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MD Research News

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Drug treatment

Ther Adv Chronic Dis. 2012 Jul;3(4):153-61. doi: 10.1177/2040622312446007.

Aflibercept in wet age-related macular degeneration: a perspective review.

Ohr M, Kaiser PK.

Cleveland Clinic - Cole Eye Institute, Cleveland, OH, USA.

Abstract: In the treatment of neovascular age-related macular degeneration (AMD), vascular endothelial growth factor (VEGF) has emerged as a key target of therapy. Currently, patients with neovascular AMD are treated with monthly intravitreal injections of anti-VEGF medications. Aflibercept is a novel recombinant fusion protein engineered to bind all isoforms of VEGF-A, VEGF-B, and placental growth factor. It is the latest medication to receive US Federal Drug Administration (FDA) approval for the treatment of neovascular AMD. Theoretical models suggest this molecule may have a longer duration of action compared with current treatments. The results of the VEGF Trap-Eye: Investigation of Efficacy and Safety in wet Age-related Macular Degeneration studies (VIEW 1 and VIEW 2) support this by demonstrating that aflibercept, dosed every 2 months after a monthly loading dose for 3 months, was noninferior in the proportion of patients who maintained or improved vision at 52 weeks compared with monthly injections of ranibizumab. These results were maintained over the 2 years of the studies. Aflibercept (Eylea; Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA and Bayer, Basel, Switzerland) was approved by the FDA for the treatment of neovascular AMD on 18 November 2011.

PMID: 23342231 [PubMed]

Ophthalmology. 2013 Jan 18. pii: S0161-6420(12)01154-2. doi: 10.1016/j.ophtha.2012.11.037. [Epub ahead of print]

Pharmacogenetics for Genes Associated with Age-Related Macular Degeneration in the Comparison of AMD Treatments Trials (CATT).

Hagstrom SA, Ying GS, Pauer GJ, Sturgill-Short GM, Huang J, Callanan DG, Kim IK, Klein ML, Maguire MG, Martin DF; Comparison of AMD Treatments Trials Research Group(□).

Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio; Department of Ophthalmology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio. Electronic address: hagstrs@ccf.org.

PURPOSE: To evaluate the pharmacogenetic relationship between genotypes of single nucleotide polymorphisms (SNPs) known to be associated with age-related macular degeneration (AMD) and response to treatment with ranibizumab (Lucentis, Genentech, South San Francisco, CA) or bevacizumab (Avastin, Genentech) for neovascular AMD.

DESIGN: Clinical trial.

PARTICIPANTS: Eight hundred thirty-four (73%) of 1149 patients participating in the Comparison of AMD Treatments Trials (CATT) were recruited through 43 CATT clinical centers.

METHODS: Each patient was genotyped for SNPs rs1061170 (CFH), rs10490924 (ARMS2), rs11200638 (HTRA1), and rs2230199 (C3), using TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA).

MAIN OUTCOMES MEASURES: Genotypic frequencies were compared with clinical measures of response to therapy at one year, including mean visual acuity (VA), mean change in VA, 15-letter or more increase in VA, retinal thickness, mean change in total foveal thickness, presence of fluid on OCT, presence of leakage on fluorescein angiography (FA), mean change in lesion size, and mean number of injections administered. Differences in response by genotype were evaluated with tests of linear trend calculated from logistic regression models for categorical outcomes and linear regression models for continuous outcomes. To adjust for multiple comparisons, P≤0.01 was considered statistically significant.

RESULTS: No statistically significant differences in response by genotype were identified for any of the clinical measures studied. Specifically, there were no high-risk alleles that predicted final VA or change in VA, the degree of anatomic response (fluid on OCT or FA, retinal thickness, change in total foveal thickness, change in lesion size), or the number of injections. Furthermore, a stepwise analysis failed to show a significant epistatic interaction among the variants analyzed; that is, response did not vary by the number of risk alleles present. The lack of association was similar whether patients were treated with ranibizumab or bevacizumab or whether they received monthly or pro re nata dosing.

CONCLUSIONS: Although specific alleles for CFH, ARMS2, HTRA1, and C3 may predict the development of AMD, they did not predict response to anti-vascular endothelial growth factor therapy.

PMID: 23337555 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Jan 24. pii: iovs.12-11046v1. doi: 10.1167/iovs.12-11046. [Epub ahead of print]

Correlation of OCT characteristics and Retinal Sensitivity in Neovascular age-related Macular Degeneration (AMD) in the course of monthly Ranibizumab treatment.

Sulzbacher F, Kiss C, Kaider A, Roberts P, Munk M, Kroh ME, Sayegh R, Schmidt-Erfurth U.

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

PURPOSE: To evaluate the functional treatment response 3 months and 12 months after monthly ranibizumab in neovascular age-related macular degeneration (nAMD). Methods: Twenty-six eyes showing treatment naive nAMD were examined with the Heidelberg Spectralis-OCT (SD-OCT) and the NIDEK MP-1 microperimeter (MP) at baseline, after 3 months and after 12 months of monthly ranibizumab therapy. Each test point of light sensitivity was transferred to the corresponding location on SD-OCT and subsequently the microperimetric results were evaluated with respect to the following OCT-findings: neovascular complex (NVC), subretinal fluid (SRF), intraretinal fluid (IRF), intraretinal cystoid space (IRCS), serous pigment epithelium detachment (SPED), fibrovascular pigment epithelium detachment (FPED).

RESULTS: Loci of an initial NVC improved significantly from a mean retinal sensitivity value of 2.6dB ± 0.8dB at baseline to 7.4dB ± 0.9dB (p<0.0001) at month 12. Initial SRF, IRF or IRCS improved significantly

from a mean value of 5.1dB ± 0.9dB to 12.4dB ± 0.9dB (p<0.0001), 4.0dB ±1.0dB to 9.3dB ± 0.9dB (p<0.0001) and 3.4dB ± 0.9dB to 8.2dB ± 0.9dB (p<0.0001), respectively. An initial serous PED improved significantly from a mean retinal sensitivity value of 1.9dB ±1.1dB at baseline to 9. ± 1.1dB (p<0.0001) at month 12, a fibrovascular PED improved significantly from 5.2dB ± 0.9dB at baseline to 7.6dB ± 0.9dB (p<0.0001) at month 12.

CONCLUSIONS: Functional benefit could be detected at all locations of macular pathology with a lower benefit in case of FPED and in case of additional IRCS and a marked benefit for all types of macular edema.

PMID: 23349430 [PubMed - as supplied by publisher]

Retina. 2013 Jan 23. [Epub ahead of print]

CORRELATION OF FOVEAL MICROSTRUCTURAL CHANGES WITH VISION AFTER ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY IN AGE-RELATED MACULAR DEGENERATION.

Shin HJ, Chung H, Chan Kim H.

Department of Ophthalmology, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Republic of Korea.

PURPOSE: To investigate the correlation of foveal microstructural changes with vision after intravitreal ranibizumab injection in eye with choroidal neovascularization (CNV) secondary to age-related macular degeneration.

METHODS: We retrospectively studied 40 eyes of 40 patients with neovascular age-related macular degeneration who had no previous treatment history of age-related macular degeneration. All patients were treated with 3 monthly intravitreal ranibizumab (0.5 mg/0.05 mL) injections. One month after the third consecutive injection, best-corrected visual acuity (BCVA) was evaluated and the eyes were categorized into 2 groups according to the change in BCVA (good function group: BCVA improvement ≥ logarithm of minimum angle of resolution 0.3; poor function group: BCVA improvement < logarithm of minimum angle of resolution 0.3). Changes of foveal photoreceptor layer integrity, CNV size (diameter and thickness), central macular thickness, center point thickness, outer nuclear layer thickness, and subretinal fluid in each group were also evaluated using spectral-domain optical coherence tomography.

RESULTS: The good function group is 20 eyes, and the poor function group is 20 eyes. No significant differences in baseline characteristics of variables including CNV type, initial BCVA, photoreceptor integrity, and CNV size were observed between the two groups. Best-corrected visual acuity in the good function group was 0.30 ± 0.17 (logarithm of minimum angle of resolution) and that in the poor function group was 0.48 ± 0.40 (logarithm of minimum angle of resolution). Decreased disrupted length of photoreceptor layer (1,020.80 ± 974.60) and decreased CNV thickness (78.86 ± 50.78) were found in the good function group at the end of follow-up. However, no significant differences in changes of CNV diameter, central macular thickness, center point thickness, outer nuclear layer thickness, and resolution of subretinal fluid were observed between the two groups.

CONCLUSION: Restoration of foveal photoreceptor integrity and decreased CNV thickness are closely associated with visual improvement in neovascular age-related macular degeneration after treatment.

PMID: 23348865 [PubMed - as supplied by publisher]

Case Report Ophthalmol. 2012 Sep;3(3):443-51. doi: 10.1159/000346045. Epub 2012 Dec 22.

A clear cell renal cell carcinoma inhibiting the response to intravitreal antivascular endothelial growth factor therapy in wet age-related macular disease.

Falcão MS, Vinagre J, Soares P, Lopes JM, Brandão E, Carneiro AM.

Faculty of Medicine, University of Porto, Porto, Portugal ; Department of Ophthalmology, Hospital de São João, Porto, Portugal.

PURPOSE: Wet age-related macular degeneration (AMD) is an ocular disorder that can be successfully treated with intravitreal antivascular endothelial growth factor (VEGF) therapy. We report a case of incomplete response to intravitreal therapy associated with a clear cell renal cell carcinoma (ccRCC).

METHODS: A 72-year-old male with wet AMD responded poorly to intravitreal bevacizumab and ranibizumab injections. The removal of a ccRCC led to the spontaneous stabilization of the choroidal neovascular lesion. The renal carcinoma was examined for Von Hippel-Lindau (VHL) gene alterations. Immunohistochemical profiling of the hypoxia-inducible factor (HIF) pathway addressing the marker HIF-1α and its downstream targets VEGF, glucose transporter 1 and carbonic anhydrase IX was performed.

RESULTS: Genotyping of the ccRCC revealed the presence of a truncating VHL mutation (p.E134fs*25). Immunohistochemistry displayed HIF pathway target activation and VEGF expression in the ccRCC tumour cells. Following tumour removal, the neovascular lesion remained stable for 6 months without any further anti-VEGF therapy.

CONCLUSION: The somatic VHL mutation correlates with persistent high levels of HIF-1α pathway targets and VEGF expression in the ccRCC. We postulate that this increased VEGF in the tumour and subsequently in the plasma levels could have caused the incomplete response to intravitreal anti-VEGF therapy. Stabilization of the wet AMD following tumour removal indicates that the angiogenic secreting tumour (ccRCC) abrogates the response to VEGF inhibitor therapy. Thus, in cases of poor response to intravitreal anti-VEGF therapy, systemic evaluation including plasma levels of VEGF and/or systemic screening for VEGF-producing tumours should be considered.

PMID: 23341823 [PubMed]

Clin Experiment Ophthalmol. 2013 Jan 21. doi: 10.1111/ceo.12074. [Epub ahead of print]

Subconjunctival bleb that forms at the injection site after intravitreal injection is drug, not vitreous.

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Abstract: The treatment of ophthalmologic conditions by intravitreal injection of therapeutic agents has taken an increasingly central role in conditions such as age-related macular degeneration, diabetic retinopathy and retinal vein occlusions. At the time of needle withdrawal following intravitreal injection, material may reflux through the needle incision into the subconjunctival space and form a bleb. This has been estimated to occur in about 20-30% of clinical cases.(1) However, it is unclear whether the refluxed material is drug or vitreous. Drug reflux may result in lower intravitreal agent dosage, while vitreous reflux may be associated with vitreous wick syndrome, predisposition to the formation of retinal holes and an increased risk of endophthalmitis by providing a track for bacteria through the incision site and into the vitreous cavity.(2).

PMID: 23331405 [PubMed - as supplied by publisher]

Case Report Ophthalmol. 2012 Sep;3(3):424-7. doi: 10.1159/000346041. Epub 2012 Dec 18.

Recurrence of macular hole retinal detachment after intravitreal ranibizumab injection for the treatment of choroidal neovascularization from the remaining macular hole edge.

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PURPOSE: To report a case who had recurrence of macular hole retinal detachment (MHRD) after intravitreal ranibizumab injection (IVR) for the treatment of choroidal neovascularization (CNV) that arose from the damaged retinal pigment epithelium of the remaining macular hole (MH) edge, which had been successfully treated by pars plana vitrectomy (PPV) 15 years previously.

CASE REPORT: A 67-year-old man with previous PPV for MHRD secondary to high myopia in the right eye had been under observation for 15 years after surgery. The retina had been successfully attached, but the MH remained open. He had CNV which arose from the remaining MH edge. IVR was performed for the treatment of CNV. One month after the injection, CNV was contracted but recurrence of MHRD occurred. PPV with an additional internal limiting membrane peeling, removal of the CNV membrane and 20% SF6 gas tamponade was performed. One year after the last surgery, his right retina was attached and the MH was closed successfully.

CONCLUSION: We propose that patients who undergo IVR should be carefully maintained and followed up for possible complications including the recurrence of MHRD.

PMID: 23341819 [PubMed]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2013 Jan 24. pii: iovs.12-10578v1. doi: 10.1167/iovs.12-10578. [Epub ahead of print]

Semi-automated Segmentation of the Choroid in Spectral-domain Optical Coherence Tomography Volume Scans.

Hu Z, Wu X, Ouyang Y, Ouyang Y, Sadda SR.

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Purpose: Changes in the choroid, in particular its thickness, are believed to be of importance in the pathophysiology of a number of retinal diseases. The purpose of this study is to adapt the graph search algorithm to semi-automatically identify the choroidal layer in spectral-domain optical coherence tomography (SD-OCT) volume scans and compare its performance to manual delineation.

Methods: A graph-based multi-stage segmentation approach was used to identify the choroid, defined as the layer between the outer border of the retinal pigment epithelium (RPE) band and the choroid-sclera junction. Thirty randomly chosen macular SD-OCT (Heidelberg Spectralis) volumes were obtained from 20 healthy and 10 subjects with non-neovascular age-related macular degeneration (AMD). The positions of the choroidal borders and resultant thickness were compared with consensus manual delineation by two graders.

Results: The algorithm-defined position of the outer RPE border and choroid-sclera junction was consistent with manual delineation, resulting in highly correlated choroidal thickness values with r = 0.91-0.93 for the normal subjects and 0.94 for patients with non-neovascular AMD. Across all cases, the mean and absolute differences between the algorithm and manual segmentation for outer rpe boundary was -0.74 3.27 m and 3.15 3.07 m; and for choroid-sclera junction was -3.90 15.93 m and 21.39 10.71 m.

Conclusions: Excellent agreement was observed between the algorithm and manual choroidal segmentation in both normal eyes and those with non-neovascular AMD. The choroid was thinner in AMD eyes. Semi-automated choroidal thickness calculation may be useful for large scale quantitative studies of the choroid.

PMID: 23349432 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Jan 15. pii: S0161-6420(12)01055-X. doi: 10.1016/j.ophtha.2012.10.036. [Epub ahead of print]

Clinical Classification of Age-Related Macular Degeneration.

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OBJECTIVE: To develop a clinical classification system for age-related macular degeneration (AMD).

DESIGN: Evidence-based investigation, using a modified Delphi process.

PARTICIPANTS: Twenty-six AMD experts, 1 neuro-ophthalmologist, 2 committee chairmen, and 1 methodologist.

METHODS: Each committee member completed an online assessment of statements summarizing current AMD classification criteria, indicating agreement or disagreement with each statement on a 9-step scale. The group met, reviewed the survey results, discussed the important components of a clinical classification system, and defined new data analyses needed to refine a classification system. After the meeting, additional data analyses from large studies were provided to the committee to provide risk estimates related to the presence of various AMD lesions.

MAIN OUTCOME MEASURES: Delphi review of the 9-item set of statements resulting from the meeting.

RESULTS: Consensus was achieved in generating a basic clinical classification system based on fundus lesions assessed within 2 disc diameters of the fovea in persons older than 55 years. The committee agreed that a single term, age-related macular degeneration, should be used for the disease. Persons with no visible drusen or pigmentary abnormalities should be considered to have no signs of AMD. Persons with small drusen (<63 μm), also termed drupelets, should be considered to have normal aging changes with no clinically relevant increased risk of late AMD developing. Persons with medium drusen (≥63-<125 μm), but without pigmentary abnormalities thought to be related to AMD, should be considered to have early AMD. Persons with large drusen or with pigmentary abnormalities associated with at least medium drusen should be considered to have intermediate AMD. Persons with lesions associated with neovascular AMD or geographic atrophy should be considered to have late AMD. Five-year risks of progressing to late AMD are estimated to increase approximately 100 fold, ranging from a 0.5% 5-year risk for normal aging changes to a 50% risk for the highest intermediate AMD risk group.

CONCLUSIONS: The proposed basic clinical classification scale seems to be of value in predicting the risk of late AMD. Incorporating consistent nomenclature into the practice patterns of all eye care providers may improve communication and patient care.

PMID: 23332590 [PubMed - as supplied by publisher]

Mol Vis. 2013;19:54-61. Epub 2013 Jan 10.

Choroidal neovascularization reduced by targeted drug delivery with cationic liposome-

encapsulated paclitaxel or targeted photodynamic therapy with verteporfin encapsulated in cationic liposomes.

Gross N, Ranjbar M, Evers C, Hua J, Martin G, Schulze B, Michaelis U, Hansen LL, Agostini HT.

Augenklinik, Universitätsklinikum Freiburg, Freiburg, Germany.

PURPOSE: Intravitreal antivascular endothelial growth factor (anti-VEGF) application has revolutionized the treatment of choroidal neovascularization (CNV), a hallmark of wet age-related macular degeneration. However, additional treatment options are desirable as not all CNV lesions respond to anti-VEGF injections. Here, we assessed the feasibility of targeted delivery of cationic liposome-encapsulated paclitaxel (EndoTAG-1) in treating CNV. Furthermore, we investigated whether a new formulation of verteporfin encapsulated in cationic liposomes (CL-VTP) enhances the effect of photodynamic therapy (PDT).

METHODS: EndoTAG-1, LipoSPA, and CL-VTP were produced by encapsulating paclitaxel, succinyl-paclitaxel, or verteporfin in cationic liposomes (CL). Mice underwent argon laser coagulations at day 0 (D0) to induce CNV. EndoTAG-1 and LipoSPA were injected into the tail vein at D1, D3, D5, D7, and D9. Taxol, CL, or trehalose buffer alone was injected in control animals. At D10, all animals were perfused with fluorescein isothiocyanate (FITC)-dextran. Flatmounts comprising the retinal pigment epithelium, choroid, and sclera were prepared for quantifying the CNV by measuring the area of lesions perfused with FITC-dextran. For PDT, mice received an injection with CL-VTP or Visudyne at D10. One eye was treated with PDT while the other served as a control. Evaluation of RPE-choroid-scleral and retinal flatmounts was performed at D12, D14, or D17. Perfusion with FITC-dextran and tetramethylrhodamine-5-(and 6)-isothiocyanate-lectin staining was used to distinguish between perfused and non-perfused choroidal vessels.

RESULTS: EndoTAG-1 or LipoSPA significantly reduced CNV size to 15% compared to trehalose controls. The mean CNV area of mice treated with CL was reduced (though not significantly) to about one-half of the value of the trehalose control group. The same was observed for paclitaxel. Thus, the reduction in the CNV size between treatment with CL and treatment with EndoTAG-1 or LipoSPA was 40%, which was not significant. PDT using either CL-VTP or Visudyne reduced CNV size to 65% (D17) of trehalose control size. CNV size was further diminished to 56% with Visudyne and 53% with CL-VTP when PDT was repeated twice. Most importantly, PDT-associated retinal damage was less pronounced using CL-VTP compared to Visudyne.

CONCLUSIONS: Systemic intravenous injection of paclitaxel (EndoTAG-1)- or succinyl-paclitaxel (LipoSPA)-loaded CL had a significant antiangiogenic effect in a CNV mouse model. PDT with CL-VTP was as effective as Visudyne in neovascular obliteration but induced less tissue damage. Our data suggest that systemic application of cationic liposome formulations may serve to treat ocular neovascular diseases. This approach may reduce the need for intraocular injections and may benefit patients with neovascular lesions irresponsive to anti-VEGF treatment.

PMID: 23335851 [PubMed - in process]

Pathogenesis

Klin Oczna. 2012;114(2):115-20.

PEDF and VEGF plasma level alterations in patients with dry form of age-related degeneration--a possible link to the development of the disease.

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PURPOSE: The aim of the study is to explore the interaction between stimulators and inhibitors of angiogenesis by measuring pigment epithelium-derived factor (PEDF) and vascular endothelial growth factor

(VEGF) plasma levels in patients with the wet and dry forms of age-related macular degeneration (AMD).

MATERIAL AND METHODS: Forty-six subjects with the wet form, 31 with the dry form of AMD as well as 47 non-AMD healthy controls were enrolled in the study. Plasma concentrations of VEGF and PEDF were measured using ELISA test.

RESULTS: A significant decrease in the PEDF plasma level in patients with the dry form of AMD was found. Multivariate analyses of patients and controls adjusted for age, sex, smoking, and concomitant vascular diseases as independent variables revealed that the dry form of AMD was the only independent factor associated with lower plasma PEDF levels (beta = -0.34; p = 0.026). On the contrary, in the wet AMD group, a strong positive correlation between VEGF and PEDF concentrations was observed (Rs = +0.63; p = 0.002), and significantly higher PEDF and VEGF plasma levels in patients with bilateral manifestations of the disease were also found.

CONCLUSIONS: These findings suggest that different manifestations of AMD, i.e. the dry and wet forms, may be associated with various altered concentrations of counterbalancing stimulators and inhibitors of the angiogenesis process.

PMID: 23346798 [PubMed - in process]

Proc Natl Acad Sci U S A. 2013 Jan 22. [Epub ahead of print]

JNK inhibition reduces apoptosis and neovascularization in a murine model of age-related macular degeneration.

Du H, Sun X, Guma M, Luo J, Ouyang H, Zhang X, Zeng J, Quach J, Nguyen DH, Shaw PX, Karin M, Zhang K.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of registered blindness among the elderly and affects over 30 million people worldwide. It is well established that oxidative stress, inflammation, and apoptosis play critical roles in pathogenesis of AMD. In advanced wet AMD, although, most of the severe vision loss is due to bleeding and exudation of choroidal neovascularization (CNV), and it is well known that vascular endothelial growth factor (VEGF) plays a pivotal role in the growth of the abnormal blood vessels. VEGF suppression therapy improves visual acuity in AMD patients. However, there are unresolved issues, including safety and cost. Here we show that mice lacking c-Jun N-terminal kinase 1 (JNK1) exhibit decreased inflammation, reduced CNV, lower levels of choroidal VEGF, and impaired choroidal macrophage recruitment in a murine model of wet AMD (laser-induced CNV). Interestingly, we also detected a substantial reduction in choroidal apoptosis of JNK1-deficient mice. Intravitreal injection of a pan-caspase inhibitor reduced neovascularization in the laser-induced CNV model, suggesting that apoptosis plays a role in laser-induced pathological angiogenesis. Intravitreal injection of a specific JNK inhibitor decreased choroidal VEGF expression and reduced pathological CNV. These results suggest that JNK1 plays a key role in linking oxidative stress, inflammation, macrophage recruitment apoptosis, and VEGF production in wet AMD and pharmacological JNK inhibition offers a unique and alternative avenue for prevention and treatment of AMD.

PMID: 23341606 [PubMed - as supplied by publisher]

Mutat Res. 2013 Jan 19. pii: S1383-5742(13)00021-5. doi: 10.1016/j.mrrev.2013.01.001. [Epub ahead of print]

Environmental light and endogenous antioxidants as the main determinants of non-cancer ocular diseases.

Saccà SC, Roszkowska A, Izzotti A.

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Abstract: The human eye is constantly exposed to sunlight and artificial lighting. Exogenous sources of reactive oxygen species (ROS) such as UV light, visible light, ionizing radiation, chemotherapeutics, and environmental toxins contribute to oxidative damage in ocular tissues. Long-term exposure to these insults places the aging eye at considerable risk for pathological consequences of oxidative stress. Furthermore, in eye tissues, mitochondria are an important endogenous source of ROS. Over time, all ocular structures, from the tear film to the retina, undergo oxidative stress, and therefore, the antioxidant defenses of each tissue assume the role of a safeguard against degenerative ocular pathologies. The ocular surface and cornea protect the other ocular tissues and are significantly exposed to oxidative stress of environmental origin. Overwhelming of antioxidant defenses in these tissues clinically manifests as pathologies including pterygium, corneal dystrophies, and endothelial Fuch's dystrophy. The crystalline lens is highly susceptible to oxidative damage in aging because its cells and their intracellular proteins are not turned over or replaced, thus providing the basis for cataractogenesis. The trabecular meshwork, which is the anterior chamber tissue devoted to aqueous humor drainage, has a particular susceptibility to mitochondrial oxidative injury that affects its endothelium and leads to an intraocular pressure increase that marks the beginning of glaucoma. Photo-oxidative stress can cause acute or chronic retinal damage. The pathogenesis of age-related macular degeneration involves oxidative stress and death of the retinal pigment epithelium followed by death of the overlying photoreceptors. Accordingly, converging evidence indicates that mutagenic mechanisms of environmental and endogenous sources play a fundamental pathogenic role in degenerative eye diseases.

PMID: 23337404 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Jan 22. pii: iovs.12-11091v1. doi: 10.1167/iovs.12-11091. [Epub ahead of print]

Oral proton pump inhibitors disrupt horizontal cell-cone feedback and enhance visual hallucinations in macular degeneration patients.

Hanneken AM, Babai N, Thoreson WB.

Department of Molecular &amp.

PURPOSE: Visual hallucinations (VH) occur in macular degeneration patients with poor vision but normal cognitive function. The underlying mechanisms are poorly understood. We report the identification of pharmaceutical agents that enhance VH and use these agents to examine the contribution of retinal neurons to this syndrome.

METHODS: We detail clinical observations on VH in five macular degeneration patients treated with proton pump inhibitors having the core structure, 2-pyridyl-methylsulfinyl-benzimidazole. We tested possible retinal mechanisms using paired whole cell recordings to examine effects of these compounds on feedback interactions between horizontal cells and cones in amphibian retina. Results: Five patients with advanced wet macular degeneration described patterned VH that were induced or enhanced by oral proton pump inhibitors. The abnormal images increased with light, disappeared in the dark and originated in the retina, based on ophthalmodynamometry. Simultaneous paired whole cell recordings from cones and horizontal cells showed that 2-pyridyl-methylsulfinyl-benzimidazoles blocked the negative shift in voltage-dependence and increase in amplitude of the calcium current (ICa) in cones that is induced by changes in horizontal cell membrane potential. These effects disrupt the negative feedback from horizontal cells to cones that is critical for formation of center-surround receptive fields in bipolar and ganglion cells, and thus for normal spatial and chromatic perception.

CONCLUSIONS: Our study suggests that changes in the output of retinal neurons caused by disturbances

in outer retinal feedback mechanisms can enhance patterned visual hallucinations.

PMID: 23341015 [PubMed - as supplied by publisher]

Epidemiology

JAMA Intern Med. 2013 Jan 21:1-7. doi: 10.1001/jamainternmed.2013.1583. [Epub ahead of print]

The Association of Aspirin Use With Age-Related Macular Degeneration.

Liew G, Mitchell P, Wong TY, Rochtchina E, Wang JJ.

OBJECTIVE: To determine whether regular aspirin use is associated with a higher risk for developing age-related macular degeneration (AMD) by using analyzed data from a 15-year prospective cohort.

METHODS: A prospective analysis was conducted of data from an Australian population-based cohort with 4 examinations during a 15-year period (1992-1994 to 2007-2009). Participants completed a detailed questionnaire at baseline assessing aspirin use, cardiovascular disease status, and AMD risk factors. Age-related macular degeneration was graded side-by-side from retinal photographs taken at each study visit to assess the incidence of neovascular (wet) AMD and geographic atrophy (dry AMD) according to the international AMD classification.

RESULTS: Of 2389 baseline participants with follow-up data available, 257 individuals (10.8%) were regular aspirin users and 63 of these (24.5%) developed neovascular AMD. Persons who were regular aspirin users were more likely to have incident neovascular AMD: the 15-year cumulative incidence was 9.3% in users and 3.7% in nonusers. After adjustment for age, sex, smoking, history of cardiovascular disease, systolic blood pressure, and body mass index, persons who were regular aspirin users had a higher risk of developing neovascular AMD (odds ratio [OR], 2.46; 95% CI, 1.25-4.83). The association showed a dose-response effect (multivariate-adjusted P = .01 for trend). Aspirin use was not associated with the incidence of geographic atrophy (multivariate-adjusted OR, 0.99; 95% CI, 0.59-1.65).

CONCLUSION: Regular aspirin use is associated with increased risk of incident neovascular AMD, independent of a history of cardiovascular disease and smoking.

PMID: 23337937 [PubMed - as supplied by publisher]

JAMA Intern Med. 2013 Jan 21:1. doi: 10.1001/jamainternmed.2013.2790. [Epub ahead of print]

The Incremental Nature of Clinical Research: Comment on "The Association of Aspirin Use With Age-Related Macular Degeneration"

Covinsky KE.

PMID: 23338524 [PubMed - as supplied by publisher]

JAMA Intern Med. 2013 Jan 21:1-2. doi: 10.1001/jamainternmed.2013.2530. [Epub ahead of print]

Relationship of Aspirin Use With Age-Related Macular Degeneration: Association or Causation? Comment on "The Association of Aspirin Use With Age-Related Macular Degeneration"

Kaul S, Diamond GA.

PMID: 23338290 [PubMed - as supplied by publisher]

Genetics

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Association of LIPC and advanced age-related macular degeneration.

Lee J, Zeng J, Hughes G, Chen Y, Grob S, Zhao L, Lee C, Krupa M, Quach J, Luo J, Zeng J, Wei X, Zhang X, Zhu J, Duan Y, Ferreyra H, Goldbaum M, Haw W, Shaw PX, Tang L, Zhang K.

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Purpose: To determine whether there is an association between hepatic lipase (LIPC) and age-related macular degeneration (AMD) in two independent Caucasian cohorts.

Methods: A discovery cohort of 1626 patients with advanced AMD and 859 normal controls and a replication cohort of 2159 cases and 1150 controls were genotyped for two single-nucleotide polymorphisms (SNPs) in the promoter region of LIPC. The associations between the SNPs and AMD were examined by $\chi(2)$ tests.

Results: In the discovery cohort, rs493258 and rs10468017 were both associated with advanced AMD (P=9.63E-3 and P=0.048, respectively). The association was corroborated in the replication cohort (P=4.48E-03 for rs493258 and P=0.015 for rs10468017). Combined analysis resulted in even more significant associations (P=1.21E-04 for rs493258 and P=1.67E-03 for rs10468017).

Conclusion: The LIPC promoter variants rs493258 and rs10468017 were associated with advanced AMD in two independent Caucasian populations, confirming that LIPC polymorphisms may be a genetic risk factor for AMD in the Caucasian population.Eye advance online publication, 25 January 2013; doi:10.1038/eye.2012.276.

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DNA Sequence Variants in PPARGC1A, a Gene Encoding a Coactivator of the ω-3 LCPUFA Sensing PPAR-RXR Transcription Complex, Are Associated with NV AMD and AMD-Associated Loci in Genes of Complement and VEGF Signaling Pathways.

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BACKGROUND: Increased intake of ω-3 long-chain polyunsaturated fatty acids (LCPUFAs) and use of peroxisome proliferator activator receptor (PPAR)-activating drugs are associated with attenuation of pathologic retinal angiogenesis. ω-3 LCPUFAs are endogenous agonists of PPARs. We postulated that DNA sequence variation in PPAR gamma (PPARG) co-activator 1 alpha (PPARGC1A), a gene encoding a co-activator of the LCPUFA-sensing PPARG-retinoid X receptor (RXR) transcription complex, may influence neovascularization (NV) in age-related macular degeneration (AMD).

METHODS: We applied exact testing methods to examine distributions of DNA sequence variants in PPARGC1A for association with NV AMD and interaction of AMD-associated loci in genes of complement, lipid metabolism, and VEGF signaling systems. Our sample contained 1858 people from 3 elderly cohorts of western European ancestry. We concurrently investigated retinal gene expression profiles in 17-day-old neonatal mice on a 2% LCPUFA feeding paradigm to identify LCPUFA-regulated genes both associated with pathologic retinal angiogenesis and known to interact with PPARs or PPARGC1A.

RESULTS: A DNA coding variant (rs3736265) and a 3'UTR-resident regulatory variant (rs3774923) in PPARGC1A were independently associated with NV AMD (exact P=0.003, both SNPs). SNP-SNP interactions existed for NV AMD (P<0.005) with rs3736265 and a AMD-associated variant in complement factor B (CFB, rs512559). PPARGC1A influences activation of the AMD-associated complement component 3 (C3) promoter fragment and CFB influences activation and proteolysis of C3. We observed interaction (P≤0.003) of rs3736265 with a variant in vascular endothelial growth factor A (VEGFA, rs3025033), a key molecule in retinal angiogenesis. Another PPARGC1A coding variant (rs8192678) showed statistical interaction with a SNP in the VEGFA receptor fms-related tyrosine kinase 1 (FLT1, rs10507386; P≤0.003). C3 expression was down-regulated 2-fold in retinas of ω-3 LCPUFA-fed mice - these animals also showed 70% reduction in retinal NV (P≤0.001).

CONCLUSION: Ligands and co-activators of the ω-3 LCPUFA sensing PPAR-RXR axis may influence retinal angiogenesis in NV AMD via the complement and VEGF signaling systems. We have linked the co-activator of a lipid-sensing transcription factor (PPARG co-activator 1 alpha, PPARGC1A) to age-related macular degeneration (AMD) and AMD-associated genes.

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Synthesis of Antioxidants for Prevention of Age-Related Macular Degeneration.

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Abstract: Photooxidation of A2E may be involved in diseases of the macula, and antioxidants could serve as therapeutic agents for these diseases. Inhibitors of A2E photooxidation were prepared by Mannich reaction of the antioxidant quercetin. These compounds contain water-solubilizing amine groups, and several were more potent inhibitors of A2E photooxidation than quercetin.

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