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MD Research News

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Drug treatment

Ophthalmology. 2012 Jun 8. [Epub ahead of print]

Evaluation of the siRNA PF-04523655 versus Ranibizumab for the Treatment of Neovascular Age-related Macular Degeneration (MONET Study).

Nguyen QD, Schachar RA, Nduaka CI, Sperling M, Klamerus KJ, Chi-Burris K, Yan E, Paggiarino DA, Rosenblatt I, Aitchison R, Erlich SS; MONET Clinical Study Group.

Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland.

OBJECTIVE: To evaluate the efficacy of different dosing paradigms of PF-04523655 (PF) versus ranibizumab (comparator) in subjects with neovascular age-related macular degeneration (AMD).

DESIGN: Multicenter, open-label, prospective, randomized, comparator-controlled exploratory study.

PARTICIPANTS: A total of 151 patients with subfoveal choroidal neovascularization (CNV) secondary to neovascular AMD who were naive to AMD therapy.

METHODS: In this phase 2 study, patients were randomized to 1 of 5 treatment groups with equal ratio. All groups received ranibizumab 0.5 mg at baseline and (a) PF 1 mg every 4 weeks (Q4W) from week 4 to week 12; (b) PF 3 mg Q4W from week 4 to week 12; (c) PF 3 mg every 2 weeks (Q2W) from week 4 to week 12; (d) PF 1 mg + ranibizumab (combination) Q4W from baseline to week 12; and (e) ranibizumab Q4W to week 12. All study treatments were given as intravitreal injections.

MAIN OUTCOME MEASURES: The primary end point was the mean change in best-corrected visual acuity (BCVA) from baseline at week 16; secondary end points included the percentage of patients gaining ≥10 and ≥15 letters in BCVA and mean change in retinal central subfield thickness, lesion thickness, and CNV area.

RESULTS: At week 16, the PF 1 mg + ranibizumab combination group achieved numerically greater improvement in mean BCVA from baseline (9.5 letters) than the ranibizumab group (6.8 letters). The difference was not statistically significant. The BCVA improvement in the PF monotherapy groups was less than in the ranibizumab group. Similar trends were observed in the percentage of patients who gained ≥10 and ≥15 letters. From baseline to week 16 (last observed carried forward), the combination and ranibizumab groups had similar mean reductions in central subfield retinal thickness and total CNV area, which were greater than in all PF monotherapy groups. There were no clinically meaningful differences in reduction of lesion thickness among treatment groups.

CONCLUSIONS: In this, early, underpowered study evaluating treatments for neovascular AMD, the combi-

nation of PF with ranibizumab led to an average gain in BCVA that was more than with ranibizumab monotherapy. No safety concerns were identified.

PMID: 22683252 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2012 Jun;47(3):227-35. Epub 2012 May 12.

Canadian expert consensus: optimal treatment of neovascular age-related macular degeneration.

Cruess AF, Berger A, Colleaux K, Greve M, Harvey P, Kertes PJ, Sheidow T, Tourville E, Williams G, Wong D.

Dalhousie University, Halifax, NS.

BACKGROUND: New therapeutic approaches, particularly anti-vascular endothelial growth factor (anti-VEGF) therapies, prevent, and in some cases reverse, vision damage caused by age-related macular degeneration (AMD). Unequal access to care across Canada remains a problem for many retina specialists and their patients.

OBJECTIVE: To develop a consensus concerning the management of patients with exudative age-related macular degeneration (AMD).

DESIGN: Consensus document.

PARTICIPANTS: Ten Canadian retina specialists.

METHODS: The development of a consensus among Canadian experts concerning optimal treatment of AMD began with a review of the clinical evidence, daily practices, existing guidelines, and current national and international approvals and policies. The experts met on June 29, 2010, in Quebec City to discuss their findings and to propose strategies for consensus.

RESULTS: The result of this expert panel is a consensus proposal for Canadian ophthalmologists and retina specialists who are treating patients with or at risk for developing neovascular AMD.

CONCLUSIONS: The consensus provides guidelines to aid retina specialists in managing exudative AMD. Currently, ranibizumab is the only agent with sufficient Level I evidence and a Health Canada-approved indication for the treatment of wet AMD. Bevacizumab has been shown to be noninferior in preserving and improving visual acuity when compared to ranibizumab. Potential safety differences between the 2 drugs remain to be elucidated. The positioning of ranibizumab in this therapeutic area will be further defined as additional data for existing and emerging therapies become available. Until then, this agent remains the therapy of choice for individuals with neovascular AMD.

PMID: 22687297 [PubMed - in process]

Can J Ophthalmol. 2012 Jun;47(3):275-9.

Rate of serious adverse effects in a series of bevacizumab and ranibizumab injections.

Sharma S, Johnson D, Abouammoh M, Hollands S, Brissette A.

Department of Ophthalmology, Queen's University, Kingston, Ont.

OBJECTIVE: To compare the rate of serious ocular and systemic adverse effects of intravitreal bevacizumab and ranibizumab in the treatment of a variety of eye diseases.

DESIGN: Retrospective chart review.

PARTICIPANTS: Consecutive series of intravitreal injections of bevacizumab (n = 693) and ranibizumab (n = 891).

METHODS: Medical records of all patients receiving injections in the series were retrieved. We considered the rate of both serious ocular adverse effects (e.g., acute intraocular inflammation, infectious endophthalmitis, retinal detachment, vitreous hemorrhage) and of arterial thromboembolic events that occurred within 1 month of injection.

RESULTS: Subjects who received bevacizumab were 12 times more likely to develop severe intraocular inflammation following each injection than were those who received ranibizumab (OR = 11.71; 95% CI 1.5-93). The 1 case of acute intraocular inflammation following ranibizumab injection was mild and not associated with vision loss. No other serious ocular complications were noted. A trend was also noted toward an increased risk for arterial thromboembolic events in patients receiving bevacizumab, although the confidence interval was wide (OR = 4.26; 95% CI 0.44-41).

CONCLUSIONS: Significant concern still exists regarding the safety of off-label use of intravitreal bevacizumab. Patients receiving bevacizumab should be counselled regarding a possible increased risk for serious adverse events.

PMID: 22687306 [PubMed - in process]

Clin Ophthalmol. 2012;6:837-44. Epub 2012 May 30.

Choroidal thickness after intravitreal ranibizumab injections for choroidal neovascularization.

Ellabban AA, Tsujikawa A, Ogino K, Ooto S, Yamashiro K, Oishi A, Yoshimura N.

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan.

PURPOSE: To study changes in choroidal thickness with ranibizumab treatment for choroidal neovascularization (CNV).

DESIGN: Prospective case series.

METHODS: This prospective study consisted of 60 CNV-affected eyes of 60 patients treated with intravitreal injections of ranibizumab using an on-demand protocol after an initial loading phase. The eyes studied included 20 with age-related macular degeneration (AMD), 20 with polypoidal choroidal vasculopathy (PCV), and 20 with myopic CNV. In the eyes with AMD and PCV, choroidal thickness at the fovea was measured with optical coherence tomography using enhanced depth imaging. In eyes with myopic CNV, the choroidal thickness was measured using standard optical coherence tomography without the enhanced depth imaging technique.

RESULTS: With ranibizumab treatment, central retinal thickness decreased significantly ($P < 0.001$) and visual acuity improved significantly ($P < 0.001$). However, central choroidal thickness (167.2 ± 108.3 μm) showed no significant change at 1 month after the loading phase (165.2 ± 107.8 μm, $P = 0.120$) or at final examination (164.8 ± 107.7 μm, $P = 0.115$). At baseline, central retinal thickness in eyes with AMD was significantly greater that those with PCV ($P = 0.005$) or high myopia ($P = 0.029$). However, central choroidal thickness in eyes with myopic CNV was significantly thinner than in eyes with AMD ($P < 0.001$) or PCV ($P < 0.001$). In each type of disease, there was no significant change in central choroidal thickness with ranibizumab treatment.

CONCLUSION: The effect of ranibizumab on the choroidal thickness is minimal, if any.

PMID: 22701085 [PubMed - in process]

Nat Rev Drug Discov. 2012 Jun 15. doi: 10.1038/nrd3745. [Epub ahead of print]

Ophthalmic drug discovery: novel targets and mechanisms for retinal diseases and glaucoma.

Zhang K, Zhang L, Weinreb RN.

1] Department of Ophthalmology and Molecular Medicine Research Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China. [2] Department of Ophthalmology, University of California San Diego, La Jolla, California 92093, USA. [3] Institute for Genomic Medicine, University of California San Diego, La Jolla, California 92093, USA.

Abstract

Blindness affects 60 million people worldwide. The leading causes of irreversible blindness include age-related macular degeneration, retinal vascular diseases and glaucoma. The unique features of the eye provide both benefits and challenges for drug discovery and delivery. During the past decade, the landscape for ocular drug therapy has substantially changed and our knowledge of the pathogenesis of ophthalmic diseases has grown considerably. Anti-angiogenic drugs have emerged as the most effective form of therapy for age-related macular degeneration and retinal vascular diseases. Lowering intraocular pressure is still the mainstay for glaucoma treatment but neuroprotective drugs represent a promising next-generation therapy. This Review discusses the current state of ocular drug therapy and highlights future therapeutic opportunities.

PMID: 22699774 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Jun 14. doi: 10.1111/j.1755-3768.2012.02457.x. [Epub ahead of print]

Three-year results of visual outcome with disease activity-guided ranibizumab algorithm for the treatment of exudative age-related macular degeneration.

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Purpose: To evaluate 3-year follow-up treatment outcomes with ranibizumab (Lucentis(®)) 0.5 mg administered either monthly or quarterly on a pro re nata (PRN) basis according to a disease activity-guided monitoring and treatment algorithm.

Methods: A total of 316 treatment-naive eyes of 316 patients with exudative age-related macular degeneration met the criteria for inclusion in this retrospective, interventional case series. Patients were treated with ranibizumab 0.5 mg according to a disease activity-guided algorithm with monthly monitoring. Optical coherence tomography and fluorescein angiography were routinely used to assess disease activity: active lesions were treated with a series of three monthly injections, whereas inactive lesions were treated with quarterly injections.

Results: Mean Early Treatment Diabetic Retinopathy Study best-corrected visual acuity improved from 52 letters at baseline to 59 letters at 12 months, achieved with a mean of 7.1 injections, 61 letters at 24 months with a mean of 5.0 injections administered in the second year and 60 letters at 36 months with a mean number of 5.2 injections.

Conclusions: Monthly visits and a morphology-driven PRN regimen with 3 injections in case of recurrence plus quarterly injections in case of inactive CNV resulted in an average VA gain of 7-9 letters that could be maintained over 3 years.

PMID: 22697404 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Stem Cell Res. 2012 May 16;9(2):101-109. [Epub ahead of print]

Generation of retinal pigment epithelial cells from human embryonic stem cell-derived spherical neural masses.

Cho MS, Kim SJ, Ku SY, Park JH, Lee H, Yoo DH, Park UC, Song SA, Choi YM, Yu HG.

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Abstract

Dysfunction and loss of retinal pigment epithelium (RPE) are major pathologic changes observed in various retinal degenerative diseases such as aged-related macular degeneration. RPE generated from human pluripotent stem cells can be a good candidate for RPE replacement therapy. Here, we show the differentiation of human embryonic stem cells (hESCs) toward RPE with the generation of spherical neural masses (SNMs), which are pure masses of hESCs-derived neural precursors. During the early passaging of SNMs, cystic structures arising from opened neural tube-like structures showed pigmented epithelial morphology. These pigmented cells were differentiated into functional RPE by neuroectodermal induction and mechanical purification. Most of the differentiated cells showed typical RPE morphologies, such as a polygonal-shaped epithelial monolayer, and transmission electron microscopy revealed apical microvilli, pigment granules, and tight junctions. These cells also expressed molecular markers of RPE, including Mitf, ZO-1, RPE65, CRALBP, and bestrophin. The generated RPE also showed phagocytosis of isolated bovine photoreceptor outer segment and secreting pigment epithelium-derived factor and vascular endothelial growth factor. Functional RPE could be generated from SNM in our method. Because SNMs have several advantages, including the capability of expansion for long periods without loss of differentiation capability, easy storage and thawing, and no need for feeder cells, our method for RPE differentiation may be used as an efficient strategy for generating functional RPE cells for retinal regeneration therapy.

PMID: 22683799 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2012 Jun 13. [Epub ahead of print]

High-resolution optical coherence tomography of subpigment epithelial structures in patients with pigment epithelium detachment secondary to age-related macular degeneration.

Clemens CR, Krohne TU, Charbel Issa P, Helb HM, Kosanetzky N, Lommatzsch A, Holz FG, Eter N.

University of Muenster, Muenster, Germany.

BACKGROUND: The pathophysiology of pigment epithelial detachment (PED) secondary to age-related macular degeneration (AMD) is as yet incompletely understood and treatment remains challenging. Spectral domain optical coherence tomography (SD-OCT) allows for improved morphological characterisation of the space underneath the retinal pigment epithelium (RPE).

OBJECTIVE: To investigate eyes with PED for structures underneath the detached RPE cell layer.

METHODS: In a retrospective observational case study, SD-OCT scans of AMD-related PEDs were assessed for the presence of distinctive morphological features in the space between the detached RPE and inner Bruch's membrane.

RESULTS: Structures present in the space between the detached RPE and Bruch's membrane were found in 14 of 90 eyes with AMD-related PED. Each of these eyes shows hyper-reflective material underneath the PED, presenting as highly reflective, multilayered, laminar structures, usually orientated parallel to Bruch's membrane.

CONCLUSIONS: The findings indicate that SD-OCT may be useful for a more refined phenotypic stratification of AMD-associated PED. Further studies are warranted to explore the correlates on other imaging modalities, to investigate the composition of this material and to assess the potential prognostic relevance of this new finding.

PMID: 22694959 [PubMed - as supplied by publisher]

Cochrane Database Syst Rev. 2012 Jun 13;6:CD006757.

Surgery for cataracts in people with age-related macular degeneration.

Casparis H, Lindsley K, Kuo IC, Sikder S, Bressler NB.

Unité de Chirurgie Vitréorétinienne, Jules Gonin Eye Hospital, CH-1004 Lausanne, Switzerland.

BACKGROUND: Cataract and age-related macular degeneration (AMD) are common causes of decreased vision that often occur simultaneously in people over age 50. Although cataract surgery is an effective treatment for cataract-induced visual loss, some clinicians suspect that such an intervention may increase the risk of worsening of underlying AMD and thus have deleterious effects on vision.

OBJECTIVES: The objective of this review was to evaluate the effectiveness and safety of cataract surgery in eyes with AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 4), MEDLINE (January 1950 to April 2012), EMBASE (January 1980 to April 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to April 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 16 April 2012.

SELECTION CRITERIA: We included randomized controlled trials (RCTs) and quasi-randomized trials of eyes affected by both cataract and AMD in which cataract surgery would be compared to no surgery.

DATA COLLECTION AND ANALYSIS: Two authors independently evaluated the search results against the inclusion and exclusion criteria. Two authors independently extracted data and assessed risk of bias for included studies. We resolved discrepancies by discussion.

MAIN RESULTS: One RCT with 60 participants with visually significant cataract and AMD was included in this review. Participants were randomized to immediate cataract surgery (within two weeks of enrollment) (n = 29) or delayed cataract surgery (six months after enrollment) (n = 31). At six months, four participants were lost to follow-up; two participants from each group. The immediate surgery group showed mean improvement in best-corrected visual acuity (BCVA) compared with the delayed surgery group at six months (mean difference (MD) 0.15 LogMAR, 95% confidence interval (CI) 0.28 to 0.02). There was no significant difference in the development of choroidal neovascularization between groups (1/27 eyes in the immediate surgery group versus 0/29 eyes in the delayed surgery group). Results from Impact of Vision Impairment (IVI) questionnaires suggested that the immediate surgery group faired better with quality of life outcomes than the delayed surgery group (MD in IVI logit scores 1.60, 95% CI 0.61 to 2.59). No postoperative complication was reported. We identified a second potentially relevant study of immediate versus delayed cataract surgery in 54 people with AMD. Results for the study are not yet available, but may be eligible for future updates of this review.

AUTHORS' CONCLUSIONS: At this time, it is not possible to draw reliable conclusions from the available data to determine whether cataract surgery is beneficial or harmful in people with AMD. Physicians will have to make practice decisions based on best clinical judgment until controlled trials are conducted and their findings published.It would be valuable for future research to investigate prospective RCTs comparing

cataract surgery to no surgery in patients with AMD to better evaluate whether cataract surgery is beneficial or harmful in this group. However ethical considerations need to be addressed when delaying a potentially beneficial treatment and it may not be feasible to conduct a long-term study where surgery is withheld from the control group. Utilization of pre-existing, standardized systems for grading cataract and AMD and measuring outcomes (visual acuity, change in visual acuity, worsening of AMD and quality of life measures) should be encouraged.

PMID: 22696359 [PubMed - in process]

Stem Cells Int. 2012;2012:946090. Epub 2012 May 23.

Effect of In Vitro Exposure of Corticosteroid Drugs, Conventionally Used in AMD Treatment, on Mesenchymal Stem Cells.

Nuzzi R, Gunetti M, Rustichelli D, Roagna B, Fronticelli Bardelli F, Fagioli F, Ferrero I.

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Abstract

Age-related macular degeneration (AMD) is a leading cause of legal blindness in individuals over 60 years of age, characterized by the dysfunction of retinal pigmented epithelium cells, specifically in the macular area. Despite several treatment options, AMD therapy remains difficult, especially for exudative AMD. Multipotent mesenchymal stem cells (MSCs), with great plasticity and immunomodulant properties, are a promising cell source for cellular therapy and tissue engineering. We evaluated the effects of steroid drugs, often used to treat AMD, in association with MSCs, in view of a possible application together to treat AMD. Morphology, viability, growth kinetics, and immunophenotype were evaluated on healthy donors' MSCs, treated with triamcinolone acetonide, alcohol-free triamcinolone acetonide, micronized intravitreal triamcinolone and dexamethasone at different concentrations, and in a human retinal pigment epithelial cell line supernatant (ARPE-19). The morphological analysis of MSCs in their standard medium showed a negative correlation with drug concentrations, due to the numerous crystals. Dexamethasone was the least toxic corticosteroid used in this study. ARPE-19 seemed to help cells preserve the typical MSC morphology. In conclusion, this in vitro study demonstrated that high doses of corticosteroid drugs have a negative effect on MSCs, reduced in the presence of a conditioned media.

PMID: 22693520 [PubMed - in process] PMCID: PMC3366253 Free PMC Article

Pathogenesis

Immunol Lett. 2012 Jun 11. [Epub ahead of print]

Oxidative stress activates NLRP3 inflammasomes in ARPE-19 cells -implications for age-related macular degeneration (AMD).

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Abstract

Oxidative stress and inflammation are known to be associated with age-related macular degeneration (AMD). Retinal pigment epithelial (RPE) cells play the principal role in the immune defense of macula, and their dysfunction is a crucial event leading to clinically relevant changes seen in AMD. In the present study, we have examined the ability of oxidative stress to activate inflammasome signaling in the human ARPE-19

cells by adding the lipid peroxidation end product 4-hydroxynonenal (HNE) to cell cultures pre-treated or not treated with the endotoxin, LPS. Our results indicate that LPS and HNE significantly increased the production of IL-6 and IL-18, respectively. LPS treatment preceding HNE induced an even greater increase in the production of IL-18 than HNE alone. In addition to IL-18, HNE significantly increased the production of IL-1β. The productions of IL-1β and IL-18 were reduced in the cell cultures pre-treated with the Caspase-1 inhibitor. PCR analysis revealed that HNE induced an over 5-fold increase in the amount of NLRP3 mRNA compared to control cells; LPS had no effect. In conclusion, our present data suggest that oxidative stress can activate NLRP3 inflammasomes in RPE cells which occupy centre stage in the pathogenesis of AMD.

PMID: 22698681 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Jun 14. [Epub ahead of print]

Neuroprotective Effects of Non-Feminizing Estrogens in Retinal Photoreceptor Neurons.

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Department of Pharmacology & Neuroscience, University of North Texas Health Science Center, Institute for Aging and Alzheimer's Disease Research, Fort Worth, TX, United States.

Purpose: Retinal diseases such as macular degeneration and glaucoma are disorders that target specific retinal neurons which can ultimately lead to vision loss. Under these conditions and pathologies, retinal neurons can die via apoptosis that may be due to increased oxidative stress. Here we test the neuroprotective effects of E2 and three synthetic non-feminizing estrogen analogues (ZYC-26, ZYC-23, and ZYC-3) to examine their abilities to protect retinal neurons against glutamate toxicity.

Methods: Utilizing an in vitro model of glutamate-induced cell death in 661W cells, a mouse cone photoreceptor cell line that we showed expressed both ERs via immunoblotting, was pretreated with E2 and its analogues and the cell viability assessed.

Results: We observed that E2 and estrogen analogues, ZYC-26 and ZYC-3, were protective against a 5 mM glutamate insult in 661W cells. The neuroprotective abilities of ZYC-26 and ZYC-3 were autonomous of estrogen receptor-α (ERα) and ERβ demonstrated by their ability to protect in the presence of ICI 182,780, a pan-ER antagonist with a high affinity for the estrogen receptor. Treatment with PPT and DPN, ERα and ERβ specific agonist respectively, did not protect the 661W cells from the glutamate insult. Studying the membrane ER (mER) or GPR30 did show that activation of the receptor by G1 protected the retinal neuron from insult while G15, an antagonist of the mER was not able to antagonize the protection previously seen.

Conclusions: These data demonstrate that non-feminizing estrogens may emerge as useful compounds for neuroprotection of retinal cells.

PMID: 22700711 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2012 Jun;47(3):264-8. Epub 2012 May 12.

Plasma antiphospholipid antibody levels in age-related macular degeneration.

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PURPOSE: To investigate the association of age-related macular degeneration (AMD) with plasma antiphospholipid antibody levels.

METHODS: This prospective study included 19 patients diagnosed as having dry-type AMD, 23 patients

with exudative-type AMD, and 25 control subjects. Venous blood samples of the participants were obtained. Anticardiolipin antibodies (aCL) isotypes IgG and IgM were measured by means of an enzyme-linked immunosorbent assay. Lupus anticoagulant (LA) antibodies were measured by the dilute Russell viper venom time screen test.

RESULTS: The mean aCL IgG concentration in patients with exudative-type AMD was significantly higher than in patients with dry-type AMD and control subjects. The mean ± SE of aCL IgG levels in patients with exudative-type AMD and dry-type AMD and control subjects was 5.46 ± 1.26; 2.55 ± 0.78; and 0.32 ± 0.1, respectively. The mean aCL IgM levels and LA levels in the 3 groups were not statistically different.

CONCLUSIONS: Our findings suggest that elevated levels of serum aCL, a risk factor for cardiovascular and cerebrovascular diseases, may be associated with exudative-type AMD.

PMID: 22687304 [PubMed - in process]

Exp Eye Res. 2012 Jun 8. [Epub ahead of print]

Pathological Consequences of Long-term mitochondrial oxidative stress in the mouse retinal pigment epithelium.

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Abstract

Oxidative stress in the retinal pigment epithelium (RPE) is hypothesized to be a major contributor to the development of age-related macular degeneration (AMD). Mitochondrial manganese superoxide dismutase (MnSOD) is a critical antioxidant protein that scavenges the highly reactive superoxide radical. We speculated that specific reduction of MnSOD in the RPE will increase the level of reactive oxygen species in the retina/RPE/choroid complex leading to pathogenesis similar to geographic atrophy. To test this hypothesis, an Sod2-specific hammerhead ribozyme (Rz), delivered by AAV2/1 and driven by the human VMD2 promoter was injected subretinally into C57BL/6J mice. Dark-adapted full field electroretinogram (ERG) detected a decrease in the response to light. We investigated the age-dependent phenotypic and morphological changes of the outer retina digital fundus imaging and SD-OCT measurement of ONL thickness. Fundus microscopy revealed pigmentary abnormalities in the retina and these corresponded to sub-retinal and sub-RPE deposits seen in SD-OCT B-scans. Light and electron microscopy documented the localization of apical deposits and thickening of the RPE. In RPE flat-mounts we observed abnormally displaced nuclei and regions of apparent fibrosis in the central retina of the oldest mice. This region was surrounded by enlarged and irregular RPE cells that have been observed in eyes donated by AMD patients and in other mouse models of AMD.

PMID: 22687918 [PubMed - as supplied by publisher]

Am J Pathol. 2012 Jun 6. [Epub ahead of print]

Prevention of Age-Related Macular Degeneration-Like Retinopathy by Rapamycin in Rats.

Kolosova NG, Muraleva NA, Zhdankina AA, Stefanova NA, Fursova AZ, Blagosklonny MV.

Institute of Cytology and Genetics SB RAS, Acad. Lavrentjev, Novosibirsk, Russia.

Abstract

Age-related macular degeneration, a neurodegenerative and vascular retinal disease, is the most common

cause of blindness in the Western countries. Evidence accumulates that target of rapamycin is involved in aging and age-related diseases, including neurodegeneration. The target of rapamycin inhibitor, rapamycin, suppresses the senescent cell phenotype and extends life span in diverse species, including mice. Rapamycin decreases senescence-associated phenotypes in retinal pigment epithelial cells in culture. Herein, we investigated the effect of rapamycin on spontaneous retinopathy in senescence-accelerated OXYS rats, an animal model of age-related macular degeneration. Rats were treated with either 0.1 or 0.5 mg/kg rapamycin, which was given orally as a food mixture. In a dose-dependent manner, rapamycin decreased the incidence and severity of retinopathy. Rapamycin improved some (but not all) histological abnormalities associated with retinopathy. Thus, in retinal pigment epithelial cell layers, rapamycin decreased nuclei heterogeneity and normalized intervals between nuclei. In photoreceptor cells, associated neurons, and radial glial cells, rapamycin prevented nuclear and cellular pyknosis. More important, rapamycin prevented destruction of ganglionar neurons in the retina. Rapamycin did not exert any adverse effects on the retina in control disease-free Wistar rats. Taken together, our data suggest the therapeutic potential of rapamycin for treatment and prevention of retinopathy.

Epidemiology

Acta Ophthalmol. 2012 Jun 8. doi: 10.1111/j.1755-3768.2012.02447.x. [Epub ahead of print]

Visual impairment and blindness in rural central India: the Central India Eye and Medical Study.

Nangia V, Jonas JB, Gupta R, Khare A, Sinha A.

Suraj Eye Institute, Nagpur, Maharashtra, India Department of Ophthalmology, Medical Faculty Mannheim of the Ruprecht-Karls-University Heidelberg, Mannheim, Germany.

Purpose: The aim of the study was to investigate prevalence of visual impairment in rural central India.

Methods: The population-based Central India Eye and Medical Study included 4711 subjects with an age of 30+ years. Presenting visual acuity (PRVA) and best-corrected visual acuity (BCVA) were recorded. Visual impairment and blindness were defined using the World Health Organization (WHO) standard and United States (US) standard.

Results: On the basis of PRVA and using WHO and US standards, 1049 [22%; 95% confidence interval (CI): 21.1, 23.5] subjects and 1290 (27%; 95% CI: 26.1, 28.7) subjects, respectively, were visually impaired, and 35 (0.7%; 95% CI: 0.5, 1.0) subjects and 116 (2.5%; 95% CI: 2.0, 2.9) subjects, respectively, were blind. The corresponding age-standardized prevalence figures were 17%, 21%, 0.5% and 2%, respectively. Using best-correcting glasses could eliminate PRVA-visual impairment/blindness in 729 subjects (67% of all subjects with visual impairment/blindness). On the basis of BCVA and using WHO and US standards, 333 (7%; 95% CI: 6.3, 7.8) subjects and 473 (10%; 95% CI: 9.2, 10.9) subjects, respectively, had visual impairment, and 22 (0.5%; 95% CI: 0.3, 0.7) and 31 (0.7%; 95% CI: 0.4, 0.9) subjects, respectively, were blind. Corresponding age-standardized prevalence figures were 5%, 8%, 0.4% and 0.5%, respectively. Causes for BCVA-visual impairment/blindness were cataract (75%), postoperative posterior capsular opacification (4%), surgical complications (2%), corneal opacifications (2%), age-related macular degeneration (2%), other macular diseases (1%), and glaucoma (1%).

Conclusions: Age-standardized prevalence of PRVA-visual impairment/blindness (WHO definition) in the adult population of rural central India was 17%. Most frequent cause was undercorrected refractive error. Supply of correct glasses is the most efficient way to improve vision in the rural central India.

PMID: 22682108 [PubMed - as supplied by publisher] PMID: 22683466 [PubMed - as supplied by publisher]

Beijing Da Xue Xue Bao. 2012 Jun 18;44(3):407-11.

[Mendelian randomization study of the relationship between high-density lipoprotein cholesterol and age-related macular degeneration].

[Article in Chinese]

Qin XY, Tian J, Fang K, Li J, Yu WZ, Hou J, Chen da F, Li XX, Hu YH.

Department of Epidemiology and Biostatistics, Peking University School of Public Health, Beijing 100191, China.

OBJECTIVE: To explore genetic variants robustly associated with high-density lipoprotein cholesterol (HDL -C) by Mendelian randomization analysis and to examine its causal association with age-related macular degeneration (AMD).

METHODS: AMD cases and controls were selected from several hospitals nationwide. Their AMD was diagnosed by eye examination, serum HDL-C levels were examined by blood tests, and other informations were also collected including demographic characteristics, high risk behaviors and so on. The genetic loci hepatic lipase gene (LIPC) rs10468017 was used as instrumental variables for HDL-C.

RESULTS: The study population contained hospital-based 545 AMD patients and 480 controls. The LIPC genotypes were unrelated to all potentially confounding factors measured in this study. In conventional multivariable analyses, the HDL-C level was positively associated with AMD. The odds ratio was 2.00 (95%CI: 1.41-2.86). Instrumental variable analyses (Mendelian randomization approach) showed an increasing odds ratio of HDL-C and AMD, which was 7.15 (95%CI: 0.80-64.13).

CONCLUSION: Being different with previous observational analysis, this study did not support the status of increasing serum HDL-C level as a risk factor for AMD by Mendelian randomization analysis.

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Genetics

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Genome-wide association study of age-related macular degeneration identifies associated variants in the TNXB-FKBPL-NOTCH4 region of chromosome 6p21.3.

Cipriani V, Leung HT, Plagnol V, Bunce C, Khan JC, Shahid H, Moore AT, Harding SP, Bishop PN, Hayward C, Campbell S, Armbrecht AM, Dhillon B, Deary IJ, Campbell H, Dunlop M, Dominiczak AF, Mann SS, Jenkins SA, Webster AR, Bird AC, Lathrop M, Zelenika D, Souied EH, Sahel JA, Léveillard T; French AMD Investigators, Cree AJ, Gibson J, Ennis S, Lotery AJ, Wright AF, Clayton DG, Yates JR.

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Abstract

Age-related macular degeneration (AMD) is a leading cause of visual loss in Western populations. Susceptibility is influenced by age, environmental and genetic factors. Known genetic risk loci do not account for all the heritability. We therefore carried out a genome-wide association study of AMD in the UK population with 893 cases of advanced AMD and 2199 controls. This showed association with the well established AMD risk loci ARMS2-HTRA1 (P = 2.7 x 10(-72)), CFH (P = 2.3 x 10(-47)), C2-CFB (P = 5.2 x 10(-9)), C3 (P = 2.2 x 10(-3)) and CFI (P = 3.6 x 10(-3)) and with more recently reported risk loci at VEGFA (P = 1.2 x 10(-3)) and LIPC (P = 0.04). Using a replication sample of 1411 advanced AMD cases and 1431 examined controls we confirmed a novel association between AMD and single nucleotide polymorphisms on chromosome 6p21.3 at TNXB-FKBPL (rs12153855/rs9391734; discovery P = 4.3 x 10(-7), replication P = 3.0 x 10(-4),

combined P = 1.3 x 10(-9), OR = 1.4, 95% CI = 1.3 - 1.6) and the neighbouring gene NOTCH4 (rs2071277; discovery P = 3.2 x 10(-8), replication P = 3.8 x 10(-5), combined P = 2.0 x 10(-11), OR = 1.3, 95% CI = 1.2 - 1.4). These associations remained significant in conditional analyses which included the adjacent C2-CFB locus. TNXB, FKBPL and NOTCH4 are all plausible AMD susceptibility genes, but further research will be needed to identify the causal variants and determine whether any of these genes are involved in the pathogenesis of AMD.

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Genetic analysis of simultaneous geographic atrophy and choroidal neovascularization.

Grob S, Luo J, Hughes G, Lee C, Zhou X, Lee J, Du H, Ferreyra H, Freeman WR, Kozak I, Zhang K.

Source

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Aim: To investigate clinical presentation and genotypes in patients with simultaneous geographic atrophy (GA) and choroidal neovascularization (CNV) and to compare with patients with GA or CNV only.

Patients and methods: Twenty patients with combined CNV-GA and 154 CNV only and 154 GA only were chosen based on clinical exam and imaging. Six single-nucleotide polymorphisms (SNPs)-rs2274700 and rs1061170 (complement factor H), rs10490924 and rs11200638 (HTRA1/LOC387715), rs2230199 (C3), rs9332739 (C2)-were genotyped using the SNaPshot method. Chi-squared tests were used for genetic analysis.

Results: In patients with CNV-GA, GA progressed slowly and often preceded CNV. CNV presented as subretinal haemorrhage or fluid, with a sudden drop in visual acuity (VA). Comparing combined CNV-GA to GA and CNV only, patients with both had a higher frequency of at-risk alleles at both SNPs within the HTRA1 gene-rs10490924 (52.5%), rs11200638 (52.6%). Statistical significance was not achieved. CNV-GA patients had no protective alleles at SNP rs9332739 (C2), compared with GA (27%) and CNV only (10%).

Conclusion: There is a paucity of reports describing simultaneous CNV-GA. Clinical and genetic results may support the fact that GA and CNV fit on an age-related macular degeneration (AMD)-disease continuum and may clarify the disease processes in AMD.Eye advance online publication, 15 June 2012; doi:10.1038/eye.2012.107.

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Diet

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Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration.

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BACKGROUND: There is inconclusive evidence from observational studies to suggest that people who eat

a diet rich in antioxidant vitamins (carotenoids, vitamins C and E) or minerals (selenium and zinc) may be less likely to develop age-related macular degeneration (AMD).

OBJECTIVES: To examine the evidence as to whether or not taking antioxidant vitamin or mineral supplements prevents the development of AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2011, Issue 12), MEDLINE (January 1950 to January 2012), EMBASE (January 1980 to January 2012), Open Grey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on 26 January 2012.

SELECTION CRITERIA: We included all randomised controlled trials (RCTs) comparing an antioxidant vitamin and/or mineral supplement (alone or in combination) to control.

DATA COLLECTION AND ANALYSIS: Both review authors independently assessed risk of bias in the included studies and extracted data. One author entered data into RevMan 5 and the other author checked the data entry. We pooled data using a fixed-effect model.

MAIN RESULTS: We included four RCTs in this review; 62,520 people were included in the analyses. The trials were conducted in Australia, Finland and the USA and investigated vitamin E and beta-carotene supplements. Overall the quality of the evidence was high. People who took these supplements were not at decreased (or increased) risk of developing AMD. The pooled risk ratio for any antioxidant supplement in the prevention of any AMD was 0.98 (95% confidence interval 0.89 to 1.08) and for advanced AMD was 1.05 (95% CI 0.80 to 1.39). Similar results were seen when the analyses were restricted to beta-carotene and alpha-tocopherol alone.

AUTHORS' CONCLUSIONS: There is accumulating evidence that taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. There is no evidence with respect to other antioxidant supplements, such as vitamin C, lutein and zeaxanthin, or any of the commonly marketed multivitamin combinations. Although generally regarded as safe, vitamin supplements may have harmful effects and clear evidence of benefit is needed before they can be recommended. People with AMD should see the related Cochrane review 'Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration' written by the same review team.

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