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MD Research News

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Drug treatment

Macromol Biosci. 2013 Jan 11. doi: 10.1002/mabi.201200384. [Epub ahead of print]

An Anti-angiogenic Reverse Thermal Gel as a Drug-Delivery System for Age-Related Wet Macular Degeneration.

Park D, Shah V, Rauck BM, Friberg TR, Wang Y.

Department of Bioengineering, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado 80045, USA.

Abstract: Reverse thermal gels have numerous biomedical implications, as they undergo physical gelation upon temperature increases and can incorporate biomolecules to promote tissue repair. Such a material is developed for the sustained release of bevacizumab (Avastin), a drug used to treat age-related macular degeneration. The polymer, poly(ethylene glycol)-poly(serinol hexamethylene urethane) (ESHU), forms a physical gel when heated to 37 °C and shows good cytocompatibility with ocular cells. ESHU is capable of sustaining bevacizumab release over 17 weeks in vitro, and the release kinetics can be altered by changing the drug dose and the ESHU concentration. These results suggest that ESHU is biologically safe, and suitable for ocular drug delivery.

PMID: 23316011 [PubMed - as supplied by publisher]

BMC Pharmacol Toxicol. 2013 Jan 14;14(1):7. [Epub ahead of print]

Vascular disrupting agent for neovascular age related macular degeneration: a pilot study of the safety and efficacy of intravenous combretastatin a-4 phosphate.

Ibrahim MA, Do DV, Sepah YJ, Shah SM, Van Anden E, Hafiz G, Donahue JK, Rivers R, Balkissoon J, Handa JT, Campochiaro PA, Nguyen QD.

BACKGROUND: This study was designed to assess the safety, tolerability, and efficacy of intravenous infusion of CA4P in patients with neovascular age-related macular degeneration (AMD).

METHODS: Prospective, interventional, dose-escalation clinical trial. Eight patients with neovascular AMD refractory to at least 2 sessions of photodynamic therapy received CA4P at a dose of 27 or 36 mg/m2 as weekly intravenous infusion for 4 consecutive weeks. Safety was monitored by vital signs, ocular and physical examinations, electrocardiogram, routine laboratory tests, and collection of adverse events. Efficacy was assessed using retinal fluorescein angiography, optical coherence tomography, and best

corrected visual acuity (BCVA).

RESULTS: The most common adverse events were elevated blood pressure (46.7%), QTc prolongation (23.3%), elevated temperature (13.3%), and headache (10%), followed by nausea and eye injection (6.7%). There were no adverse events that were considered severe in intensity and none resulted in discontinuation of treatment. There was reduction of the excess foveal thickness by 24.15% at end of treatment period and by 43.75% at end of the two-month follow-up (p = 0.674 and 0.161, respectively). BCVA remained stable throughout the treatment and follow-up periods.

CONCLUSIONS: The safety profile of intravenous CA4P was consistent with that reported in oncology trials of CA4P and with the class effects of vascular disruptive agents; however, the frequency of adverse events was different. There are evidences to suggest potential efficacy of CA4P in neovascular AMD. However, the level of systemic safety and efficacy indicates that systemic CA4P may not be suitable as an alternative monotherapy to current standard-of-care therapyTrial registration: ClinicalTrials.gov NCT01570790.

PMID: 23316779 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Jan 16. [Epub ahead of print]

A retrospective evaluation of the effect of hydroxyquinine on RPE thickness.

Pikkel J, Chassid O, Sharabi-Nov A, Beiran I.

Department of Ophthalmology, Ziv Medical Center, Safed, Israel.

BACKGROUND: To investigate a possible structural difference in the retina of hydroxychloroquine (Plaquenil)-treated patients as an explanation for the protective effect of this medication against age-related macular degeneration (AMD).

METHODS: In this retrospective study, we compared the mean thickness of the retinal outer band (consisting of the Bruch's membrane and retinal pigment epithelium layer), as measured by optical coherence tomography (OCT), of 54 eyes of 27 hydroxychloroquine-treated rheumatoid arthritis patients (study group), 40 eyes of 20 healthy similar aged individuals (control group I), and 22 eyes of 11 non-hydroxychloroquine-treated rheumatoid arthritis patients (control group II).

RESULTS: The mean thicknesses of the outer band of the retinal pigment epithelium layer was 60.4 ± 7.4, 43.3 ± 2.7, and 39.7 ± 3.6 μm for the study group, control group I, and control group II, respectively. P values for differences in mean thicknesses were < 0.0001 between the study group and each of the control groups, and 0.086 between the two control groups.

CONCLUSION: Treatment with hydroxychloroquine was associated with increased thickness of the outer band of the retinal pigment epithelium layer. This finding may explain the protective effect of hydroxychloroquine against age-related macular degeneration (AMD).

PMID: 23322085 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Int J Telemed Appl. 2012;2012:806464. doi: 10.1155/2012/806464. Epub 2012 Dec 19.

Fundus autofluorescence imaging in an ocular screening program.

Kolomeyer AM, Nayak NV, Szirth BC, Khouri AS.

The Institute of Ophthalmology and Visual Science, University of Medicine and Dentistry of New Jersey,

Newark, NJ 07101, USA.

Purpose: To describe integration of fundus autofluorescence (FAF) imaging into an ocular screening program.

Methods: Fifty consecutive screening participants were included in this prospective pilot imaging study. Color and FAF (530/640 nm exciter/barrier filters) images were obtained with a 15.1MP Canon nonmydriatic hybrid camera. A clinician evaluated the images on site to determine need for referral. Visual acuity (VA), intraocular pressure (IOP), and ocular pathology detected by color fundus and FAF imaging modalities were recorded.

Results: Mean ± SD age was 47.4 ± 17.3 years. Fifty-two percent were female and 58% African American. Twenty-seven percent had a comprehensive ocular examination within the past year. Mean VA was 20/39 in the right eye and 20/40 in the left eye. Mean IOP was 15 mmHg bilaterally. Positive color and/or FAF findings were identified in nine (18%) individuals with diabetic retinopathy or macular edema (n = 4), focal RPE defects (n = 2), age-related macular degeneration (n = 1), central serous retinopathy (n = 1), and ocular trauma (n = 1).

Conclusions: FAF was successfully integrated in our ocular screening program and aided in the identification of ocular pathology. Larger studies examining the utility of this technology in screening programs may be warranted.

PMID: 23316224 [PubMed] PMCID: PMC3536047

IEEE Trans Biomed Eng. 2013 Jan 9. [Epub ahead of print]

Segmentation of Choroidal Neovascularization in Fundus Fluorescein Angiograms.

Abdelmoula W, Shah S, Fahmy A.

Abstract: Choroidal neovascularization (CNV) is a common manifestation of age-related macular degeneration (AMD). It is characterized by the growth of abnormal blood vessels in the chroidal layer causing blurring and deterioration of the vision. In late stages, these abnormal vessels can rupture the retinal layers causing complete loss of vision at the affected regions. Determining the CNV size and type in fluorescein angiograms is required for proper treatment and prognosis of the disease. Computer aided methods for CNV segmentation is needed not only to reduce the burden of manual segmentation but also to reduce inter- and intra- observer variability. In this work, we present a framework for segmenting CNV lesions based on parametric modeling of the intensity variation in fundus fluorescein angiograms. First, a novel model is proposed to describe the temporal intensity variation at each pixel in image sequences of acquired by fluorescein angiography. The set of model parameters at each pixel are used to segment the image into regions of homogeneous parameters. Preliminary results on datasets from 21 patients with Wet-AMD show the potential of the method to segment CNV lesions in close agreement with the manual segmentation.

PMID: 23314765 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2013 Jan 14. [Epub ahead of print]

Segmentation error and macular thickness measurements obtained with spectral-domain optical coherence tomography devices in neovascular age-related macular degeneration.

Moosang K, Jun LS, Jisang H, Seung-Young Y, Hyung-Woo K.

Department of Ophthalmology, Kyung Hee University Hospital, Seoul, Korea.

Purpose: To evaluate frequency and severity of segmentation errors of two spectral-domain optical coherence tomography (SD-OCT) devices and error effect on central macular thickness (CMT) measurements.

Materials and Methods: Twenty-seven eyes of 25 patients with neovascular age-related macular degeneration, examined using the Cirrus HD-OCT and Spectralis HRA + OCT, were retrospectively reviewed. Macular cube 512 × 128 and 5-line raster scans were performed with the Cirrus and 512 × 25 volume scans with the Spectralis. Frequency and severity of segmentation errors were compared between scans.

Results: Segmentation error frequency was 47.4% (baseline), 40.7% (1 month), 40.7% (2 months), and 48.1% (6 months) for the Cirrus, and 59.3%, 62.2%, 57.8%, and 63.7%, respectively, for the Spectralis, differing significantly between devices at all examinations ($P < 0.05$), except at baseline. Average error score was 1.21 ± 1.65 (baseline), 0.79 ± 1.18 (1 month), 0.74 ± 1.12 (2 months), and 0.96 ± 1.11 (6 months) for the Cirrus, and 1.73 ± 1.50, 1.54 ± 1.35, 1.38 ± 1.40, and 1.49 ± 1.30, respectively, for the Spectralis, differing significantly at 1 month and 2 months ($P < 0.02$). Automated and manual CMT measurements by the Spectralis were larger than those by the Cirrus.

Conclusions: The Cirrus HD-OCT had a lower frequency and severity of segmentation error than the Spectralis HRA + OCT. SD-OCT error should be considered when evaluating retinal thickness.

PMID: 23314254 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Jan 11. pii: S0002-9394(12)00784-2. doi: 10.1016/j.ajo.2012.11.001. [Epub ahead of print]

Thinner Choroid and Greater Drusen Extent in Retinal Angiomatous Proliferation Than in Typical Exudative Age-Related Macular Degeneration.

Kim JH, Kim JR, Kang SW, Kim SJ, Ha HS.

Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

PURPOSE: To compare choroidal thickness and extent and density of drusen between eyes with typical exudative age-related macular degeneration (AMD) and eyes with retinal angiomatous proliferation (RAP).

DESIGN: Observational case series.

METHODS: Twenty-four eyes with typical exudative AMD and 20 eyes with RAP were included. Subfoveal choroidal thickness was measured using enhanced depth imaging optical coherence tomography. Eyes were classified into 3 groups according to the extent of drusen distribution in the fundus photograph. Density of drusen was estimated based on optical coherence tomography images of the fellow eye. The proportion of the length beneath the drusen per the entire length of the Bruch membrane was defined as the density of drusen. Subfoveal choroidal thickness, extent of drusen distribution, and the density of drusen were compared between typical exudative AMD and RAP.

RESULTS: Mean ± standard deviation subfoveal choroidal thickness in eyes with typical exudative AMD and eyes with RAP was 184.9 ± 68.5 μm and 139.0 ± 65.5 μm, respectively ($P = .035$). The mean density of drusen was 0.06 ± 0.08 and 0.24 ± 0.12, respectively ($P < .001$). In the typical exudative AMD group, 19, 3, and 2 eyes were included in the small extent group (<one third), intermediate extent group (one third to two thirds), and large extent group (>two thirds), respectively. In the RAP group, 3, 14, and 3 eyes were included in each aforementioned group, respectively ($P = .001$).

CONCLUSIONS: The thinner subfoveal choroidal thickness and greater extent and density of drusen in RAP than the typical exudative AMD may suggest compromised choroidal perfusion in the development of

RAP.

PMID: 23317655 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2013 Jan 11. pii: S0002-9394(12)00786-6. doi: 10.1016/j.ajo.2012.11.003. [Epub ahead of print]

Predictive Value of Spectral-Domain Optical Coherence Tomography Features in Assessment of Visual Prognosis in Eyes With Neovascular Age-Related Macular Degeneration Treated with Ranibizumab.

Mathew R, Richardson M, Sivaprasad S.

Laser and Retinal Research Unit, Department of Ophthalmology, King's College Hospital, London, United Kingdom. Electronic address: r_mathew@hotmail.com.

PURPOSE: To determine whether pretreatment (baseline) optical coherence tomography (OCT) features can be used as predictors of visual acuity outcome at 12 months in eyes with neovascular age-related macular degeneration treated with intravitreal ranibizumab and to assess whether baseline OCT features can predict a change in visual acuity from baseline to 12 months.

DESIGN: Retrospective, observational study.

METHODS: We retrospectively evaluated the serial cross-sectional images of the macula obtained using the Spectralis OCT (HRA+OCT; Heidelberg Engineering) in 100 eyes of 94 patients attending a single center and undergoing treatment with intravitreal ranibizumab for neovascular age-related macular degeneration. The baseline OCT characteristics and visual acuity were correlated to the final visual acuity (Early Treatment Diabetic Retinopathy Study letters) and change in visual acuity after 12 months of monitoring and treatment. Univariate and multivariate analyses were carried out to correlate these morphologic features with the final visual acuity and the change in visual acuity.

RESULTS: Intact ellipsoid zone (P = .0001) and external limiting membrane in the subfoveal area (P < .0001) at baseline were the only 2 independent good prognostic indicators of final visual acuity at 12 months. However, none of the morphologic features at baseline could predict the change in visual acuity by 12 months.

CONCLUSIONS: The results suggest that integrity of the outer retinal layers at baseline is crucial for determining final visual acuity at 12 months in eyes undergoing treatment with ranibizumab for neovascular age-related macular degeneration.

PMID: 23317653 [PubMed - as supplied by publisher]

Ophthalmologe. 2013 Jan;110(1):68-74. doi: 10.1007/s00347-012-2749-y.

[Effects of transcorneal electrical stimulation in patients with Stargardt's disease].[Article in German]

Röck T, Schatz A, Naycheva L, Gosheva M, Pach J, Wilhelm B, Peters T, Bartz-Schmidt KU, Zrenner E, Willmann G, Gekeler F.

Universitäts-Augenklinik, Schleichstr. 12-16, 72076, Tübingen, Deutschland.

Abstract: Stargardt's disease is an autosomal recessive inherited juvenile macular degeneration and at present no acknowledged science-based therapy is available for these patients. Recently, reports have been published on the effectiveness of electrical stimulation in experimental animal models and in patients

with neurodegenerative ocular disease, particularly retinitis pigmentosa. This study included 12 patients with Stargardt's disease who were randomized into one of three groups (n = 4) with 0% (sham), 66% or 150% of the individual electrically stimulated phosphene threshold. Outcome measures of the study were safety and efficacy of transcorneal electrical stimulation (TES) with DTL electrodes in subjective and objective parameters of visual function under therapy. In general TES was well tolerated and no adverse or serious events were noted. Neither Ganzfeld, multifocal ERG, OCT nor visual field testing showed statistically significant changes in any group.

PMID: 23329121 [PubMed - in process]

Pathogenesis

Retina. 2013 Jan 9. [Epub ahead of print]

ROLE OF STATINS IN THE DEVELOPMENT AND PROGRESSION OF AGE-RELATED MACULAR DEGENERATION.

Vanderbeek BL, Zacks DN, Talwar N, Nan B, Stein JD.

*Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan †Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan.

PURPOSE: To determine if statins are associated with the development or progression of age-related macular degeneration (AMD).

METHODS: A large, national insurance claims database was reviewed to identify individuals aged 60 years or older who were enrolled for ≥2 years and had ≥1 visits to an eye provider. Prescription claims for statins within a 24-month look-back period and outpatient lipid laboratory values were also reviewed. Cox regression analysis was used to determine whether statin use was associated with the development of nonexudative or exudative AMD or progressing from nonexudative to exudative AMD.

RESULTS: Of the 107,007 beneficiaries eligible for the nonexudative AMD analysis, 4,647 incident cases of nonexudative AMD occurred. Seven hundred and ninety-two incident cases of exudative AMD were found among the 113,111 beneficiaries eligible for the exudative AMD analysis. Of the 10,743 beneficiaries with known nonexudative AMD eligible for the progression model, 404 progressed to exudative AMD during their time in the plan. After multivariable analysis, statin use was not associated with the development of nonexudative AMD ($P > 0.05$). Statin use of >12 months was associated with an increased hazard for developing exudative AMD ($P < 0.005$). Among those taking statins, only enrollees with the highest lipid levels had an increased hazard of developing exudative AMD ($P < 0.05$).

CONCLUSION: In those with elevated lipid levels, >1 year of statin use was associated with an increased hazard for exudative AMD. Lipid status influences the relationship between statins and the risk of AMD. Because of a number of limitations in study design, these observations warrant further study and should not be the rationale for any changes in the use of statins to treat dyslipidemias.

PMID: 23314233 [PubMed - as supplied by publisher]

J Control Release. 2013 Jan 10. pii: S0168-3659(13)00019-9. doi: 10.1016/j.jconrel.2013.01.004. [Epub ahead of print]

Specific uptake of folate-decorated triamcinolone-encapsulating nanoparticles by retinal pigment epithelium cells enhances and prolongs antiangiogenic activity.

Suen WL, Chau Y.

Department of Chemical and Biomolecular Engineering, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, China.

Abstract: We are proposing folate-decorated polymeric nanoparticles as carriers of poorly soluble drug molecules for intracellular and prolonged delivery to retinal pigment epithelium (RPE) cells. RPE is a monolayer of epithelial cells that forms the outer blood-retinal barrier in the posterior segment of the eye, and is also implicated in the pathology of, such as neovascularization in age-related macular degeneration (AMD). In this study, folate-functionalized poly(ethylene glycol)-b-polycaprolactone (folate-PEG-b-PCL) were synthesized for assembling into nanoparticles of ~ 130 nm. These nanoparticles were internalized into ARPE-19 (human RPE cell line) via receptor-mediated endocytosis, and the cellular uptake was significantly higher than particles without folate modification. Triamcinolone acetonide (TA) was efficiently encapsulated (>97%) into the folate-decorated nanoparticles and was slowly released over a period of 4 weeks at pH 5.5 and 8 weeks at pH 7.4. The enhanced uptake and controlled release resulted in prolonged anti-angiogenic gene expression of RPE cells. In cell culture, the down-regulation of vascular endothelial growth factor (VEGF) and up-regulation of pigment epithelium derived factor (PEDF) lasted for at least 3 weeks. Unlike benzyl alcohol, the surfactant found in commercial formulation, folate-modified nanoparticles were non-toxic. Furthermore, TA became less cytotoxic by being encapsulated in the nanoparticles. Our findings suggest that folate-PEG-PCL nanoparticles are promising drug carriers for RPE targeting.

PMID: 23313961 [PubMed - as supplied by publisher]

Am J Pathol. 2013 Jan 9. pii: S0002-9440(12)00897-8. doi: 10.1016/j.ajpath.2012.11.031. [Epub ahead of print]

Interferon γ-Dependent Migration of Microglial Cells in the Retina after Systemic Cytomegalovirus Infection.

Zinkernagel MS, Chinnery HR, Ong ML, Petitjean C, Voigt V, McLenachan S, McMenamin PG, Hill GR, Forrester JV, Wikstrom ME, Degli-Esposti MA.

Ocular Immunology, Centre for Ophthalmology and Visual Science, The University of Western Australia, Perth, Australia; Department of Ophthalmology, Sir Charles Gairdner Hospital, Perth, Australia.

Abstract: Microglial cells are the resident macrophages of the central nervous system and participate in both innate and adaptive immune responses but can also lead to exacerbation of neurodegenerative pathologies after viral infections. Microglia in the outer layers of the retina and the subretinal space are thought to be involved in retinal diseases where low-grade chronic inflammation and oxidative stress play a role. This study investigated the effect of systemic infection with murine cytomegalovirus on the distribution and dynamics of retinal microglia cells. Systemic infection with murine cytomegalovirus elicited a significant increase in the number of microglia in the subretinal space and an accumulation of iris macrophages, along with morphological signs of activation. Interferon γ (IFN-γ)-deficient mice failed to induce changes in microglia distribution. Bone marrow chimera experiments confirmed that microglial cells in the subretinal space were not recruited from the circulating monocyte pool, but rather represented an accumulation of resident microglial cells from within the retina. Our results demonstrate that a systemic viral infection can lead to IFN-γ-mediated accumulation of microglia into the outer retinal layers and offer proof of concept that systemic viral infections alter the ocular microenvironment and therefore, may influence the course of diseases such as macular degeneration, diabetic retinopathy, or autoimmune uveitis, where low-grade inflammation is implicated.

PMID: 23313136 [PubMed - as supplied by publisher]

J Ocul Biol Dis Infor. 2010 Dec;3(4):144-60. doi: 10.1007/s12177-011-9076-4. Epub 2012 Jan 12.

RPE-secreted factors: influence differentiation in human retinal cell line in dose- and density-dependent manner.

Dutt K, Douglas P, Cao Y.

Morehouse School of Medicine, Atlanta, GA 30310 USA ; Department of Pathology, Morehouse School of Medicine, Atlanta, GA 30310 USA.

Abstract: Retinal pigment epithelial (RPE) cells play an important role in normal functioning of retina and photoreceptors, and some retinal degenerations arise due to malfunctioning RPE. Retinal pigment epithelium transplantation is being explored as a strategy to rescue degenerating photoreceptors in diseases such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). Additionally, RPE-secreted factors could rescue degenerating photoreceptors by prolonging survival or by their ability to differentiate and give rise to photoreceptors by transdifferentiation. In this study, we have explored what role cell density could play in differentiation induced in a human retinal progenitor cell line, in response to RPE-secreted growth factors. Retinal progenitors plated at low (1 × 10(4) cells/cm(2)), medium (2-4 × 10(4) cells/cm(2)), and high (1 × 10(5) cells/cm(2)) cell density were exposed to various dilutions of RPE-conditioned medium (secreted factors) under conditions of defined medium culture. Progenitor cell differentiation was monitored phenotypically (morphological, biochemical analysis, and immunophenotyping, and western blot analysis were performed). Our data show that differentiation in response to RPE-secreted factors is modulated by cell density and dilutions of conditioned medium. We conclude that before embarking on RPE transplantation as a modality for treatment of RP and AMD, one will have to determine the role that cell density and inhibitory and stimulatory neurotrophins secreted by RPE could play in the efficacy of survival of transplants. We report that RPE-conditioned medium enhances neuronal phenotype (photoreceptors, bipolars) at the lowest cell density in the absence of cell-cell contact. Eighty percent to 90% of progenitor cells differentiate into photoreceptors and bipolars at 50% concentration of conditioned medium, while exposure to 100% conditioned medium might increase multipolar neurons (ganglionic and amacrine phenotypes) to a small degree. However, no clear-cut pattern of differentiation in response to RPE-secreted factors is noted at higher cell densities.

PMID: 23316262 [PubMed]

J Immunol. 2013 Jan 14. [Epub ahead of print]

IL-23-Independent Induction of IL-17 from γδT Cells and Innate Lymphoid Cells Promotes Experimental Intraocular Neovascularization.

Hasegawa E, Sonoda KH, Shichita T, Morita R, Sekiya T, Kimura A, Oshima Y, Takeda A, Yoshimura T, Yoshida S, Ishibashi T, Yoshimura A.

Department of Microbiology and Immunology, Keio University School of Medicine, Shinjuku-ku, Tokyo 160-8582, Japan;

Abstract: Choroidal neovascularization (CNV) is a characteristic of age-related macular degeneration. Genome-wide association studies have provided evidence that the immune system is involved in the pathogenesis of age-related macular degeneration; however, the role of inflammatory cytokines in CNV has not been established. In this study, we demonstrated that IL-17 had a strong potential for promoting neovascularization in a vascular endothelial growth factor-independent manner in laser-induced experimental CNV in mice. Infiltrated γδT cells and Thy-1(+) innate lymphoid cells, but not Th17 cells, were the main sources of IL-17 in injured eyes. IL-23 was dispensable for IL-17 induction in the eye. Instead, we found that IL-1β and high-mobility group box 1 strongly promoted IL-17 expression by γδT cells. Suppression of IL-1β and high-mobility group box 1, as well as depletion of γδT cells, reduced IL-17 levels and ameliorated experimental CNV. Our findings suggest the existence of a novel inflammatory cytokine

network that promotes neovascularization in the eye.

PMID: 23319736 [PubMed - as supplied by publisher]

J Mol Med (Berl). 2013 Jan 18. [Epub ahead of print]

Ocular neovascularization.

Campochiaro PA.

Departments of Ophthalmology and Neuroscience, Johns Hopkins University School of Medicine, Maumenee 719, 600 N. Wolfe Street, Baltimore, 21287-9277, MD, USA, pcampo@jhmi.edu.

Abstract: Retinal and choroidal vascular diseases constitute the most common causes of moderate and severe vision loss in developed countries. They can be divided into retinal vascular diseases, in which there is leakage and/or neovascularization (NV) from retinal vessels, and subretinal NV, in which new vessels grow into the normally avascular outer retina and subretinal space. The first category of diseases includes diabetic retinopathy, retinal vein occlusions, and retinopathy of prematurity, and the second category includes neovascular age-related macular degeneration (AMD), ocular histoplasmosis, pathologic myopia, and other related diseases. Retinal hypoxia is a key feature of the first category of diseases resulting in elevated levels of hypoxia-inducible factor-1 (HIF-1) which stimulates expression of vascular endothelial growth factor (VEGF), platelet-derived growth factor-B (PDGF-B), placental growth factor, stromal-derived growth factor-1 and their receptors, as well as other hypoxia-regulated gene products such as angiopoietin-2. Although hypoxia has not been demonstrated as part of the second category of diseases, HIF-1 is elevated and thus the same group of hypoxia-regulated gene products plays a role. Clinical trials have shown that VEGF antagonists provide major benefits for patients with subretinal NV due to AMD and even greater benefits are seen by combining antagonists of VEGF and PDGF-B. It is likely that addition of antagonists of other agents listed above will be tested in the future. Other appealing strategies are to directly target HIF-1 or to use gene transfer to express endogenous or engineered anti-angiogenic proteins. While substantial progress has been made, the future looks even brighter for patients with retinal and choroidal vascular diseases.

PMID: 23329331

[PubMed - as supplied by publisher]

Genetics

PLoS One. 2013;8(1):e53830. doi: 10.1371/journal.pone.0053830. Epub 2013 Jan 11.

Insights into the genetic architecture of early stage age-related macular degeneration: a genome-wide association study meta-analysis.

Holliday EG, Smith AV, Cornes BK, Buitendijk GH, Jensen RA, Sim X, Aspelund T, Aung T, Baird PN, Boerwinkle E, Cheng CY, van Duijn CM, Eiriksdottir G, Gudnason V, Harris T, Hewitt AW, Inouye M, Jonasson F, Klein BE, Launer L, Li X, Liew G, Lumley T, McElduff P, McKnight B, Mitchell P, Psaty BM, Rochtchina E, Rotter JI, Scott RJ, Tay W, Taylor K, Teo YY, Uitterlinden AG, Viswanathan A, Xie S; Wellcome Trust Case Control Consortium 2, Vingerling JR, Klaver CC, Tai ES, Siscovick D, Klein R, Cotch MF, Wong TY, Attia J, Wang JJ.

Centre for Clinical Epidemiology and Biostatistics, and School of Medicine and Public Health, University of Newcastle, Newcastle, New South Wales, Australia.

Abstract: Genetic factors explain a majority of risk variance for age-related macular degeneration (AMD).

While genome-wide association studies (GWAS) for late AMD implicate genes in complement, inflammatory and lipid pathways, the genetic architecture of early AMD has been relatively under studied. We conducted a GWAS meta-analysis of early AMD, including 4,089 individuals with prevalent signs of early AMD (soft drusen and/or retinal pigment epithelial changes) and 20,453 individuals without these signs. For various published late AMD risk loci, we also compared effect sizes between early and late AMD using an additional 484 individuals with prevalent late AMD. GWAS meta-analysis confirmed previously reported association of variants at the complement factor H (CFH) (peak P=1.5×10(-31)) and age-related maculopathy susceptibility 2 (ARMS2) (P=4.3×10(-24)) loci, and suggested Apolipoprotein E (ApoE) polymorphisms (rs2075650; P=1.1×10(-6)) associated with early AMD. Other possible loci that did not reach GWAS significance included variants in the zinc finger protein gene GLI3 (rs2049622; P=8.9×10(-6)) and upstream of GLI2 (rs6721654; P=6.5×10(-6)), encoding retinal Sonic hedgehog signalling regulators, and in the tyrosinase (TYR) gene (rs621313; P=3.5×10(-6)), involved in melanin biosynthesis. For a range of published, late AMD risk loci, estimated effect sizes were significantly lower for early than late AMD. This study confirms the involvement of multiple established AMD risk variants in early AMD, but suggests weaker genetic effects on the risk of early AMD relative to late AMD. Several biological processes were suggested to be potentially specific for early AMD, including pathways regulating RPE cell melanin content and signalling pathways potentially involved in retinal regeneration, generating hypotheses for further investigation.

PMID: 23326517 [PubMed - in process]

PLoS One. 2013;8(1):e53665. doi: 10.1371/journal.pone.0053665. Epub 2013 Jan 9.

Genetic and Functional Dissection of ARMS2 in Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy.

Cheng Y, Huang L, Li X, Zhou P, Zeng W, Zhang C.

Department of Ophthalmology, People's Hospital, Peking University, Beijing, China ; Key Laboratory of Vision Loss and Restoration, Ministry of Education, Beijing, China.

Abstract: Age-related maculopathy susceptibility 2(ARMS2) was suggested to be associated with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) in multiple genetic studies in Caucasians and Japanese. To date, no biological properties have been attributed to the putative protein in nAMD and PCV. The complete genes of ARMS2 and HTRA1 including all exons and the promoter region were assessed using direct sequencing technology in 284 unrelated mainland northern Chinese individuals: 96 nAMD patients, 92 PCV patients and 96 controls. Significant associations with both nAMD and PCV were observed in 2 polymorphisms of ARMS2 and HTRA1 rs11200638, with different genotypic distributions between nAMD and PCV (p<0.001). After adjusting for rs11200638, ARMS2 rs10490924 remained significantly associated with nAMD and PCV (p<0.001). Then we overexpressed wild-type ARMS2 and ARMS2 A69S mutation (rs10490924) in RF/6A cells and RPE cells as in vitro study model. Cell proliferation, attachment, migration and tube formation were analyzed for the first time. Compare with wild-type ARMS2, A69S mutation resulted in a significant increase in proliferation and attachment but inhibited cell migration. Moreover, neither wild-type ARMS2 nor A69S mutation affected tube formation of RF/6A cells. There is a strong and consistent association of the ARMS2/HTRA1 locus with both nAMD and PCV, suggesting the two disorders share, at least partially, similar molecular mechanisms. Neither wild-type ARMS2 nor A69S mutation had direct association with neovascularisation in the pathogenesis of AMD.

PMID: 23326481 [PubMed - in process]

Diet

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Serum and macular responses to multiple xanthophyll supplements in patients with early age-related macular degeneration.

Huang YM, Yan SF, Ma L, Zou ZY, Xu XR, Dou HL, Lin XM.

Department of Nutrition and Food Hygiene, School of Public Health, Beijing University, Beijing, China.

OBJECTIVE: This randomized controlled trial examined serum and macular (in vivo measured macular pigment optical density [MPOD]) responses to supplemental lutein and zeaxanthin in Chinese subjects with early age-related macular degeneration.

METHODS: One hundred and eight patients with early age-related macular degeneration older than 50 y were randomized to low lutein (LL; 10 mg/d), high lutein (HL; 20 mg/d), lutein plus zeaxanthin (LZ; each 10 mg/d), or placebo during a 48-wk intervention. Serum concentrations were quantified by C(30) high-performance liquid chromatography (at baseline and 4, 12, 24, and 48 wk), and MPOD was measured by analysis of autofluorescence images (at baseline and 24 and 48 wk).

RESULTS: Serum lutein levels in the LL, LZ, and HL groups increased significantly in the first 4 wk and then increased 4.24-, 4.66-, and 6.23-fold during the trial, respectively (all $P < 0.001$). The serum lutein level in the HL group was significantly higher than that in the LL or LZ group at 48 wk ($P < 0.05$). Similarly, the serum zeaxanthin concentration in the LZ group increased 3.11-fold at 48 wk. MPOD increased smoothly in all treated groups, and the increase from baseline was greatest in the HL group at 24 and 48 wk (both $P < 0.05$). MPOD and serum lutein levels increased linearly with the dosage and their increasing rates were statistically correlated (all $P < 0.05$). No notable changes were detected in the placebo group for MPOD and serum concentrations.

CONCLUSION: Xanthophyll supplementation significantly increased serum concentrations and MPOD in patients with early age-related macular degeneration, and a higher lutein supplementation (20 mg/d) might be more effective in increasing these two biochemical markers in Chinese patients without significant side effects.

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