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MD Research News

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Drug treatment

Retina. 2011 Dec 18. [Epub ahead of print]

TIME TO FIRST TREATMENT: The Significance of Early Treatment of Exudative Age-related Macular Degeneration.

Rauch R, Weingessel B, Maca SM, Vecsei-Marlovits PV.

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PURPOSE: To determine whether the time span between initial symptoms and treatment with ranibizumab in patients with neovascular age-related macular degeneration has an effect on visual outcome.

METHOD: In this retrospective study, 45 patients with exudative age-related macular degeneration were split into 3 groups depending on the duration of visual symptoms-Group I: <1 month, Group II: 1 month to 6 months, and Group III: >6 months. Best-corrected visual acuity, clinical ophthalmologic examination, and central retinal thickness as measured by optical coherence tomography were recorded at baseline and 2 months later. Fluorescein angiography was performed at baseline. Treatment consisted of 2 intravitreal injections of 1.25 mg of ranibizumab at baseline and after 4 weeks.

RESULTS: The mean time span between initial symptoms and treatment was 59 ± 62 days. In all groups, a reduction of retinal thickness was observed. Shorter disease duration, as estimated by persistence of visual symptoms, was correlated with a better visual outcome after treatment. Patients in Group I demonstrated a significant increase in best-corrected visual acuity (P = 0.007). Patients of Group II (P = 0.095) and Group III (P = 0.271) still achieved a visual improvement in best-corrected visual acuity, albeit not significant. The mean change in best-corrected visual acuity was 0.08 ± 0.1 in all patients and was not statistically significant between groups (P = 0.87).

CONCLUSION: Duration of visual symptoms <1 month before treatment is associated with a better visual outcome. Treatment of new-onset wet age-related macular degeneration should be initiated as soon as possible.

PMID:22186738 [PubMed - as supplied by publisher]

Retina. 2011 Dec 16. [Epub ahead of print]

THREE-YEAR FOLLOW-UP OF A PILOT STUDY OF RANIBIZUMAB COMBINED WITH PROTON BEAM IRRADIATION AS TREATMENT FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

Park SS, Daftari I, Phillips T, Morse LS.

From the *Department of Ophthalmology & Vision Science, University of California, Davis Eye Center, Sacramento, California; and †Department of Radiation Oncology, University of California, San Francisco, San Francisco, California.

BACKGROUND: To investigate the safety and tolerability of ranibizumab combined with proton beam irradiation in treating exudative age-related macular degeneration.

METHODS: Six eyes (6 subjects) with exudative age-related macular degeneration (4 newly diagnosed; 2 previous treated with ranibizumab) were treated with 4 monthly ranibizumab and 24 GyE proton beam irradiation (2 fractions, 24 hours apart) and seen monthly thereafter and retreated with ranibizumab for decrease in best-corrected visual acuity of ≥2 lines, new macular hemorrhage or fluid noted on optical coherence tomography.

RESULTS: Follow-up ranged from 12 months to 36 months (mean, 28 months). Baseline best-corrected visual acuity ranged from 20/40 to 20/250. Final best-corrected visual acuity ranged from 20/25 to 20/400. No radiation retinopathy was noted in any eye. Calculated radiation distribution dose curves indicate that ≤10% of retina received ≥90% of radiation dose in all eyes. Two subjects lost ≥3 lines of best-corrected visual acuity during follow-up, 1 subject in both eyes from enlarging geographic atrophy and the other from worsening fibrovascular pigment epithelial detachment, which was refractory to multiple ranibizumab treatments before enrollment. Among 4 eyes with newly diagnosed exudative age-related macular degeneration, 3 had no fluid on optical coherence tomography at month 12 without further treatment.

CONCLUSION: No safety concerns were noted after 3 years in eyes with exudative age-related macular degeneration treated with ranibizumab combined with proton beam irradiation in this small pilot study. A larger randomized prospective study is under way to further evaluate this combination therapy.

PMID:22183743 [PubMed - as supplied by publisher]

Retina. 2011 Dec 18. [Epub ahead of print]

PHARMACOKINETIC RATIONALE FOR DOSING EVERY 2 WEEKS VERSUS 4 WEEKS WITH INTRAVITREAL RANIBIZUMAB, BEVACIZUMAB, AND AFLIBERCEPT (VASCULAR ENDOTHELIAL GROWTH FACTOR TRAP-EYE).

Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lopez E, Lopez PF.

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PURPOSE: Monthly dosing with inhibitors of vascular endothelial growth factor (VEGF) results in stable or improved visual acuity in most patients with neovascular age-related macular degeneration. However, a minority of patients show little if any response to therapy with persistent or worsening macular fluid. Pharmacokinetic modeling was performed to determine if more frequent dosing with anti-VEGF drugs could be theoretically beneficial.

METHODS: A mathematical model comparing the time-dependent relative binding activities of ranibizumab, bevacizumab, and aflibercept (VEGF Trap-eye; VTE) was used to determine the theoretical peak and trough binding activities when the drugs were injected every 14 days and every 28 days. The intravitreal half-lives of ranibizumab, bevacizumab, and the VTE were estimated to be 3.2, 5.6, and 4.8 days, respectively. The relative molar binding activities of ranibizumab, bevacizumab, and the VTE used in the analyses were 1, 0.05 to 0.2, and 140, respectively. The expected peak and trough binding activities for

ranibizumab, bevacizumab, and VTE were calculated. Dosing every 2 weeks was performed on selected patients who had a poor response to monthly therapy.

RESULTS: Dosing of a drug every 2 weeks resulted in markedly improved trough binding activity, but had little impact on the peak binding activity when calculated through Day 28. The dosing of bevacizumab every 2 weeks resulted in trough binding levels that were superior to monthly dosing with ranibizumab at a dose of 0.5 mg and potentially superior to the levels achieved when ranibizumab was dosed monthly at a dose of 2.0 mg. The VTE displayed superior binding levels for both peak and trough levels even when compared with ranibizumab doses given every 2 weeks. Two case reports demonstrate the clinical usefulness of dosing with anti-VEGF therapy every 2 weeks in eyes with VEGF-dependent macular fluid appearing to be refractory to monthly dosing.

CONCLUSION: The theoretical increase in trough binding levels when anti-VEGF drugs are dosed every 2 weeks most likely explains the clinical benefit observed in patients who received biweekly injections after their poor response to monthly therapy. The short-term use of biweekly dosing may be an attractive treatment option for those eyes that show a treatment response within 2 weeks of an injection, but rebound with increased macular fluid after a month. In the future, VTE should provide higher trough levels of anti-VEGF binding activity and eliminate the need for biweekly dosing in those eyes with VEGF-mediated exudation that appear unresponsive to monthly ranibizumab or bevacizumab.

PMID:22186739 [PubMed - as supplied by publisher]

Med Sci Monit. 2011 Dec 22;18(1):CR32-38.

Retinal pigment epithelial tears following ranibizumab therapy for fibrovascular retinal pigment epithelial detachment due to occult age-related macular degeneration.

Figurska M.

Department of Ophthalmology Military Institute of Medicine, Warsaw, Poland.

Background: The aim of this paper is to report the incidence of retinal pigment epithelial (RPE) tears in patients treated with ranibizumab for subfoveal fibrovascular retinal pigment epithelial detachment (FVPED) due to occult age-related macular degeneration (AMD).

Material/Methods: Thirty patients were treated according to the following schedule: saturation phase, further treatment was based on activity of the degeneration process. Visual acuity (VA), optical coherence tomography (OCT) and fluorescein angiography (FA) parameters were evaluated and compared.

Results: Patients had a mean improvement of +4.7±8.1 letters at month 12. The mean number of needed injections was 6.8±1.8 (range, 3 to 9). RPE tears in fovea occurred in 8 cases (27% of all patients). Analysis of variance revealed significant upper mean values of ETDRS letters for the subgroup without RPE tears. Mean values of PED height were significant upper for RPE tears without baseline. Statistical analysis revealed that in the subgroup without RPE tears mean values of VA significantly differed in succeeding periods compare to baseline (P<0.001). Visual improvement or stabilization was observed in 90.9% of patients without RPE tears (significant improvement of 15 or more letters in 22.7% - 5/22) and in 87.5% of patients with RPE tears (significant improvement was not observed). Baseline leakage parameters, lesion and leakage parameters at month 12 were significantly higher in patients with RPE tears. The chi-square test revealed statistically significant associations between RPE tears and subretinal fluid in OCT (P<0.05) at month 12.

Conclusions: In eyes with FVPED and RPE tears treated with ranibizumab, stabilization of visual acuity without significant improvement is predictable. One of the risk factors common to RPE tears may be baseline leakage parameters and pretreatment distorted RPE contour in OCT. During ranibizumab therapy in eyes with RPE tears, upper parameters of FVPED height may occur without significant differences in fovea and macula volume compare to eyes without RPE tears.

PMID:22207117 [PubMed - in process]

N Engl J Med. 2011 Dec 8;365(23):2238.

Safe preparation and administration of intravitreal bevacizumab injections.

Frost BA, Kainer MA.

Comment on

N Engl J Med. 2011 May 19;364(20):1897-908.

PMID:22150051 [PubMed - indexed for MEDLINE]

Med Sci Monit. 2011 Dec 22;18(1):LE1-2.

Is lipoxins A4 a better alternative to anti-VEGF and anti-TNF-alpha antibody to prevent and treat age-related macular degeneration, diabetic macular edema and retinopathy?

Das UN.

UND Life Sciences, 13800 Fairhill Road, #321, Fairhill Road, Shaker Heights, OH 44120, U.S.A. and School of Biotechnology, Jawaharlal Nehru Technological University, Kakinada-533 003, India, Bio-Science Research Centre, Gayatri Vidya Parishad College of Engineering, Visakhapatnam-530 048, India.

PMID:22207123 [PubMed - as supplied by publisher]

Am J Health Syst Pharm. 2012 Jan 1;69(1):6.

Aflibercept approved for macular degeneration.

Traynor K.

PMID:22180543[PubMed - in process] Related citations

Other treatment & diagnosis

Retina. 2011 Dec 18. [Epub ahead of print]

PILOT STUDY FOR THE DETECTION OF EARLY EXUDATIVE AGE-RELATED MACULAR DEGENERATION WITH OPTICAL COHERENCE TOMOGRAPHY.

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BACKGROUND: Optical coherence tomography (OCT) provides microscopic retinal images. Optical coherence tomography is noninvasive, using light waves to produce detailed retinal images. Here, we investigate the ability of OCT to detect early choroidal neovascularization in age-related macular degeneration.

METHODS: Seventy-nine patients, diagnosed with nonexudative macular degeneration in one eye and exudative macular degeneration in the other were enrolled in this prospective, observational, nonrandomized study. Participants underwent examination (visual acuity, intraocular pressure, biomicroscopy, and ophthalmoscopy) followed by OCT in the study eye (nonexudative macular

degeneration eye) every 3 months for 2 years. If examination did not show choroidal neovascularization, but OCT images raised suspicion, patients were reexamined in 4 weeks to 6 weeks and/or fluorescein angiography was performed. Visual acuity, OCT anomaly detected, and time between OCT and fluorescein angiography detection were examined.

RESULTS: Fifteen (19%) patients developed exudative macular degeneration, as confirmed by fluorescein angiography, in the study eye. Four additional patients showed potential exudative macular degeneration on OCT only. Of the 15 patients who developed exudative macular degeneration, 13 had disease progression identified on OCT before examination and/or fluorescein angiography showed changes. Subretinal pigment epithelium fluid was the most common OCT anomaly, with development of sub-/intraretinal fluid also visible.

CONCLUSION: Optical coherence tomography could be a powerful screening tool for patients with age-related macular degeneration at high risk for developing choroidal neovascularization.

PMID:22186740 [PubMed - as supplied by publisher]

Eye (Lond). 2011 Dec 23. doi: 10.1038/eye.2011.335. [Epub ahead of print]

Optical coherence tomography changes before the development of choroidal neovascularization in second eyes of patients with bilateral wet macular degeneration.

Amissah-Arthur KN, Panneerselvam S, Narendran N, Yang YC.

1] Wolverhampton Eye Infirmary, New Cross Hospital, Wolverhampton, UK [2] Birmingham and Midland Eye Centre, City Hospital, Birmingham, UK.

Aim: To describe the frequency of neovascular age-related macular degeneration (nAMD) in second eyes of patients undergoing ranibizumab therapy in their first eye and to evaluate the patterns of optical coherence tomography (OCT) abnormalities in fellow eyes before nAMD.

Method: Patients who developed choroidal neovascularization (CNV) in the second eye while on treatment for the first eye were identified. OCT scans of the second eyes, performed before the onset of CNV, were retrospectively examined and graded. Frequency of second eye involvement was estimated and patterns of progression of OCT abnormalities were described and classified.

Results: In all, 65 out of 749 consecutive patients required ranibizumab in their second eye for treatment-naïve nAMD over a 2-year period. The mean interval from commencement of ranibizumab in first eye to conversion in second eye was 12 months (2-35.5 months). There were three patterns of CNV development: group A (12%, n=8) had no OCT abnormalities in the second eye just before developing CNV; group B (38%, n=25) had no abnormalities at baseline but developed OCT changes more than one visit before conversion and group C (50%, n=32) had OCT changes from baseline, which did not progress until just before conversion.

Conclusion: Patients with retinal pigment epithelial elevation without sub-retinal fluid on OCT in their fellow eyes have a high risk of progression to require therapy within a 2-year period. An anticipatory approach may be warranted, but a small group with completely normal OCT appearances can still develop lesions between visits.Eye advance online publication, 23 December 2011; doi:10.1038/eye.2011.335.

PMID:22193875 [PubMed - as supplied by publisher]

Pathogenesis

J Biol Chem. 2011 Dec 19. [Epub ahead of print]

Mechanism of all-trans-retinal toxicity: implications for Stargardt's disease and age-related macular degeneration.

Chen Y, Okano K, Maeda T, Chauhan V, Golczak M, Maeda A, Palczewski K.

Case Western Reserve University, United States;

Abstract

Compromised clearance of all-trans-retinal (atRAL), a component of the retinoid cycle, increases the susceptibility of mouse retina to acute light-induced photoreceptor degeneration. Abca4-/-Rdh8-/- mice featuring defective atRAL clearance were used to examine the underlying molecular mechanism(s) because exposure to intense light causes severe photoreceptor degeneration in these animals. Here we report that bright light exposure of Abca4-/-Rdh8-/- mice increased atRAL levels in the retina that induced rapid NADPH oxidase-mediated overproduction of intracellular reactive oxygen species (ROS). Moreover, such ROS generation was inhibited by blocking phospholipase C and IP3-induced Ca2+ release, indicating that activation occurs upstream of NADPH oxidase-mediated ROS generation. Because multiple upstream G protein-coupled receptors (GPCRs) can activate phospholipase C, we then tested the effects of antagonists of serotonin 2A (5-HT2AR) and M3-muscarinic (M3R) receptors and found they both protected Abca4-/-Rdh8-/- mouse retinas from light-induced degeneration. Thus, a cascade of signaling events appears to mediate the toxicity of atRAL in light-induced photoreceptor degeneration of Abca4-/-Rdh8-/- mice. A similar mechanism may be operative in human Stargardts disease and age-related macular degeneration.

PMID:22184108 [PubMed - as supplied by publisher]

Vis Neurosci. 2011 Nov;28(6):543-6.

Glatiramer acetate elevates cell production in the mature retinal pigment epithelium.

Shahabi G, Jeffery G.

Institute of Ophthalmology, University College London, London, UK.

Abstract

The retinal-pigmented epithelium (RPE) is critical for visual function. Throughout life, central RPE cells are lost but replenished by peripheral cell production. Glatiramer acetate increases neuronal production in mature brains and is thought to erode age-related deposits in the human retina that are risk factors for macular degeneration. Here, we ask whether this agent also elevates RPE production in mature rat eyes. If so, it may be used to replenish these cells in damaged eyes. Glatiramer acetate was given systemically for 14 days combined with Bromodeoxyuridine (BrdU) to mark cell division. One eye was then processed for the cell cycle marker Ki67 and the other for BrdU. Glatiramer acetate significantly elevated the number of RPE cells in the cell cycle, with more labeled with Ki67. There were also significantly more BrdU-labeled cells over the 14 days, confirming that some cells divided. However, while Ki67 positive cell numbers increased by approximately 100% following examination at one time point, BrdU cell numbers increased by only 3% when averaged per day. Hence, glatiramer acetate induces cells to proliferate, but many may fail either to complete division or to survive. This may have long-term consequences for this tissue.

PMID:22192509 [PubMed - in process]

Vis Neurosci. 2011 Nov;28(6):529-41.

Residual abilities in age-related macular degeneration to process spatial frequencies during natural scene categorization.

Musel B, Hera R, Chokron S, Alleysson D, Chiquet C, Romanet JP, Guyader N, Peyrin C.

Laboratoire de Psychologie et NeuroCognition, Centre National de la Recherche Scientifique UMR 5105, Université Pierre Mendès France, Grenoble, France.

Abstract

Age-related macular degeneration (AMD) is characterized by a central vision loss. We explored the relationship between the retinal lesions in AMD patients and the processing of spatial frequencies in natural scene categorization. Since the lesion on the retina is central, we expected preservation of low spatial frequency (LSF) processing and the impairment of high spatial frequency (HSF) processing. We conducted two experiments that differed in the set of scene stimuli used and their exposure duration. Twelve AMD patients and 12 healthy age-matched participants in Experiment 1 and 10 different AMD patients and 10 healthy age-matched participants in Experiment 2 performed categorization tasks of natural scenes (Indoors vs. Outdoors) filtered in LSF and HSF. Experiment 1 revealed that AMD patients made more no-responses to categorize HSF than LSF scenes, irrespective of the scene category. In addition, AMD patients had longer reaction times to categorize HSF than LSF scenes only for indoors. Healthy participants' performance was not differentially affected by spatial frequency content of the scenes. In Experiment 2, AMD patients demonstrated the same pattern of errors as in Experiment 1. Furthermore, AMD patients had longer reaction times to categorize HSF than LSF scenes, irrespective of the scene category. Again, spatial frequency processing was equivalent for healthy participants. The present findings point to a specific deficit in the processing of HSF information contained in photographs of natural scenes in AMD patients. The processing of LSF information is relatively preserved. Moreover, the fact that the deficit is more important when categorizing HSF indoors, may lead to new perspectives for rehabilitation procedures in AMD.

PMID:22192508 [PubMed - in process]

Anat Rec (Hoboken). 2011 Dec 21. doi: 10.1002/ar.21519. [Epub ahead of print]

Localization of Papillofoveal Bundles in Primates.

Hiraoka M, Inoue K, Kawano H, Takada M.

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Abstract

Axons in the fovea are precisely organized to ensure accurate vision. We investigated the morphologic characteristics and localization of nerve bundles in the optic nerve in primates. Macaque eyes were studied for conventional and immunostaining, and also marmoset eyes for carbocyanine dye tracing. Locally confined lesions associated with similar findings to human age-related macular degeneration (ARMD) were also evaluated. Axons of retinal ganglion cells formed fasciculi near their origin, and these fasciculi formed bundles thereafter. In the retinal nerve fiber layer, ascending bundles assembled stratification adding proximal bundle underneath successively. Bundles in the arcuate zone displayed a characteristic fine, parallel arrangement, whereas those in the outside zone intermingled with undefined reticular bundles as they approached the optic nerve head. Macular bundles remained in groups and were distributed in the temporal wedge of the optic nerve head. Orthograde and retrograde tracing revealed that these bundles formed confined groups of various sizes and, ultimately, a specific group of small bundles located in the innermost row, near the central vessels. In addition, these bundles showed evidence of focal degenerative

deterioration in eyes with ARMD. Papillomacular bundles have a characteristic alignment and configuration. Foveal bundles that compose the confined group closest to the optic trunk (which we term papillofoveal bundles) appear to have functional significance with respect to the isolated lesions that accompany central vision loss or preservation.

PMID:22190466 [PubMed - as supplied by publisher]

PLoS One. 2011;6(12):e28933. Epub 2011 Dec 19.

Suppression and Regression of Choroidal Neovascularization in Mice by a Novel CCR2 Antagonist, INCB3344.

Xie P, Kamei M, Suzuki M, Matsumura N, Nishida K, Sakimoto S, Sakaguchi H, Nishida K.

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PURPOSE: To investigate the effect of an intravitreally administered CCR2 antagonist, INCB3344, on a mouse model of choroidal neovascularization (CNV).

METHODS: CNV was induced by laser photocoagulation on Day 0 in wild type mice. INCB3344 or vehicle was administered intravitreally immediately after laser application. On Day 14, CNV areas were measured on retinal pigment epithelium (RPE)-choroid flat mounts and histopathologic examination was performed on 7 μm-thick sections. Macrophage infiltration was evaluated by immunohistochemistry on RPE-choroid flat mounts and quantified by flow cytometry on Day 3. Expression of vascular endothelial growth factor (VEGF) protein in RPE-choroid tissue was examined by immunohistochemistry and ELISA, VEGF mRNA in sorted macrophages in RPE-choroid tissue was examine by real-time PCR and expression of phosphorylated extracellular signal-regulated kinase (p-ERK 1/2) in RPE-choroid tissue was measured by Western blot analysis on Day 3. We also evaluated the efficacy of intravitreal INCB3344 to spontaneous CNV detected in Cu, Zn-superoxide dismutase (SOD1) deficient mice. Changes in CNV size were assessed between pre- and 1week post-INCB3344 or vehicle administration in fundus photography and fluorescence angiography (FA).

RESULTS: The mean CNV area in INCB3344-treated mice decreased by 42.4% compared with the vehicle-treated control mice ($p<0.001$). INCB3344 treatment significantly inhibited macrophage infiltration into the laser-irradiated area ($p<0.001$), and suppressed the expression of VEGF protein ($p=0.012$), VEGF mRNA in infiltrating macrophages ($p<0.001$) and the phosphorylation of ERK1/2 ($p<0.001$). The area of spontaneous CNV in Sod1(-/-) mice regressed by 70.35% in INCB3344-treated animals while no change was detected in vehicle-treated control mice ($p<0.001$).

CONCLUSIONS: INCB3344 both inhibits newly forming CNV and regresses established CNV. Controlling inflammation by suppressing macrophage infiltration and angiogenic ability via the CCR-2/MCP-1 signal may be a useful therapeutic strategy for treating CNV associated with age-related macular degeneration.

PMID:22205983 [PubMed - in process]

Front Biosci (Schol Ed). 2012 Jan 1;4:392-411.

Oxidative stress induced cellular signaling in RPE cells.

Klettner A.

University of Kiel, University Medical Center, Department of Ophthalmology, Arnold-Heller-Str. 3, 24105 Kiel, Germany.

Abstract

Oxidative stress is an important factor in the etiology of age-related macular degeneration. In the retinal pigment epithelium, oxidative stress induces protective pathways, notably the phosphatidylinositide 3-kinase (PI3K)/Akt and the nuclear factor erythroid-2 related factor 2 (Nrf2) pathways, but also vascular endothelial growth factor (VEGF) and neuroprotectin D1 (NPD-1) signaling conduct cell protection. Strong oxidative insults result in cell death, mainly mediated via a mitochondrial apoptotic pathway, including cytochrome c release and caspase activation. The role of mitogen activated protein kinases (MAPK) in oxidative stress signaling is diverse and conflicting, conducting protective as well as apoptotic pathways, in addition to involvement in a variety of other cell responses, such as VEGF or matrix metalloproteinases (MMP) upregulation. In addition to signaling deciding cell fate, first insights in inflammatory and extracellular matrix-altering signaling are emerging.

PMID:22202067[PubMed - in process]

Front Biosci. 2012 Jan 1;17:1976-95.

Oxidative stress: The achilles' heel of neurodegenerative diseases of the retina.

Cai X, McGinnis JF.

Department of Ophthalmology, Dean McGee Eye Institute.

Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness among adults in the developed countries. It is characterized by the progressive loss of central vision. AMD is classified into two forms: dry and wet. Dry AMD involves the accumulation of deposits in the RPE and Bruch's membrane; Wet AMD is characterized by neovascularization in the choroid. Whether the two forms of AMD share the same mechanism for the disease development is presently not clear. Oxidative stress, inflammation, and ER-stress are the common modes for the pathogenesis of AMD. In addition, other risk factors and several signaling pathways have been implicated as causative factors of AMD. In this paper, the mechanisms underlying AMD, risk factors involved in the pathology, representative animal models, and therapeutic treatment strategies are reviewed.

PMID:22201850 [PubMed - in process]

Adv Exp Med Biol. 2012;723:513-8.

Biology of retinoschisin.

Vijayasarathy C, Ziccardi L, Sieving PA.

Section for Translation Research in Retinal and Macular Degeneration, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bethesda, MD, 20892, USA.

PMID:22183371 [PubMed - in process]

Adv Exp Med Biol. 2012;723:83-90.

Autophagy in the retina: a potential role in age-related macular degeneration.

Mitter SK, Rao HV, Qi X, Cai J, Sugrue A, Dunn WA Jr, Grant MB, Boulton ME.

Department of Anatomy and Cell Biology, University of Florida, 1600 SW Archer Road, 100235, Gainesville, FL, 32610, USA.

PMID:22183319 [PubMed - in process]

Adv Exp Med Biol. 2012;723:37-42.

Microglia in the outer retina and their relevance to pathogenesis of age-related macular degeneration.

Ma W, Zhao L, Wong WT.

Unit on Neuron-Glia Interactions in Retinal Disease, National Eye Institute, 6 Center Drive, Building 6, Room 215, Bethesda, MD, 20892, USA.

PMID:22183313 [PubMed - in process]

Adv Exp Med Biol. 2012;723:17-22.

Local Vs. Systemic Mononuclear Phagocytes in Age-Related Macular Degeneration and Their Regulation by CCL2-CCR2 and CX3CL1-CX3CR1 Chemokine Signalling.

Luhmann UF, Ali RR.

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PMID:22183310 [PubMed - in process]

Adv Exp Med Biol. 2012;723:11-6.

Autoimmune biomarkers in age-related macular degeneration: a possible role player in disease development and progression.

Iannaccone A, Neeli I, Krishnamurthy P, Lenchik NI, Wan H, Gerling IC, Desiderio DM, Radic MZ.

Department of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center, Memphis, TN, 38163, USA, aiannacc@uthsc.edu.

PMID:22183309 [PubMed - in process]

Genetics

Invest Ophthalmol Vis Sci. 2011 Dec 21. [Epub ahead of print]

C9-R95X Polymorphism in Patients with Neovascular Age-Related Macular Degeneration.

Nishiguchi KM, Yasuma TR, Tomida D, Nakamura M, Ishikawa K, Kikuchi M, Ohmi Y, Niwa T, Hamajima N, Furukawa K, Terasaki H.

Department of Ophthalmology.

Purpose: A non-sense mutation at codon 95 in the gene encoding complement factor C9 (C9-R95X) is found frequently among Japanese. We investigated the association between C9-R95X and Japanese patients with neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

Methods:The presence of C9-R95X polymorphism was assessed in Japanese patients with either PCV (N = 105) or neovascular AMD (N = 198) and 396 control subjects by direct sequencing. Multivariate regression analyses were conducted. Photocoagulation was applied in the eyes of mice with heterozygous defect in

C3 gene and control wildtype mice. Photocoagulation was also applied to wildtype mice before either anti-C9 antibody or isotype IgG was injected into the eyes. The eyes were collected later for the measurement of vascular endothelial growth factor (VEGF) and evaluation of choroidal neovascularization (CNV).

Results:The frequency of those with one or two C9-R95X variant was lower in neovascular AMD (2.02%) than in PCV (5.71%) and controls (6.05%). The presence of C9-R95X conferred 4.7-fold reduction (1.2-18.1; 95% confidence interval; P = 0.021) in the risk of neovascular AMD after adjusting for the major AMD-risk factors. Heterozygous defect in C3 gene was associated with reduced growth of laser-induced CNV as was intraocular injection of anti-C9 antibody. This reduced CNV growth was accompanied by a decreased level of secreted VEGF in the intraocular fluid.

Conclusion:Our findings support the notion that the haploinsufficiency of C9, a terminal complement complex component, engenders reduced intraocular secretion of VEGF and decreased risk of CNV development.

PMID:22190594 [PubMed - as supplied by publisher]

Adv Exp Med Biol. 2012;723:365-70.

The chromosome 10q26 susceptibility locus in age-related macular degeneration.

Stanton CM, Chalmers KJ, Wright AF.

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PMID:22183354 [PubMed - in process]

Epidemiology

Ophthalmology. 2011 Dec 23. [Epub ahead of print]

Age-Related Macular Degeneration and Incident Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis.

Fernandez AB, Wong TY, Klein R, Collins D, Burke G, Cotch MF, Klein B, Sadeghi MM, Chen J.

Division of Cardiology, The Warren Alpert School of Medicine, Brown University, Providence, Rhode Island.

OBJECTIVE: To determine whether age-related macular degeneration (AMD) is a risk indicator for coronary heart disease (CHD) and cardiovascular disease (CVD) events independent of other known risk factors in a multi-ethnic cohort.

DESIGN: Population-based prospective cohort study.

PARTICIPANTS: A diverse population sample of 6233 men and women aged 45 to 84 years without known CVD from the Multi-Ethnic Study of Atherosclerosis (MESA).

METHODS: Participants in the MESA had retinal photographs taken between 2002 and 2003. Photographs were evaluated for AMD. Incident CHD and CVD events were ascertained during clinical follow-up visits for up to 8 years after the retinal images were taken.

MAIN OUTCOME MEASURES: Incident CHD and CVD events.

RESULTS: Of the 6814 persons at risk of CHD, there were 893 participants with early AMD (13.1%) and 27 patients (0.5%) at baseline. Over a mean follow-up period of 5.4 years, there was no statistically significant

difference in incident CHD or CVD between the AMD and non-AMD groups (5.0% vs. 3.9%, P = 0.13 for CHD and 6.6% vs. 5.5%, P = 0.19 for CVD). In Cox regression models adjusting for CVD risk factors, there was no significant relationship between presence of any AMD and any CHD/CVD events (hazard ratio 0.99; 95% confidence interval, 0.74-1.33; P = 0.97). No significant association was found between subgroups of early AMD or late AMD and incident CHD/CVD events.

CONCLUSIONS: In persons without a history of CVD, AMD was not associated with an increased risk of CHD or CVD.

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Age and Gender Variations in Age-related Macular Degeneration Prevalence in Populations of European Ancestry: A Meta-analysis.

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OBJECTIVE: To obtain prevalence estimates of age-related macular degeneration (AMD; late, geographic atrophy, neovascular) by age and gender amongst populations of European ancestry taking into account study design and time trends.

DESIGN: Systematic review of population-based studies published by September 2010 with quantitative estimates of geographic atrophy (GA), neovascular (NV), and late AMD prevalence. Studies were identified by a literature search of MEDLINE (from 1950), EMBASE (from 1980), and Web of Science (from 1980) databases.

PARTICIPANTS: Data from 25 published studies (57 173 subjects: 455 with GA, 464 with NVAMD, and 1571 with late AMD).

METHODS: Bayesian meta-regression of the log odds of AMD with age, gender, and year of study allowing for differences in study design characteristics, to estimate prevalences of AMD (late, GA, NVAMD) along with 95% credible intervals (CrI).

MAIN OUTCOME MEASURES: Log odds and prevalence of AMD.

RESULTS: There was considerable heterogeneity in prevalence rates between studies; for late AMD, 20% of the variability in prevalence rates was explained by differences in age and 50% by study characteristics. The prevalence of AMD increased exponentially with age (odds ratio [OR], 4.2 per decade; 95% CrI, 3.8-4.6), which did not differ by gender. There was some evidence to suggest higher risk of NVAMD in women compared with men (OR, 1.2; 95% CrI, 1.0-1.5). Compared with studies using fundus imaging and international classification systems, studies using fundus imaging with alternative classifications were more likely (OR, 2.7; 95% CrI, 1.1-2.8), and studies using alternative classifications without fundus imaging most likely to diagnose late AMD (OR, 2.9; 95% CrI, 1.3-7.8). There was no good evidence of trends in AMD prevalence over time. Estimated prevalence of late AMD is 1.4% (95% CrI, 1.0%-2.0%) at 70 years of age, rising to 5.6% (95% CrI, 3.9%-7.7%) at age 80 and 20% (95% CrI, 14%-27%) at age 90.

CONCLUSIONS: Studies using recognized classifications systems with fundus photography reported the lowest prevalences of AMD taking account of age and gender, and were stable over time, with a potentially higher risk of NVAMD for women. These prevalence estimates can be used to guide health service provision in populations of European ancestry.

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[A prevalence investigation of blindness and vision impairment in 2009 in older adults of Dachang Blocks of Baoshan District, Shanghai, China].

[Article in Chinese]

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OBJECTIVE: To investigate the prevalence of blindness and low vision and the leading causes of blindness in residents aged ≥ 60 years in Dachang Blocks of Baoshan District, Shanghai, China.

METHODS: A cross-sectional study was carried out by Shanghai Eye Disease Prevention & Treatment Center and the Center for Disease Control and Prevention in Baoshan District of Shanghai from October to December in 2009. Randomly cluster sampling was used to identify the adults aged ≥ 60 years who had lived in Dachang Blocks of Baoshan District, Shanghai for more than 10 years. Presenting visual acuity (PVA) and best-corrected visual acuity (BCVA) based on autorefraction and subjective refraction were measured separately in each eye. External eye, anterior segment and ocular fundus were examined by the ophthalmologist using slit lamp-microscopes direct ophthalmoscopy and non-mydriatic digital camera. And the leading causes of visual impairment were assured. The Chi square test was used between the groups of rate comparison.

RESULTS: Of 5199 enumerated subjects ≥ 60 years of age, 87.42% (4545/5199) were examined. All subjects were urban population who were originally changed from the rural population in nearly 10 years. In this population, with best-corrected visual acuity, 30 persons were diagnosed as blindness, 145 persons were diagnosed as low vision. The prevalence of blindness and low vision were 0.67%, 3.19%, respectively. Low vision was associated with female gender. It was statistically significant difference ($\chi(2) = 4.88$, $P < 0.05$). The leading causes of blindness were cataract, macular degeneration, ocular absence or atrophy, glaucoma, and diabetic retinopathy or corneal diseases. With presenting visual acuity, 39 persons were diagnosed as blindness, 401 persons were diagnosed as low vision. The prevalence of blindness and low vision were 0.86%, 8.82%, respectively. Blindness and low vision were associated with older age. The prevalence of blindness and low vision increased rapidly in aged 75 years or older people. The leading causes of blindness were cataract, uncorrected refractive error, macular degeneration, ocular absence or atrophy, glaucoma. Low vision was associated with female gender. It had statistically significant difference ($\chi(2) = 13.345$, $P < 0.01$).

CONCLUSIONS: In rapidly urbanized and aging community of Shanghai, cataract, uncorrected refractive error, macular degeneration were the leading causes of blindness with presenting visual acuity. The prevalence of low vision in females was higher than that of males which had statistically significant difference. These kinds of residents needed more targeted eye health education and services.

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Diet

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Natural History of Age-Related Retinal Lesions that Precede AMD in Mice Fed High or Low Glycemic Index Diets.

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Purpose: Epidemiologic data indicate that people who consume low glycemic index (GI) diets are at a reduced risk for the onset and progress of age-related macular degeneration (AMD). We sought corroboration of this observation in an animal model.

Methods: Five and 16-month-old C57BL/6 mice were fed high or low GI diets until they were 17- and 23.5-months of age, respectively. Retinal lesions were evaluated by transmission electron microscopy and advanced glycation end products (AGEs) were evaluated by immunohistochemistry.

Results: Retinal lesions including basal laminar deposits, loss of basal infoldings, and vacuoles in the retinal pigment epithelium were more prevalent in the 23.5- than in the 17-month-old mice. Within each age group, consumption of a high GI diet increased risk for lesions, as well as risk for photoreceptor abnormalities and accumulation of AGEs.

Conclusion: Consuming high GI diets accelerates the appearance of age-related retinal lesions that precede AMD in mice, perhaps by increasing deposition of toxic AGEs in the retina. The data support the hypothesis that consuming lower GI diets, or simulation of their effects with nutraceuticals or drugs, may protect against AMD. The high GI-fed C57BL/6 mouse is a new model of age-related retinal lesions that precede AMD that mimics the early stages of disease and may be useful for drug discovery.

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Essential role of ELOVL4 in very long chain fatty acid synthesis and retinal function.

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Abstract

Very long chain polyunsaturated fatty acid (VLC-PUFA) containing glycerophospholipids are highly enriched in the retina, however details regarding the specific synthesis and function of these highly unusual retinal glycerophospholipids are lacking. ELOVL4 has been identified as a fatty acid elongase protein involved in the synthesis of VLC-PUFAs. Mutations in ELOVL4 have also been implicated in an autosomal dominant form of Stargardt disease (STGD3), a type of juvenile macular degeneration. We have generated photoreceptor specific conditional knockout mice and have used high performance liquid chromatography-mass spectrometry (HPLC-MS) to examine and analyze the fatty acid composition of retinal membrane glycerophosphocholine (PC) and glycerophosphoethanolamine (PE) species. We also used immunofluorescent staining and histology, coupled with electrophysiological data, to assess retinal morphology and visual response. The conditional knockout mice showed a significant decrease in retinal glycerophospholipids containing VLC-PUFAs, specifically contained in the sn-1 position of PCs, implicating the role of Elovl4 in their synthesis. Conditional knockout mice were also found to have abnormal accumulation of lipid droplets and lipofuscin-like granules, while demonstrating photoreceptor-specific abnormalities in visual response, indicating the critical role of Elovl4 for proper rod or cone photoreceptor function. Together, this study demonstrates the essential role of ELOVL4 in VLC-PUFA synthesis and retinal function.

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Dietary antioxidants prevent age-related retinal pigment epithelium actin damage and blindness in mice lacking αvβ5 integrin.

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Abstract

In the aging human eye, oxidative damage and accumulation of pro-oxidant lysosomal lipofuscin cause functional decline of the retinal pigment epithelium (RPE), which contributes to age-related macular degeneration. In mice with an RPE-specific phagocytosis defect due to lack of αvβ5 integrin receptors, RPE accumulation of lipofuscin suggests that the age-related blindness we previously described in this model may also result from oxidative stress. Cellular and molecular targets of oxidative stress in the eye remain poorly understood. Here we identify actin among 4-hydroxynonenal (HNE) adducts formed specifically in β5 (-/-) RPE but not in neural retina with age. HNE modification directly correlated with loss of resistance of actin to detergent extraction, suggesting cytoskeletal damage in aging RPE. Dietary enrichment with natural antioxidants, grapes or marigold extract containing macular pigments lutein/zeaxanthin, was sufficient to prevent HNE-adduct formation, actin solubility, lipofuscin accumulation, and age-related cone and rod photoreceptor dysfunction in β5(-/-) mice. Acute generation of HNE adducts directly destabilized actin but not tubulin cytoskeletal elements of RPE cells. These findings identify destabilization of the actin cytoskeleton as a consequence of a physiological, sublethal oxidative burden of RPE cells in vivo that is associated with age-related blindness and that can be prevented by consuming an antioxidant-rich diet.

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