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MD Research News

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Drug Management

Acta Ophthalmol. 2012 Feb 17. doi: 10.1111/j.1755-3768.2011.02353.x. [Epub ahead of print]

Short-term progression of wet AMD and correlation with 1-year treatment results.

Munk M, Kiss C, Sulzbacher F, Eisenkölbl S, Sacu S, Kalcher K, Jampol L, Schmidt-Erfurth U.

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria Department of Statistics and Probability Theory, University of Technology, Vienna, Austria Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA.

Purpose: Quantification of short-term progression of active neovascular age-related macular degeneration and correlation with 1-year outcome.

Methods: Sixty-five patients with newly diagnosed treatment-naive active subfoveal choroidal neovascularization (CNV), who had participated in clinical trials testing anti-vascular endothelial growth factor therapy, were retrospectively assessed. Early Treatment Diabetic Retinopathy Study best-corrected visual acuity (BCVA), Spectral Domain Optical Coherence Tomography (SD-OCT) and fluorescein angiography (FA) were performed twice during the pretreatment period. Changes in BCVA, central retinal thickness (CRT), average macular thickness (AMT) and leakage area were documented within this pretreatment period for all patients and for lesion type I (occult CNV, n = 42) and type II (classic CNV, n = 23). Three-month and 1-year BCVA were then correlated with the pretreatment period.

Results: The pretreatment period was 19 ± 3 days (range: 2-108). Neither type I nor type II lesions showed a significant BCVA decrease or CRT/AMT increase during this period. On FA, mean leakage area increased significantly during the pretreatment period: in the pooled group from 5.50 ± 0.62 (screening) to 7.60 ± 0.86 mm(2) (baseline) ($p < 0.0001$), in type II from 4.65 ± 0.90 to 7.83 ± 1.62 mm(2) ($p < 0.01$) and in type I from 6.08 ± 0.85 to 7.45 ± 0.96 mm(2) ($p < 0.0001$). The mean increase in leakage area per day was 0.046 ± 0.02 mm(2) , $p = 0.034$. Type II showed a daily growth of 0.09 ± 0.08 mm(2) ($p < 0.042$) and type I 0.045 ± 0.008 mm(2) per day ($p < 0.0001$). However, neither leakage area increase nor pretreatment period was correlated with 3-month or 1-year BCVA outcome.

Conclusions: SD-OCT and BCVA testing did not reveal deterioration during the pretreatment period. However, the leakage area progressed rapidly. Despite the rapid increasing leakage area, the 19-day waiting period was not associated with a poorer visual outcome at 3 months and 1 year.

PMID: 22339794 [PubMed - as supplied by publisher]

Ophthalmologica. 2012 Feb 21. [Epub ahead of print]

Safety of Submacular Suprachoroidal Drug Administration via a Microcatheter: Retrospective Analysis of European Treatment Results.

Tetz M, Rizzo S, Augustin AJ.

Berlin Eye Research Institute, Berlin, Germany.

Purpose: To investigate the safety and feasibility of using a microcatheter for drug delivery in the suprachoroidal space in eyes with advanced, exudative, age-related macular degeneration (AMD) unresponsive to conventional therapy.

Procedures: A unique microcatheter was used to deliver a drug combination consisting of bevacizumab and triamcinolone to the submacular suprachoroidal space. Twenty-one eyes of 21 patients with choroidal neovascularization (CNV) secondary to advanced, exudative AMD were followed over a 6-month postprocedure period.

Results: The microcatheter was successfully and atraumatically inserted into the suprachoroidal space of all eyes. No serious intraoperative or postoperative complications including suprachoroidal hemorrhages were encountered. Postsurgically, complications consisted of 1 eye experiencing a transient elevation in intraocular pressure at 3 months, which was medically controlled, and 2 eyes (10.5%) with an apparent increase in nuclear sclerotic cataracts.

Conclusions: Suprachoroidal drug administration was achieved without serious complication using a novel microcatheter. Direct drug delivery to the choroid can potentially increase local tissue drug levels and drug efficacy for the treatment of AMD and other diseases associated with CNV.

PMID: 22354263 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Feb 17. doi: 10.1111/j.1755-3768.2011.02363.x. [Epub ahead of print]

Long-term outcomes of intravitreal ranibizumab for choroidal neovascularization secondary to Best's disease: 3-year follow-up.

Ruiz-Moreno O, Calvo P, Ferrández B, Torrón C.

Department of Ophthalmology, Miguel Servet University Hospital, Zaragoza, Spain.

PMID:22339886 [PubMed - as supplied by publisher]

Med Lett Drugs Ther. 2012 Feb 6;54(1383):9-10.

Aflibercept (Eylea) for age-related macular degeneration.

[No authors listed]

PMID: 22354219 [PubMed - in process]

Semin Ophthalmol. 2012 Jan;27(1-2):29-32.

Management of Inflammatory Choroidal Neovascularization (CNV) Secondary to Punctate Inner Choroidopathy in a Young Female of Childbearing Age with Intra-vitreal Ranibizumab and Half-fluence Photodynamic Therapy (PDT) - A Holistic Approach.

Cornish KS, Lim LT, Imrie F.

Raigmore Hospital , Inverness , UK.

Abstract

Choroidal neovascularization (CNV) may occur in up to 40% of patients with punctate inner choroidopathy (PIC). We report a case of a young woman of childbearing age treated successfully for an inflammatory choroidal neovascular membrane (CNV) secondary to PIC with a combination of intravitreal ranibizumab and photodynamic therapy (PDT).

PMID: 22352824 [PubMed - in process]

Graefes Arch Clin Exp Ophthalmol. 2012 Feb 21. [Epub ahead of print]

Vascularized retinal pigment epithelial detachment in age-related macular degeneration: treatment and RPE tear incidence.

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BACKGROUND: To review vascularized-pigment epithelial detachment (V-PED) treatment visual outcome, and to assess acute retinal pigment epithelium (RPE) tear incidence.

METHODS: One hundred and thirty-two eyes of 125 consecutive patients with age-related macular degeneration and V-PED were included. Ninety-four eyes (71.2%) were associated with choroidal new vessels (CNV), 38 (28.8%) with retinal angiomatous proliferation (RAP). Patients, treated over a 10-year period with the time-current therapy, received: verteporfin photodynamic therapy (PDT) (group 1, 38 eyes), combined intravitreal triamcinolone acetonide (IVTA) and PDT (group 2, 44 eyes) or intravitreal anti-VEGF injection (bevacizumab or ranibizumab) (group 3, 50 eyes).

RESULTS: Mean follow-up was 20.5 months. At month 12, all eyes treated with PDT or with IVTA and PDT showed a mean significant severe visual decrease. Eyes with CNV lost -0.67 and -0.37 logMAR ($p < 0.01$ and $p < 0.01$ respectively), and eyes with RAP -0.55 and -0.31 logMAR ($p < 0.01$ and $p = 0.01$ respectively). RPE tear occurred in 14 eyes (36.8%) and in six eyes (13.6%) in groups 1 and 2 respectively. Eyes treated with anti-VEGF therapy showed slight mean visual acuity decrease at month 12. Those with CNV had a mean baseline best-corrected visual acuity (BCVA) of 0.36 ± 0.24 logMAR, final of 0.44 ± 0.30 logMAR (-0.08 logMAR, n.s.). In eyes with RAP, mean baseline BCVA was 0.58 ± 0.39 logMAR, final was 0.78 ± 0.47 logMAR (-0.20 logMAR, n.s.). RPE tear occurred in 14 eyes (36.8%). Patients with either V-PED with CNV or a better baseline BCVA showed greater risk of acute RPE tear ($p = 0.01$ and $p = 0.003$ respectively).

CONCLUSIONS: Effective treatment for vascularized PED is still lacking. Until now, only stabilization of the disease has been achieved using anti-VEGF therapy, but the risk of RPE tear can further hamper our expectations. Baseline characteristics are helpful for prognosis, but patients must be informed of the uncertain response. New therapeutic strategies are needed.

PMID: 22350060 [PubMed - as supplied by publisher]

Drugs. 2012 Mar 5;72(4):509-23. doi: 10.2165/11208410-000000000-00000.

Ranibizumab: in diabetic macular oedema.

Frampton JE.

Adis, Auckland, New Zealand.

Abstract

Ranibizumab, an intravitreally administered inhibitor of vascular endothelial growth factor (VEGF), is approved for the treatment of visual impairment associated with diabetic macular oedema (DME) in the EU. In four well designed, phase II or III trials (RESOLVE, RESTORE, RIDE and RISE), 1-2 years' treatment with ranibizumab was more effective than sham or focal/grid laser therapy in improving best corrected visual acuity (BCVA) and reducing central retinal thickness (CRT) in patients with visual impairment associated with DME. Additionally, in two well designed phase III trials (RESTORE and DRCR.net-1), 1 year of treatment with ranibizumab as an adjunct to laser therapy was more effective than laser monotherapy in improving BCVA and CRT in patients with visual impairment associated with DME. Improvements in BCVA with ranibizumab alone or as an adjunct to laser therapy were observed at the first follow-up visits in these studies (i.e. 1-4 weeks after the start of treatment), and were associated with gains in vision-related quality of life, as assessed using the National Eye Institute Visual Functioning Questionnaire-25. The ocular and non-ocular adverse event profile of ranibizumab in patients with DME is similar to that observed in patients with neovascular (wet) age-related macular degeneration or retinal vein occlusion. Based on tolerability data from clinical trials, there is no indication that ranibizumab alone or combined with laser is associated with an increased risk of cardiovascular or cerebrovascular events potentially related to systemic VEGF inhibition.

PMID: 22356289 [PubMed - in process]

Health Technol Assess. 2012 Feb;16(6):1-200.

Verteporfin photodynamic therapy for neovascular age-related macular degeneration: cohort study for the UK.

Reeves B, Harding S, Langham J, Grieve R, Tomlin K, Walker J, Guerriero C, Carpenter J, Patton W, Muldrew K, Peto T, Chakravarthy U.

London School of Hygiene and Tropical Medicine, London, UK.

OBJECTIVES: The verteporfin photodynamic therapy (VPDT) cohort study aimed to answer five questions: (a) is VPDT in the NHS provided as in randomised trials?; (b) is 'outcome' the same in the nhs as in randomised trials?; (c) is 'outcome' the same for patients ineligible for randomised trials?; (d) is VPDT safe when provided in the NHS?; and (e) how effective and cost-effective is VPDT?

DESIGN: Treatment register.

SETTING: All hospitals providing VPDT in the NHS.

PARTICIPANTS: All patients attending VPDT clinics.

INTERVENTIONS: Infusion of verteporfin followed by infrared laser exposure is called VPDT, and is used to treat neovascular age-related macular degeneration (nAMD). The VPDT cohort study advised clinicians to follow patients every 3 months during treatment or active observation, retreating based on criteria used in the previous commercial 'TAP' (Treatment of Age-related macular degeneration with Photodynamic therapy) trials of VPDT.

MAIN OUTCOME MEASURES: The primary outcome was logarithm of the minimum angle of resolution monocular best-corrected distance visual acuity (BCVA). Secondary outcomes were adverse reactions and events; morphological changes in treated nAMD (wet) lesions; and for a subset of patients, 6-monthly contrast sensitivity, generic and visual health-related quality of life (HRQoL) and resource use. Treated eyes were classified as eligible for the TAP trials (EFT), ineligible (IFT) or unclassifiable (UNC).

RESULTS: Forty-seven hospitals submitted data for 8323 treated eyes in 7748 patients; 4919 eyes in 4566 patients were treated more than 1 year before the last data submission or had completed treatment. Of 4043 eyes with nAMD in 4043 patients, 1227 were classified as EFT, 1187 as IFT and 1629 as UNC. HRQoL and resource use data were available for about 2000 patients. The mean number of treatments in years 1 and 2 was 2.3 and 0.4 respectively. About 50% of eyes completed treatment within 1 year. BCVA

deterioration in year 1 did not differ between eligibility groups. EFT eyes lost 11.6 letters (95% confidence interval 10.1 to 13.0 letters) compared with 9.9 letters in VPDT-treated eyes in the TAP trials. EFT eyes had poorer BCVA at baseline than IFT and UNC eyes. Adverse reactions and events were reported for 1.4% of first visits - less frequently than those reported in the TAP trials. Associations between BCVA in the best-seeing eye with HRQoL and community health and social care resource use showed that the 11-letter difference in BCVA between VPDT and sham treatment in the TAP trials corresponded to differences in utility of 0.012 and health and social service costs of £60 and £92 in years 1 and 2, respectively. VPDT provided an incremental cost per quality-adjusted life-year (QALY) of £170,000 over 2 years.

CONCLUSIONS: VPDT was administered less frequently than in the TAP trials, with less than half of those treated followed up for > 1 year in routine clinical practice. Deterioration in BCVA over time in EFT eyes was similar to that in the TAP trials. The similar falls in BCVA after VPDT across the pre-defined TAP eligibility groups do not mean that the treatment is equally effective in these groups because deterioration in BCVA can be influenced by the parameters that determined group membership. Safety was no worse than in the TAP trials. The estimated cost per QALY was similar to the highest previous estimate. Although VPDT is no longer in use as monotherapy for neovascular AMD, its role as adjunctive treatment has not been fully explored. VPDT also has potential as monotherapy in the management of vascular malformations of the retina and choroid and with trials underway in neovascularisation due to myopia and polypoidal choroidopathy.

PMID: 22348600 [PubMed - in process]

Other treatments & diagnosis

Clin Ophthalmol. 2012;6:219-23. Epub 2012 Feb 9.

Spectral domain OCT versus time domain OCT in the evaluation of macular features related to wet age-related macular degeneration.

Pierro L, Zampedri E, Milani P, Gagliardi M, Isola V, Pece A.

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BACKGROUND: The aim of this study was to compare the agreement between spectral domain optical coherence tomography (SD OCT) and time domain stratus OCT (TD OCT) in evaluating macular morphology alterations in wet age-related macular degeneration (AMD).

METHODS: This retrospective study was performed on 77 eyes of 77 patients with primary or recurring subfoveal choroidal neovascularization secondary to AMD. All patients underwent OCT examination using Zeiss Stratus OCT 3 (Carl Zeiss Meditec Inc, Dublin, CA) and Opko OTI Spectral SLO/OCT (Ophthalmic Technologies Inc, Toronto, Canada). In all radial line scans, the presence of intraretinal edema (IRE), serous pigment epithelium detachment (sPED), neurosensory serous retinal detachment (NSRD), epiretinal membrane (EM), inner limiting membrane thickening (ILMT), and hard exudates (HE) were evaluated. The degree of matching was quantified by Kappa measure of agreement.

RESULTS: THE PERCENTAGE DISTRIBUTION OF TD OCT FINDINGS VERSUS SD OCT FINDINGS WAS: IRE 36.3% versus 77.9%, sPED 57.1% versus 85.7%, NSRD 38.9% versus 53.2%, EM 10.5% versus 26.3%, ILMT 3.8% versus 32.4%, and HE 6.4% versus 54.5%. The agreement was as follows: sPED: kappa value 0.15; NSRD: kappa value 0.61; IRE: kappa value 0.18; EM: kappa value 0.41; ILMT: kappa value 0.02; HE: kappa value 0.06.

CONCLUSION: The agreement in the evaluation of macular lesions between the two techniques is poor and depends on the lesion considered. SD OCT allows better detection of the alterations typically related to choroidal neovascularization such as IRE, PED, ILM thickening, and HE. Consequently its use should be strongly considered in patients with wet AMD.

PMID: 22347793 [PubMed - in process] PMCID: PMC3280103

Cell Tissue Res. 2012 Feb 23. [Epub ahead of print]

Cell-replacement therapy and neural repair in the retina.

Schmeer CW, Wohl SG, Isenmann S.

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Abstract

Visual impairment severely affects the quality of life of patients and their families and is also associated with a deep economic impact. The most common pathologies responsible for visual impairment and legally defined blindness in developed countries include age-related macular degeneration, glaucoma and diabetic retinopathy. These conditions share common pathophysiological features: dysfunction and loss of retinal neurons. To date, two main approaches are being taken to develop putative therapeutic strategies: neuroprotection and cell replacement. Cell replacement is a novel therapeutic approach to restore visual capabilities to the degenerated adult neural retina and represents an emerging field of regenerative neurotherapy. The discovery of a population of proliferative cells in the mammalian retina has raised the possibility of harnessing endogenous retinal stem cells to elicit retinal repair. Furthermore, the development of suitable protocols for the reprogramming of differentiated somatic cells to a pluripotent state further increases the therapeutic potential of stem-cell-based technologies for the treatment of major retinal diseases. Stem-cell transplantation in animal models has been most effectively used for the replacement of photoreceptors, although this therapeutic approach is also being used for inner retinal pathologies. In this review, we discuss recent advances in the development of cell-replacement approaches for the treatment of currently incurable degenerative retinal diseases.

PMID: 22354517 [PubMed - as supplied by publisher]

Ophthalmic Physiol Opt. 2012 Feb 21. doi: 10.1111/j.1475-1313.2012.00897.x. [Epub ahead of print]

Sensory and demographic characteristics of deafblindness rehabilitation clients in Montréal, Canada.

Wittich W, Watanabe DH, Gagné JP.

Centre de recherche institut universitaire de gériatrie de Montréal, Montréal MAB-Mackay Rehabilitation Centre, Montréal, Canada.

Citation information: Wittich W, Watanabe DH & Gagné J-P. Sensory and demographic characteristics of deafblindness rehabilitation clients in Montréal Canada. Ophthalmic Physiol Opt 2012. doi: 10.1111/j.1475-1313.2012.00897.x

Purpose: Demographic changes are increasing the number of older adults with combined age-related vision and hearing loss, while medical advances increase the survival probability of children with congenital dual (or multiple) impairments due to pre-maturity or rare hereditary diseases. Rehabilitation services for these populations are highly in demand since traditional uni-sensory rehabilitation approaches using the other sense to compensate are not always utilizable. Very little is currently known about the client population characteristics with dual sensory impairment. The present study provides information about demographic and sensory variables of persons in the Montreal region that were receiving rehabilitation for dual impairment in December 2010. This information can inform researchers, clinicians, educators, as well as administrators about potential research and service delivery priorities.

Method: A chart review of all client files across the three rehabilitation agencies that offer integrated dual sensory rehabilitation services in Montreal provided data on visual acuity, visual field, hearing detection thresholds, and demographic variables.

Results: The 209 males and 355 females ranged in age from 4 months to 105 years (M = 71.9, S.D.

= 24.6), indicating a prevalence estimate for dual sensory impairment at 15/100 000. Only 5.7% were under 18 years of age, while 69.1% were over the age of 65 years, with 43.1% over the age of 85 years. The diagnostic combination that accounted for 31% of the entire sample was age-related macular degeneration with presbycusis. Their visual and auditory measures indicated that older adults were likely to fall into moderate to severe levels of impairment on both measures. Individuals with Usher Syndrome comprised 20.9% (n = 118) of the sample.

Conclusion: The age distribution in this sample of persons with dual sensory impairment indicates that service delivery planning will need to strongly consider the growing presence of older adults as the baby-boomers approach retirement age. The distribution of their visual and auditory limits indicates that the large majority of this client group has residual vision and hearing that can be maximized in the rehabilitation process in order to restore functional abilities and social participation. Future research in this area should identify the specific priorities in both rehabilitation and research in individuals affected with combined vision and hearing loss.

PMID: 22348651 [PubMed - as supplied by publisher]

Neurosci Lett. 2012 Feb 3. [Epub ahead of print]

Artificial vision through neuronal stimulation.

Fernandes RA, Diniz B, Ribeiro R, Humayun M.

Keck School of Medicine, University of Southern California, Doheny Eye Institute, Los Angeles, CA, United States; Universidade Federal de São Paulo, Unifesp, EPM, São Paulo, Brazil.

INTRODUCTION: The term visual prosthesis refers to any device capable of eliciting visual percepts in an individual through electrical stimulation of any part of the visual system.

BACKGROUND: Blindness can be due to eye pathology or due to damage of the lateral geniculate or visual cortex. Eye pathology other than diseases that affect the cornea and lens are numerous and some of the leading causes are diabetic retinopathy, age-related macular degeneration, retinal detachment, glaucoma, and retinal vascular occlusions. The visual prosthesis can be divided into non-retinal and retinal approaches. Non-retinal approaches include cortical and optic nerve prosthesis. Retinal approaches are aimed at eye pathologies in which at least part of the optic nerve remains intact whereas when the optic nerve is nearly completely damaged and/or the eye itself is disfigured or degenerated then a non-retinal approach is warranted. The retinal prosthesis can be placed on the surface of the retina, in the subretinal space or in the suprachoroidal space.

RESULTS: Several independent groups related variable degrees of success in promoting visual sensations through electrical stimulation of the visual system. Every technique, equipment and anatomical target has its advantages and disadvantages, and the biological/electrical-mechanical interface is still the aspect of the research towards a chronic, long term, reliable biomimetic implant.

CONCLUSIONS: The visual prostheses have achieved significant developments in recent years. We see continued improvement in visual acuity with increasing number and density of electrodes. Even though the visual acuity is still poor relative to normal vision, these subjects can read letters using their implants. Perhaps more importantly, blind patients can use these devices for mobility and orientation.

PMID: 22342306 [PubMed - as supplied by publisher]

J Cataract Refract Surg. 2012 Mar;38(3):415-8.

Implantation of multifocal intraocular lenses using a magnification strategy in cataractous eyes with age-related macular degeneration.

Gayton JL, Mackool RJ, Ernest PH, Seabolt RA, Dumont S.

From Eyesight Associates (Gayton, Seabolt, Dumont), Warner Robins, Georgia, the Mackool Eye Institute (Mackool), Astoria, New York, and TLC Eye Care of Michigan (Ernest), Jackson, Michigan, USA.

PURPOSE: To examine visual function after targeting -2.0 diopter (D) spherical equivalent (SE) when implanting a multifocal intraocular lens (IOL) in eyes with cataract and age-related macular degeneration (AMD).

SETTING: Three private practices.

DESIGN: Case series.

METHODS: Lenses of cataractous eyes with AMD were replaced with the Acrysof Restor SN60D3 multifocal IOL, targeting an SE of -2.0 D, which yielded +5.2 D near addition. Near and distance visual acuities were examined. Patients completed a visual function questionnaire preoperatively and 6 months postoperatively.

RESULTS: At 6 months, 13 patients with 20 eligible eyes were examined. The uncorrected near visual acuity improved in 18 eyes (90%) and was unchanged in 2 eyes. The corrected distance visual acuity improved in 14 eyes (70%), was unchanged in 4 eyes (20%), and decreased (≤3 lines) in 2 eyes (10%). All vision-related questionnaire items improved.

CONCLUSION: For cataractous eyes with AMD, replacing the crystalline lens with this myopia-targeted multifocal IOL improved or maintained near vision without severely compromising distance vision.

PMID: 22340604 [PubMed - in process]

Pathogenesis

J Cell Sci. 2012 Feb 22. [Epub ahead of print]

Chronic photo-oxidative stress and subsequent MCP-1 activation as causative factors for age-related macular degeneration.

Suzuki M, Tsujikawa M, Itabe H, Du ZJ, Xie P, Matsumura N, Fu X, Zhang R, Sonoda KH, Egashira K, Hazen SL, Kamei M.

Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly in developed countries. Although pathogenic factors, such as oxidative stress, inflammation, and genetics are thought to contribute to the development of AMD, little is known about the relationships and priorities between these factors. Here, we show that chronic photo-oxidative stress is an environmental factor involved in AMD pathogenesis. We first demonstrated that light exposure induced phospholipid oxidation in the mouse retina, which was more prominent in aged animals. The induced oxidized phospholipids led to an increase in the expression of monocyte chemoattractant protein-1, which then resulted in macrophage accumulation, an inflammatory process. Antioxidant treatment prevented light-induced phospholipid oxidation and the subsequent increase of monocyte chemoattractant protein-1, which are the beginnings of the light-induced changes. Subretinal application of oxidized phospholipids induced choroidal neovascularization, a characteristic feature of wet-type AMD, which was inhibited by blocking monocyte chemoattractant protein-1. These findings strongly suggest that a sequential cascade from photic stress to inflammatory processes via phospholipid oxidation has an important role in AMD pathogenesis. Finally, we succeeded in mimicking human AMD in mice with low level, long-term photic stress, in which characteristic pathological changes, including choroidal neovascularization formation, were observed. Therefore, we propose a consecutive pathogenic pathway involving photic stress, oxidation of phospholipids, and chronic inflammation, leading to angiogenesis. These findings add to the current understanding of AMD pathology and suggest protection

from oxidative stress or suppression of the subsequent inflammation as new potential therapeutic targets for AMD.

PMID: 22357958 [PubMed - as supplied by publisher]

Int J Biochem Cell Biol. 2012 Feb 13. [Epub ahead of print]

Oxidized low density lipoprotein-induced senescence of retinal pigment epithelial cells is followed by outer blood-retinal barrier dysfunction.

Kim JH, Lee SJ, Kim KW, Yu YS, Kim JH.

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Abstract

Age-related macular degeneration is the most common cause of vision loss in the elderly, which starts from aging processes of retinal pigment epithelial cells. Among variable risk factors in occurrence and progression of age-related macular degeneration, oxidized low density lipoprotein could be causally involved in pathobiological changes of RPE cells. Herein we showed that oxidized low density lipoprotein-induced senescence of retinal pigment epithelial cells is followed by outer blood-retinal barrier dysfunction. Under sub-lethal concentration, oxidized low density lipoprotein could promote advanced senescence of retinal pigment epithelial cells. Interestingly expression of CRALBP and RPE 65, indicators of retinal pigment epithelial cell differentiation, was decreased by oxidized low density lipoprotein. In addition, oxidized low density lipoprotein induced reactive oxygen species production and up-regulated inflammatory factors such as tumor necrosis factor-α and vascular endothelial growth factor, when β-catenin, a critical mediator of the canonical Wnt pathway, was also elevated. Oxidized low density lipoprotein increased paracellular permeability of retinal pigment epithelial cells, when zonula occludens-1 at intercellular junctions markedly decreased as well. Furthermore, in retinal pigment epithelial cells and choriocapillaris of human apolipoprotein E2 transgenic mouse eye, increased vascular endothelial growth factor and decreased zonula occludens-1 expression was observed. Therefore, our results suggest that oxidized low density lipoprotein could promote senescence of retinal pigment epithelial cells which leads to induce outer blood-retinal barrier dysfunction as an early pathogenesis of age-related macular degeneration.

PMID: 22349216 [PubMed - as supplied by publisher]

Am J Pathol. 2012 Feb 16. [Epub ahead of print]

Ferroxidase Hephaestin's Cell: Autonomous Role in the Retinal Pigment Epithelium.

Wolkow N, Song D, Song Y, Chu S, Hadziahmetovic M, Lee JC, Iacovelli J, Grieco S, Dunaief JL.

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Abstract

Hephaestin (Heph) is a ferroxidase protein that converts ferrous to ferric iron to facilitate cellular iron export by ferroportin. Many tissues express either Heph or its homologue, ceruloplasmin (Cp), but the retina expresses both. In mice, a combined systemic mutation of Heph and systemic knockout of Cp (Cp(-/-), Heph(sla/sla)) causes retinal iron accumulation and retinal degeneration, with features of human age-related macular degeneration; however, the role of Heph and Cp in the individual retinal cells is unclear. Herein, we used conditional knockout mice to study Heph's role in retinal pigment epithelial (RPE) and photoreceptor cells. Loss of both Heph and Cp from RPE cells alone results in RPE cell iron accumulation and degeneration. We found, however, that RPE iron accumulation in these conditional knockout mice is

not as great as in systemic knockout mice. Photoreceptor-specific Heph knockout indicates that the additional iron in the RPE cells does not result from loss of ferroxidases in the photoreceptors, and Cp and Heph play minor roles in photoreceptors. Instead, loss of ferroxidases in other retinal cells causes retinal iron accumulation and transfer of iron to the RPE cells. Cp and Heph are necessary for iron export from the retina but are not essential for iron import into the retina. Thus, our studies, revise how we think about iron import and export from the retina.

PMID: 22342521 [PubMed - as supplied by publisher]

PLoS One. 2012;7(2):e30874. Epub 2012 Feb 13.

Mitochondrial haplogroups and control region polymorphisms in age-related macular degeneration: a case-control study.

Mueller EE, Schaier E, Brunner SM, Eder W, Mayr JA, Egger SF, Nischler C, Oberkofler H, Reitsamer HA, Patsch W, Sperl W, Kofler B.

Research Program for Receptor Biochemistry and Tumor Metabolism, Department of Pediatrics, Paracelsus Medical University, Salzburg, Austria.

BACKGROUND: Onset and development of the multifactorial disease age-related macular degeneration (AMD) are highly interrelated with mitochondrial functions such as energy production and free radical turnover. Mitochondrial dysfunction and overproduction of reactive oxygen species may contribute to destruction of the retinal pigment epithelium, retinal atrophy and choroidal neovascularization, leading to AMD. Consequently, polymorphisms of the mitochondrial genome (mtDNA) are postulated to be susceptibility factors for this disease. Previous studies from Australia and the United States detected associations of mitochondrial haplogroups with AMD. The aim of the present study was to test these associations in Middle European Caucasians.

METHODOLOGY/PRINCIPAL FINDINGS: Mitochondrial haplogroups (combinations of mtDNA polymorphisms) and mitochondrial CR polymorphisms were analyzed in 200 patients with wet AMD (choroidal neovascularization, CNV), in 66 patients with dry AMD, and in 385 controls from Austria by means of multiplex primer extension analysis and sequencing, respectively. In patients with CNV, haplogroup H was found to be significantly less frequent compared to controls, and haplogroup J showed a trend toward a higher frequency compared to controls. Five CR polymorphisms were found to differ significantly in the two study populations compared to controls, and all, except one (T152C), are linked to those haplogroups.

CONCLUSIONS/SIGNIFICANCE: It can be concluded that haplogroup J is a risk factor for AMD, whereas haplogroup H seems to be protective for AMD.

PMID: 22348027 [PubMed - in process] PMCID: PMC3278404

Biochim Biophys Acta. 2012 Feb 8. [Epub ahead of print]

Sterculic acid antagonizes 7-ketocholesterol-mediated inflammation and inhibits choroidal neovascularization.

Huang JD, Amaral J, Lee JW, Larrayoz IM, Rodriguez IR.

Mechanism of Retinal Diseases Section, Laboratory of Retinal Cell and Molecular Biology, National Eye Institute, National Institutes of Health, Bethesda, MD, USA.

Abstract

Sterculic acid is a cyclopropene fatty acid with numerous biological activities. In this study we demonstrate

that sterculic acid is a potent inhibitor of endoplasmic reticulum (ER) stress and related inflammation caused by 7-ketocholesterol (7KCh). 7KCh is a highly toxic oxysterol suspected in the pathogenesis of various age-related diseases such as atherosclerosis, Alzheimer's disease and age-related macular degeneration. Sterculic acid demonstrated to be 5-10 times more effective than other anti-inflammatory fatty acids at inhibiting 7KCh-mediated inflammatory responses in cultured cells. In vivo, sterculic acid was effective at inhibiting the formation of choroidal neovascularization (CNV) in the laser-injury rat model. Our data suggests that sterculic acid may be useful in treating CNV in certain forms of age-related macular degeneration.

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Genetics

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Copy number variation of age-related macular degeneration relevant genes in the Korean population.

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PURPOSE: Studies that analyzed single nucleotide polymorphisms (SNP) in various genes have shown that genetic factors are strongly associated with age-related macular degeneration (AMD) susceptibility. Copy number variation (CNV) may be an additional type of genetic variation that contributes to AMD pathogenesis. This study investigated CNV in 4 AMD-relevant genes in Korean AMD patients and control subjects.

METHODS: Four CNV candidate regions located in AMD-relevant genes (VEGFA, ARMS2/HTRA1, CFH and VLDLR), were selected based on the outcomes of our previous study which elucidated common CNVs in the Asian populations. Real-time PCR based TaqMan Copy Number Assays were performed on CNV candidates in 273 AMD patients and 257 control subjects.

RESULTS: The predicted copy number (PCN, 0, 1, 2 or 3+) of each region was called using the CopyCaller program. All candidate genes except ARMS2/HTRA1 showed CNV in at least one individual, in which losses of VEGFA and VLDLR represent novel findings in the Asian population. When the frequencies of PCN were compared, only the gain in VLDLR showed significant differences between AMD patients and control subjects ($p=0.025$). Comparisons of the raw copy values (RCV) revealed that 3 of 4 candidate genes showed significant differences (2.03 vs. 1.92 for VEGFA, $p<0.01$; 2.01 vs. 1.97 for CFH, $p<0.01$; 1.97 vs. 2.01, $p<0.01$ for ARMS2/HTRA1).

CONCLUSION: CNVs located in AMD-relevant genes may be associated with AMD susceptibility. Further investigations encompassing larger patient cohorts are needed to elucidate the role of CNV in AMD pathogenesis.

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