in eight of nine eyes 1 month after the first injection and seven of nine eyes 1 month after the second injection ($P < 0.001$, mean baseline value, 94.7 pg/ml); the aqueous VEGF concentrations in the bimonthly injection group decreased below the lowest detectable limit in two of 17 eyes 2 months after the first injection ($P < 0.001$, mean baseline value, 152.4 pg/ml). The mean aqueous ranibizumab concentrations with monthly injections were 71.2 ng/ml 1 month after the first injection, and 96.3 ng/ml 1 month after the second injection. The mean aqueous ranibizumab concentrations in the bimonthly injection group were 2.5 ng/ml in 15 of 17 eyes, and below the lowest detectable limit in two of 17 eyes 2 months after the first injection.

CONCLUSIONS: In this pilot study with limited follow-up, intravitreal injection of ranibizumab can suppress aqueous VEGF completely for 1 month in most cases. Its effect does not last for 2 months enough to suppress VEGF completely in most cases, although aqueous VEGF at 2 months after intravitreal injection of ranibizumab is less than that before injection in most cases.

PMID: 24196779 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2013 Oct 18;6(5):600-5. doi: 10.3980/j.issn.2222-3959.2013.05.09.

Temporal pattern of resolution/recurrence of choroidal neovascularization during bevacizumab therapy for wet age-related macular degeneration.

Wang H, Barteselli G, Freeman WR, Lee SN, Chhablani J, El-Emam S, Cheng L.

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AIM: To characterize temporal pattern of resolution and recurrence of naive choroidal neovascularization (CNV) secondary to wet age-related macular degeneration (AMD) treated with intravitreal bevacizumab on as needed regimen, and to analyze baseline risk factors for CNV resolution or recurrence.

METHODS: Ninety-one eyes of 80 patients with newly diagnosed wet AMD were retrospectively studied. All eyes were treated with a round of three monthly intravitreal bevacizumab injections, followed by one additional 'bonus' injection after resolution of CNV activity. During follow-up, eyes were monitored with fluorescein angiography, optical coherence tomography, and best-corrected visual acuity (BCVA). In case of recurrences of CNV activity, eyes were retreated with other rounds of bevacizumab injections following the same treatment protocol.

RESULTS: Over a median follow-up of 532d, the median resolution time of CNV activity in the first, second, and third treatment round was 98d, 126d, and 111d, respectively. The median recurrence time for the three rounds was 154d, 126d, and 151d, respectively. No significant difference in resolution time (P=0.09) or in recurrence time (P=0.11) was detected among treatment rounds. Age (P=0.0082) and lens status (P=0.035) were found to be associated with CNV resolution; for every 1-year increase in age there was 4% greater chance of CNV resolution; Phakic eyes demonstrated a 33% better chance to experience CNV resolution than pseudophakic eyes. For CNV recurrence, lens status (P=0.0009) and gender (P=0.0446) were found to be predictive; pseudophakic eyes had a 3.69-fold greater risk to experience recurrence of CNV activity compared to phakic eyes; males had a 2.19-fold greater risk to experience recurrence of CNV activity than females. No significant BCVA changes among three treatment rounds were noted (P=0.56).

CONCLUSION: Resolution time and recurrence time of CNV activity were not significantly different among treatment rounds, suggesting absence of tachyphylaxis to bevacizumab. A cautious decision should be made upon discontinuing treatment in wet AMD eyes of younger or pseudophakic patients, which showed slower response to bevacizumab. In addition, wet AMD eyes of male or pseudophakic patients should be evaluated more carefully after stopping the treatment, because they may have early reactivation of the CNV. BCVA was preserved by bevacizumab treatment despite multiple recurrences.

PMID: 24195033 [PubMed]

Orv Hetil. 2013 Nov 1;154(45):1790-7. doi: 10.1556/OH.2013.29729.

[Long term intravitreal ranibizumab treatment for exudative age-related macular degeneration]. [Article in Hungarian]

Lukács R, Resch M, Papp A, Szabó A, Borbándy A, Menkens H, Kiss H, Németh J.

Semmelweis Egyetem, Általános Orvostudományi Kar Szemészeti Klinika Budapest Mária u. 39. 1085 Fejér Megyei Szent György Egyetemi Oktató Kórház Székesfehérvár.

Introduction: The results of intravitreal ranibizumab treatment for exudative age-related macular degeneration have been favourable until this time. Aim: To evaluate the two-year functional and anatomic results of intravitreal ranibizumab treatment.

Method: 46 patients (age: 75±9.1 years) were included in a prospective single center study. Treatment regimen was the following: monthly 0.5 mg ranibizumab was administered in the first 3 months, and later as required (pro re nata). The change of best corrected visual acuity and central retinal thickness was followed.

Results: The visus change at the end of the follow-up time was not statistically significant compared to baseline (p = 0.760) and the at the end of the first year (p = 0.154). Central retinal thickness decreased significantly compared to baseline (p = 0.000001), but the change was not statistically significant compared

to the end of the first year (p = 0.875).

Conclusions: Patients with neovascular macular degeneration treated with intravitreal ranibizumab using pro re nata regimen have stable visus for long term, and the exudation could be reduced efficiently. Orv. Hetil., 154(45), 1790-1797.

PMID: 24184931 [PubMed - in process]

Other treatment & diagnosis

Stem Cells Cloning. 2010 Dec 22;4:1-10.

Emerging options for the management of age-related macular degeneration with stem cells.

Mooney I, Lamotte J.

Eye Design, Santa Fe, NM, USA.

Abstract: Age-related macular degeneration (AMD) is a devastating retinal disease that occurs in later life as the retinal pigment epithelium (RPE) cells die, with subsequent photoreceptor degeneration. In the past, RPE transplant surgeries gave evidence that AMD was potentially treatable, but it involved limited amounts of ocular tissue, and the complication rate was high. Then, stem cell transplants offered an unlimited supply of retinal precursors for endogenous repair and exogenous cell replacement. Debate continues as to which type of stem cell is most appropriate for treating AMD. The prospects include adult-derived progenitor stem cells (including progenitor cells from ocular tissues), hematopoietic stem cells, embryonic stem cells, and induced pluripotent stem cells. Now the therapy is expanding into phase I human trials. This review examines the collective research contributions toward a clinical model of AMD management with stem cells.

PMID: 24198525 [PubMed - as supplied by publisher]

J Ophthalmol. 2013;2013:589274. doi: 10.1155/2013/589274. Epub 2013 Sep 26.

The Relationship between Neovascular Age-Related Macular Degeneration and Erectile Dysfunction.

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Department of Ophthalmology, Adnan Menderes University Medical Faculty, Merkez Kampus Kepez Mevkii, Aytepe, 09100 Aydın, Turkey.

Purpose: To evaluate association between erectile dysfunction (ED) and neovascular age-related macular degeneration (AMD).

Methods: 195 men enrolled in this cross-sectional study. 90 of them had neovascular AMD and 105 of them were healthy volunteers. The International Index of Erectile Function (IIEF) questionnaire's erectile function (EF) domain was used to assess ED. The patients in the study and control groups were statistically compared according to visual acuity, EF score, and body mass index.

Results: The mean ages were 62 (54.5-73) and 60 (54-68), in the neovascular AMD and control groups, respectively. The total EF scores were 9 (6-16) in neovascular AMD and 18 (9.5-27) in control group. The results of IIEF questionnaire on neovascular AMD patients revealed that 85 men (94.4%) had some degree of ED, whereas 68 men (64.8%) had some degree of ED on control group. Patients with neovascular AMD had a significantly higher incidence of ED than control patients (P < 0.01). There was a significant association between ED and neovascular AMD (P < 0.01).

Conclusions: Our results suggested that neovascular AMD has a high association with ED.

PMID: 24191192 [PubMed] PMCID: PMC3804368

Pathogenesis

Ophthalmology. 2013 Oct 30. pii: S0161-6420(13)00846-4. doi: 10.1016/j.ophtha.2013.09.026. [Epub ahead of print]

Assessing the Cone Photoreceptor Mosaic in Eyes with Pseudodrusen and Soft Drusen In Vivo Using Adaptive Optics Imaging.

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PURPOSE: To investigate the cone photoreceptor mosaic in eyes with pseudodrusen as evidenced by the presence of subretinal drusenoid deposits (SDD) and conventional drusen using adaptive optics (AO) imaging integrated into a multimodal imaging approach.

DESIGN: Observational case series.

PARTICIPANTS: Eleven patients (11 eyes) with pseudodrusen and 6 patients (11 eyes) with conventional drusen.

METHODS: Consecutive patients were examined using near-infrared reflectance (IR) confocal scanning laser ophthalmoscopy (SLO) and eye-tracked spectral-domain optical coherence tomography (SD-OCT) and flood-illuminated retinal AO camera of nonconfluent pseudodrusen or conventional drusen. Correlations were made between the IR-SLO, SD-OCT, and AO images. Cone density analysis was performed on AO images within 50 × 50-μm windows in 5 regions of interest overlying and in 5 located between SDD or conventional drusen with the same retinal eccentricity.

MAIN OUTCOME MEASURES: Cone densities in the regions of interest.

RESULTS: The pseudodrusen correlated with subretinal accumulations of material in SD-OCT imaging and this was confirmed in the AO images. Defects in the overlying ellipsoid zone band as seen by SD-OCT were associated with SDD but not conventional drusen. The mean ± standard deviation cone density was 8964±2793 cones/mm² between the SDD and 863±388 cones/mm² over the SDD, a 90.4% numerical reduction. By comparison the mean cone packing density was 9838±3723 cones/mm² on conventional drusen and 12 595±3323) cones/mm² between them, a 21.9% numerical reduction. The difference in cone density reduction between the two lesion types was highly significant ($P < 0.001$).

CONCLUSIONS: The pseudodrusen in these eyes correlated with subretinal deposition of material in multiple imaging modalities. Reduced visibility of cones overlying SDD in the AO images can be because of several possible causes, including a change in their orientation, an alteration of their cellular architecture, or absence of the cones themselves. All of these explanations imply that decreased cone photoreceptor function is possible, suggesting that eyes with pseudodrusen appearance may experience decreased retinal function in age-related macular degeneration independent of choroidal neovascularization or retinal pigment epithelial atrophy.

PMID: 24183341 [PubMed - as supplied by publisher]

Proc Natl Acad Sci U S A. 2013 Nov 4. [Epub ahead of print]

CNTF-mediated protection of photoreceptors requires initial activation of the cytokine receptor gp130 in Muller glial cells.

Rhee KD, Nusinowitz S, Chao K, Yu F, Bok D, Yang XJ.

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Abstract: Ciliary neurotrophic factor (CNTF) acts as a potent neuroprotective agent in multiple retinal degeneration animal models. Recently, CNTF has been evaluated in clinical trials for the inherited degenerative disease retinitis pigmentosa (RP) and for dry age-related macular degeneration (AMD). Despite its potential as a broad-spectrum therapeutic treatment for blinding diseases, the target cells of exogenous CNTF and its mechanism of action remain poorly understood. We have shown previously that constitutive expression of CNTF prevents photoreceptor death but alters the retinal transcriptome and suppresses visual function. Here, we use a lentivirus to deliver the same secreted human CNTF used in clinical trials to a mouse model of RP. We found that low levels of CNTF halt photoreceptor death, improve photoreceptor morphology, and correct opsin mislocalization. However, we did not detect corresponding improvement of retinal function as measured by the electroretinogram. Disruption of the cytokine receptor gp130 gene in Müller glia reduces CNTF-dependent photoreceptor survival and prevents phosphorylation of STAT3 and ERK in Müller glia and the rest of the retina. Targeted deletion of gp130 in rods also demolishes neuroprotection by CNTF and prevents further activation of Müller glia. Moreover, CNTF elevates the expression of LIF and endothelin 2, thus positively promoting Müller and photoreceptor interactions. We propose that exogenous CNTF initially targets Müller glia, and subsequently induces cytokines acting through gp130 in photoreceptors to promote neuronal survival. These results elucidate a cellular mechanism for exogenous CNTF-triggered neuroprotection and provide insight into the complex cellular responses induced by CNTF in diseased retinas.

PMID: 24191003 [PubMed - as supplied by publisher]

Hum Gene Ther Methods. 2013 Nov 5. [Epub ahead of print]

Laser Photocoagulation Enhances Adeno-Associated Virus Vector Transduction of Mouse Retina.

Lee SH, Colosi P, Lee H, Ohn YH, Kim SW, Kwak HW, Park TK.

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Abstract: Laser photocoagulation is a well-established treatment modality for retinal disease. Discrete laser burns can be placed anywhere in the retina, singly or multiply, and the burn intensity is controllable. This study investigates the effect of prior laser photocoagulation on the retinal transduction properties of intravitreally administered adeno-associated virus (AAV) vectors. C57BL/6J mice were subjected to unilateral laser photocoagulation 48 hours prior to bilateral intravitreal injection of self-complementary CMV EGFP vectors packaged in AAV type 2, 5 and 8 capsids. The eyes were enucleated 4 weeks after injection and examined by histochemistry and quantitative image analysis. Laser pretreatment resulted in substantially increased localized transduction around the burn site for all AAV capsid types. Without laser pretreatment, the vectors transduced only ganglion cells (AAV2) or sporadic cells around the optic nerve head (AAV5 and 8). Laser pretreatment increased AAV2 vector expression throughout the entire retina and focally at the burn site. Transduced cells at the burn site included retinal pigment epithelium (RPE), photoreceptors, Müller cells, inner nuclear layer cells, and retinal ganglion cells. The AAV5 vector showed increased RPE transduction at the burn site only. The AAV8 vector showed augmented expression in RPE, photoreceptors and Müller cells around the burn site. Migrating RPE cells, present in the neural retina near the burn site, were also transduced by all three capsid types as evidenced by colocalization of enhanced

green fluorescent protein (EGFP) and cytokeratin. Laser photocoagulation can be used to precisely direct AAV vector transduction to discrete locations in the retina. A combination of laser and AAV mediated gene expression may allow the development of improved therapies for diabetic retinopathy, branch and central vein occlusion, and age-related macular degeneration.

PMID: 24191872 [PubMed - as supplied by publisher]

Epidemiology

Orv Hetil. 2013 Nov 1;154(45):1773-80. doi: 10.1556/OH.2013.29720.

[Hypertension-related eye abnormalities].[Article in Hungarian]

Resch M, Süveges I, Németh J.

Semmelweis Egyetem, Általános Orvostudományi Kar Szemészeti Klinika Budapest Mária u. 39. 1085.

Abstract: Hypertension affects a significant proportion of the population, however, it is often diagnosed with a delay. The aim of this article is to review the well known and less known eye abnormalities related to hypertension, and place them in the context of population based studies. Hypertension affects various parts of the eye. The originally classified hypertensive retinopathy (retinal microvascular changes) is still relevant, but new features are visible in cases of controlled hypertension. Signs of mild hypertensive retinopathy are more common than expected occurring in nearly 10-15% of the adult non-diabetic population. Hypertensive retinopathy can be an indicator of other hypertensive complications such as neurologic and cardiac complications. Microvascular changes are reversible in well controlled hypertension. Proper treatment of hypertension can reduce the development and progression of diabetic retinopathy and, thus, visual loss due to severe retinal diseases such as retinal vascular occlusion (artery and vein), retinal arteriolar emboli, macroaneurysm, ischemic optic neuropathy and age-related macular degeneration.Orv. Hetil., 154(45), 1773-1780.

PMID: 24184929 [PubMed - in process]

Genetics

Oxid Med Cell Longev. 2013;2013:413024. doi: 10.1155/2013/413024. Epub 2013 Sep 25.

Sulforaphane Enhances the Ability of Human Retinal Pigment Epithelial Cell against Oxidative Stress, and Its Effect on Gene Expression Profile Evaluated by Microarray Analysis.

Ye L, Yu T, Li Y, Chen B, Zhang J, Wen Z, Zhang B, Zhou X, Li X, Li F, Cao W, Huang Z.

Institute of Biotherapy, Shenzhen University School of Medicine, Nanhai Ave 3688, Shenzhen, Guangdong 518060, China.

Abstract: To gain further insights into the molecular basis of Sulforaphane (SF) mediated retinal pigment epithelial (RPE) 19 cell against oxidative stress, we investigated the effects of SF on the regulation of gene expression on a global scale and tested whether SF can endow RPE cells with the ability to resist apoptosis. The data revealed that after exposure to H2O2, RPE 19 cell viability was increased in the cells pretreated with SF compared to the cell not treated with SF. Microarray analysis revealed significant changes in the expression of 69 genes in RPE 19 cells after 6 hours of SF treatment. Based on the functional relevance, eight of the SF-responsive genes, that belong to antioxidant redox system, and inflammatory responsive factors were validated. The up-regulating translation of thioredoxin-1 (Trx1) and the nuclear translocation of Nuclear factor-like2 (Nrf2) were demonstrated by immunoblot analysis in SF treated RPE cells. Our data indicate that SF increases the ability of RPE 19 cell against oxidative stress

through up-regulating antioxidative enzymes and down-regulating inflammatory mediators and chemokines. The results suggest that the antioxidant, SF, may be a valuable supplement for preventing and retarding the development of Age Related Macular Degeneration.

PMID: 24187606 [PubMed - in process] PMCID: PMC3800669

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