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MD Research News

Issue 187

Tuesday 1 July, 2014

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Drug treatment

Am J Ophthalmol. 2014 Jun 25. pii: S0002-9394(14)00356-0. doi: 10.1016/j.ajo.2014.06.009. [Epub ahead of print]

Serum and plasma vascular endothelial growth factor concentrations before and after intravitreal injection of aflibercept or ranibizumab for age-related macular degeneration.

Wang X, Sawada T, Sawada O, Saishin Y, Liu P, Ohji M.

PURPOSE: To evaluate serum and plasma vascular endothelial growth factor (VEGF) concentrations in neovascular age-related macular degeneration patients treated bimonthly with intravitreal injection of aflibercept or ranibizumab.

DESIGN: A prospective, interventional case series.

METHODS: This study includes 17 eyes of 17 patients treated with 2 mg of aflibercept (the aflibercept group), 15 eyes of 15 patients treated with 0.5 mg ranibizumab (the ranibizumab group) and 12 patients with cataract (the control group). Serum and plasma VEGF concentrations were quantified using the enzyme-linked immunosorbent assay.

RESULTS: At baseline, mean serum VEGF concentration (pg/ml) did not differ significantly among the three groups (P = 0.99). In the aflibercept group, it was 28.3 at baseline, decreased to below the detectable limit at 1 week (P < 0.0001), increased to 11.7 at 1 month, which was still significantly below the baseline level (P < 0.001), and returned to 23.9 (P = 0.35) at 2 months. In the ranibizumab group, there were no significant differences. At baseline, mean plasma VEGF concentration did not differ significantly among the three groups (P = 0.64). In the aflibercept group, it was 16.2 at baseline, decreased to below the detectable limit at 1 week (P < 0.01) and at 1 month (P < 0.05), and returned to 13.6 at 2 months (P = 0.73). In the ranibizumab group, there were no significant differences.

CONCLUSION: Aflibercept significantly decreased serum and plasma VEGF concentrations one month after injection, however, ranibizumab had no significant effect on either serum or plasma VEGF level.

PMID: 24973606 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2014 Jun 18;7(3):541-9. doi: 10.3980/j.issn.2222-3959.2014.03.28. eCollection 2014.

Combination of ranibizumab with photodynamic therapy vs ranibizumab monotherapy in the treatment of age-related macular degeneration: a systematic review and meta-analysis of

randomized controlled trials.

Si JK, Tang K, Bi HS, Guo DD, Guo JG, Du YX, Cui Y, Pan XM, Wen Y, Wang XR.

AIM: To compare the efficacy and safety of combination of ranibizumab with photodynamic therapy (PDT) vs ranibizumab monotherapy in the treatment of age-related macular degeneration (AMD).

METHODS: The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, Pubmed, and Embase were searched. There were no language or data restrictions in the search for trials. Only randomized controlled trials (RCTs) were included. Methodological quality of the literatures was evaluated according to the Jadad Score. RevMan 5.2.6 software was used to do the meta-analysis.

RESULTS: Seven studies were included in our systematic review, among which four of them were included in quantitative analysis. The result shows that the ranibizumab monotherapy group had a better mean best corrected visual acuity (BCVA) change vs baseline at month 12 compared with that of the combination treatment group, and the statistical difference was significant (WMD, -2.61; 95% CI, -5.08 to -0.13; P=0.04). However, after the removal of one study, the difference between the two groups showed no significant difference (WMD, -2.29; 95% CI, -4.81 to 0.23; P=0.07). Meanwhile, no significant central retinal thickness (CRT) reduction was found in the combination treatment group and the ranibizumab monotherapy group at 12 months follow-up. Nevertheless, the combination group tended to have a greater reduction in CRT (WMD, -4.13μm; 95%CI, -25.88 to 17.63, P=0.71). The proportion of patients gaining more than 3 lines at month 12 in the ranibizumab group was higher than in the combination group and there was a significant difference (RR, 0.72; 95% CI, 0.54 to 0.95; P=0.02). Whereas there was no significant difference for the proportion of patients gaining more than 0 line at month 12 between the two groups (RR, 0.93; 95% CI, 0.76 to 1.15; P=0.52). The general tendency shows a reduction in ranibizumab retreatment number in the combination treatment group compared with the ranibizumab monotherapy group. As major adverse events, the differences in the number of eye pain, endophthalmitis, hypertension and arterial thromboembolic events were not significant between the two groups, and the incidence of serious adverse events in the two groups was very low.

CONCLUSION: For the maintenance of vision, the comparison of the combination of ranibizumab with PDT vs ranibizumab monotherapy shows no apparent difference. Compared with the combination of ranibizumab and PDT, patients treated with ranibizumab monothearpy may gain more visual acuity (VA) improvement. The combination treatment group had a tendency to reduce the number of ranibizumab retreatment. Both the two treatment strategies were well tolerated.

PMID: 24967206 [PubMed] PMCID: PMC4067674

Ophthalmology. 2014 Jun 20. pii: S0161-6420(14)00380-7. doi: 10.1016/j.ophtha.2014.04.026. [Epub ahead of print]

The Neovascular Age-Related Macular Degeneration Database: Report 2: Incidence, Management, and Visual Outcomes of Second Treated Eyes.

Zarranz-Ventura J, Liew G, Johnston RL, Xing W, Akerele T, McKibbin M, Downey L, Natha S, Chakravarthy U, Bailey C, Khan R, Antcliff R, Armstrong S, Varma A, Kumar V, Tsaloumas M, Mandal K, Bunce C, Tufail A; United Kingdom Age-Related Macular Degeneration Electronic Medical Records Users Group*.

PURPOSE: To study the characteristics of second treated eyes in patients with neovascular age-related macular degeneration (nAMD) treated with ranibizumab in the United Kingdom National Health Service.

DESIGN: Multicenter national nAMD database study.

PARTICIPANTS: Twelve thousand nine hundred fifty-one treatment-naïve eyes of 11 135 patients receiving 92 976 ranibizumab injections.

METHODS: Up to 5 years of routinely collected, anonymized data within electronic medical record systems were extracted remotely from 14 centers. Participating centers exclusively used ranibizumab to treat nAMD (loading phase of 3 monthly injections followed by monthly visits and pro re nata re-treatment). The minimum data set included: age, logarithm of the minimum angle of resolution (logMAR) visual acuity (VA) at baseline and at all subsequent visits, and injection episodes.

MAIN OUTCOME MEASURES: Baseline, change and actual VA over 3 years, and number of treatments and clinic visits.

RESULTS: During the study, 1816 (16.3%) of the 11 135 patients received treatment to the fellow eye. Mean baseline and final VA were 0.66 (standard deviation, 0.32) and 0.65 (0.40) for first treated eyes and 0.41 (0.34) and 0.56 (0.40) for second treated eyes. The rate of VA loss after the loading phase was similar in first and second treated eyes (0.03 and 0.05 logMAR units/year). When fellow eyes with baseline VA worse than 20/200 were excluded to restrict analyses to eyes at risk of nAMD, the rate of second-eye involvement was 14.0% per year (42%/3 years). Mean number of injections/visits in years 1, 2, and 3 were similar for first and second treated eyes (5.6/8.2, 3.9/8.0, 3.8/8.2 and 5.5/8.7, 3.6/9.4, and 3.8/9.1, respectively).

CONCLUSIONS: Second treated eyes with nAMD commence treatment with better baseline VA, do not show significant vision gain but maintain better VA than first treated eyes at all time points for at least 3 years, making them the more important eye functionally. These data highlight the high burden of second eye involvement, with almost half of all eyes at risk requiring bilateral treatment by 3 years, and the need for regular monitoring of fellow eyes for best visual outcomes which theoretically may reduce the benefits of extended monitoring regimens.

PMID: 24953791 [PubMed - as supplied by publisher]

JAMA. 2014 Jun 11;311(22):2269-70. doi: 10.1001/jama.2014.2536.

Revolution to a new standard treatment of diabetic macular edema.

Jampol LM, Bressler NM, Glassman AR.

PMID: 24915254 [PubMed - indexed for MEDLINE]

Other treatment & diagnosis

Acta Ophthalmol. 2014 Jul;92 Suppl Thesis3:1-38. doi: 10.1111/aos.12452.

Development of gene therapy for treatment of age-related macular degeneration.

Askou AL.

Abstract: Intraocular neovascular diseases are the leading cause of blindness in the Western world in individuals over the age of 50. Age-related macular degeneration (AMD) is one of these diseases. Exudative AMD, the late-stage form, is characterized by abnormal neovessel development, sprouting from the choroid into the avascular subretinal space, where it can suddenly cause irreversible damage to the vulnerable photoreceptor (PR) cells essential for our high-resolution, central vision. The molecular basis of AMD is not well understood, but several growth factors have been implicated including vascular endothelial growth factor (VEGF), and the advent of anti-VEGF therapy has markedly changed the outcome of treatment. However, common to all current therapies for exudative AMD are the complications of repeated monthly intravitreal injections, which must be continued throughout one's lifetime to maintain visual benefits. Additionally, some patients do not benefit from established treatments. Strategies providing long-term suppression of inappropriate ocular angiogenesis are therefore needed, and gene therapy offers a potential

powerful technique. This study aimed to develop a strategy based on RNA interference (RNAi) for the sustained attenuation of VEGF. We designed a panel of anti-VEGF short hairpin RNAs (shRNA), and based on the most potent shRNAs, microRNA (miRNA)-mimicked hairpins were developed. We demonstrated an additive VEGF silencing effect when we combined the miRNAs in a tricistronic miRNA cluster. To meet the requirements for development of medical treatments for AMD with long-term effects, the shRNA/miRNA is expressed from vectors based on adeno-associated virus (AAV) or lentivirus (LV). Both vector systems have been found superior in terms of transduction efficiency and persistence in gene expression in retinal cells. The capacity of AAV-encoded RNAi effector molecules to silence endogenous VEGF gene expression was evaluated in mouse models, including the model of laser-induced choroidal neovascularization (CNV), and we found that subretinal administration of self-complementary (sc)-AAV2/8 encoding anti-VEGF shRNAs can impair vessel formation. In parallel, a significant reduction of endogenous VEGF was demonstrated following injection of scAAV2/8 vectors expressing multiple anti-VEGF miRNAs into murine hind limb muscles. Furthermore, in an ongoing project we have designed versatile, multigenic LV vectors with combined expression of multiple miRNAs and proteins, including pigment epithelium-derived factor (PEDF), a multifunctional, secreted protein that has anti-angiogenic and neurotrophic functions. Co-expression of miRNAs and proteins from a single viral vector increases safety by minimizing the viral load necessary to obtain a therapeutic effect and thereby reduces the risk of insertional mutagenesis as well as the immune response against viral proteins. Our results show co-expression of functional anti-VEGF-miRNAs and PEDF in cell studies, and in vivo studies reveal an efficient retinal pigment epithelium (RPE)-specific gene expression following the incorporation of the vitelliform macular dystrophy 2 (VMD2) promoter, demonstrating the potential applicability of our multigenic LV vectors in ocular anti-VEGF gene therapy, including combination therapy for treatment of exudative AMD. In conclusion, these highly promising data clearly demonstrate that viral-encoded RNAi effector molecules can be used for the inhibition of neovascularization and will, in combination with the growing interest of applying DNA- or RNA-based technologies in the clinic, undoubtedly contribute to the development of efficacious long-term gene therapy treatment of intraocular neovascular diseases.

PMID: 24953666 [PubMed - in process]

Eur J Ophthalmol. 2014 Jun 12:0. doi: 10.5301/ejo.5000500. [Epub ahead of print]

Vitrectomy and subretinal injection of tissue plasminogen activator for large submacular hemorrhage secondary to AMD.

Moisseiev E, Ben Ami T, Barak A.

PURPOSE: To evaluate the efficacy and safety of pars plana vitrectomy (PPV) with subretinal injection of tissue plasminogen activator (tPA) for the treatment of large submacular hemorrhage (SMH) secondary to age-related macular degeneration (AMD), and identify parameters correlated with the visual prognosis.

METHODS: Thirty-one eyes that underwent PPV with subretinal tPA injection for large SMH secondary to AMD were included in this retrospective study. Main outcome measure was improvement in at least one line in visual acuity (VA).

RESULTS: Improvement in VA was achieved in 14 (45.2%) patients. These patients had a significantly worse VA at presentation than patients who did not improve ($p = 0.05$). Central retinal thickness and earlier intervention were not correlated with the final visual prognosis. Postoperative complications included retinal detachment (19.3%), recurrent SMH (6.4%), and elevated intraocular pressure (6.4%).

CONCLUSIONS: The VA at presentation is the most significant preoperative parameter associated with improvement in VA. A cutoff value of counting fingers VA is suggested, as patients with better VA at presentation did not benefit from surgery.

PMID: 24966031 [PubMed - as supplied by publisher]

Trials. 2014 Jun 24;15(1):246. [Epub ahead of print]

Low-level night-time light therapy for age-related macular degeneration (ALight): study protocol for a randomized controlled trial.

McKeague C, Margrain TH, Bailey C, Binns AM.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of blindness among older adults in the developed world. The only treatments currently available, such as ranibizumab injections, are for neovascular AMD, which accounts for only 10 to 15% of people with the condition. Hypoxia has been implicated as one of the primary causes of AMD, and is most acute at night when the retina is most metabolically active. By increasing light levels at night, the metabolic requirements of the retina and hence the hypoxia will be considerably reduced. This trial seeks to determine whether wearing a light mask that emits a dim, green light during the night can prevent the progression of early AMD.

Methods/design: ALight is a Phase I/IIa, multicentre, randomized controlled trial. Sixty participants (55 to 88 years old) with early AMD in one eye and neovascular AMD (nAMD) in the fellow eye will be recruited from nAMD clinics. They will be randomized (in the ratio 1:1), either to receive the intervention or to be in the untreated control group, stratified according to risk of disease progression. An additional 40 participants with healthy retinal appearance, or early AMD only, will be recruited for a baseline cross-sectional analysis. The intervention is an eye mask that emits a dim green light to illuminate the retina through closed eyelids at night. This is designed to reduce the metabolic activity of the retina, thereby reducing the potential risk of hypoxia. Participants will wear the mask every night for 12 months. Ophthalmologists carrying out monthly assessments will be masked to the treatment group, but participants will be aware of their treatment group. The primary outcome measure is the proportion of people who show disease progression during the trial period in the eye with early AMD. A co-primary outcome measure is the rate of retinal adaptation. As this is a trial of a CE-marked device for an off-label indication, a further main aim of this trial is to assess safety of the mask in the cohort of participants with AMD.Trial registration: International Standard Randomised Controlled Trials Register: ISRCTN82148651.

PMID: 24965385 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2014 Jun 25;14(1):82. [Epub ahead of print]

Management of significant reactivation of old disciform scars in wet Age-Related Macular Degeneration.

Coco RM, Sala-Puigdollers A.

BACKGROUND: Fibrotic disciform scars represent the end-stage of wet age-related macular degeneration (AMD) and ophthalmologists tend not to treat them. However, reactivation can occur resulting in further worsening of patients. The aim of this study is to describe the clinical outcomes of 10 patients with disciform scars from age-related macular degeneration (AMD) that have subsequently reactivated.

METHODS: Indocyanine green angiography (ICG) was used to identify the active areas and these "hot spots" (HS) that were subsequently treated with focal laser photocoagulation.

RESULTS: In 10 out of 11 patients with potential reactivation of an AMD scar, a treatable HS was found on the ICG at the border of the disciform scar. The identified HS was treated with focal laser photocoagulation. Post treatment these areas became inactive. However in 2 cases, reactivation occurred requiring retreatment a few months later.

CONCLUSIONS: AMD patients who are noted to have disciform scars that are increasing in size and signs of activation such as lipid exudation and subretinal haemorrhage should undergo ICG imaging to look for HS. These patients could benefit from focal laser to stabilize the disease and avoid complications and further peripheral visual loss. It is suspected that these patients may have the polypoidal subtype of AMD.

PMID: 24965122 [PubMed - as supplied by publisher]

J Cataract Refract Surg. 2014 Jul;40(7):1085-91. doi: 10.1016/j.jcrs.2013.10.049.

Safety and efficacy of an intraocular Fresnel prism intraocular lens in patients with advanced macular disease: Initial clinical experience.

Potgieter FJ, Claoué CM.

PURPOSE: To perform a pilot study of a new in-the-bag Fresnel prism intraocular lens (IOL) designed to deviate the image from diseased to healthy retina in eyes with bilateral age-related macular degeneration (AMD).

SETTING: Anterior segment subspeciality practice, Pretoria, South Africa.

DESIGN: Prospective nonmasked trial.

METHOD: Cataract surgery and unilateral implantation of the prismatic IOL were performed in patients with bilateral AMD and cataract. Outcomes were surgical complications, subjective and objective visual improvement, and undesirable optical effects.

RESULTS: Three eyes of 3 patients were evaluated. All patients reported displacement of the scotoma, and no patient reported diplopia. The only complication was posterior capsule opacification (1 eye).

CONCLUSIONS: Patients noted improved vision and no diplopia. This pilot was performed using a prototype IOL with single power and single angle of deviation; however, there is scope for individual patient optimization. This new technology merits further research and development because it may benefit large numbers of patients with stable end-stage AMD.

PMID: 24957430 [PubMed - in process]

Nat Med. 2014 Jun 22. doi: 10.1038/nm.3590. [Epub ahead of print]

Noninvasive two-photon microscopy imaging of mouse retina and retinal pigment epithelium through the pupil of the eye.

Palczewska G, Dong Z, Golczak M, Hunter JJ, Williams DR, Alexander NS, Palczewski K.

Abstract: Two-photon excitation microscopy can image retinal molecular processes in vivo. Intrinsically fluorescent retinyl esters in subcellular structures called retinosomes are an integral part of the visual chromophore regeneration pathway. Fluorescent condensation products of all-trans-retinal accumulate in the eye with age and are also associated with age-related macular degeneration (AMD). Here, we report repetitive, dynamic imaging of these compounds in live mice through the pupil of the eye. By leveraging advanced adaptive optics, we developed a data acquisition algorithm that permitted the identification of retinosomes and condensation products in the retinal pigment epithelium by their characteristic localization, spectral properties and absence in genetically modified or drug-treated mice. This imaging approach has the potential to detect early molecular changes in retinoid metabolism that trigger light- and AMD-induced retinal defects and to assess the effectiveness of treatments for these conditions.

PMID: 24952647 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Jun 22. doi: 10.1111/aos.12471. [Epub ahead of print]

A noncontrolled trial of anti-TNF-α chimeric monoclonal antibody (infliximab, Remicade®) in exudative age-related macular degeneration.

van Hagen PM, Baarsma GS, van Bilsen CE, Kuijpers RW, van Laar JA, van der Ent M, van Daele PL, Veeger NJ, Vingerling JR, Missotten TO.

PMID: 24953977 [PubMed - as supplied by publisher]

Pathogenesis

Biomolecules. 2012 Feb 15;2(1):76-103. doi: 10.3390/biom2010076.

Oxysterols and their cellular effectors.

Olkkonen VM, Béaslas O, Nissilä E.

Abstract: Oxysterols are oxidized 27-carbon cholesterol derivatives or by-products of cholesterol biosynthesis, with a spectrum of biologic activities. Several oxysterols have cytotoxic and pro-apoptotic activities, the ability to interfere with the lateral domain organization, and packing of membrane lipids. These properties may account for their suggested roles in the pathology of diseases such as atherosclerosis, age-onset macular degeneration and Alzheimer's disease. Oxysterols also have the capacity to induce inflammatory responses and play roles in cell differentiation processes. The functions of oxysterols as intermediates in the synthesis of bile acids and steroid hormones, and as readily transportable forms of sterol, are well established. Furthermore, their actions as endogenous regulators of gene expression in lipid metabolism via liver X receptors and the Insig (insulin-induced gene) proteins have been investigated in detail. The cytoplasmic oxysterol-binding protein (OSBP) homologues form a group of oxysterol/cholesterol sensors that has recently attracted a lot of attention. However, their mode of action is, as yet, poorly understood. Retinoic acid receptor-related orphan receptors (ROR) α and γ, and Epstein-Barr virus induced gene 2 (EBI2) have been identified as novel oxysterol receptors, revealing new physiologic oxysterol effector mechanisms in development, metabolism, and immunity, and evoking enhanced interest in these compounds in the field of biomedicine.

PMID: 24970128 [PubMed]

Biomolecules. 2012 Feb 7;2(1):46-75. doi: 10.3390/biom2010046.

Factor h: a complement regulator in health and disease, and a mediator of cellular interactions.

Kopp A, Hebecker M, Svobodová E, Józsi M.

Abstract: Complement is an essential part of innate immunity as it participates in host defense against infections, disposal of cellular debris and apoptotic cells, inflammatory processes and modulation of adaptive immune responses. Several soluble and membrane-bound regulators protect the host from the potentially deleterious effects of uncontrolled and misdirected complement activation. Factor H is a major soluble regulator of the alternative complement pathway, but it can also bind to host cells and tissues, protecting them from complement attack. Interactions of factor H with various endogenous ligands, such as pentraxins, extracellular matrix proteins and DNA are important in limiting local complement-mediated inflammation. Impaired regulatory as well as ligand and cell recognition functions of factor H, caused by mutations or autoantibodies, are associated with the kidney diseases: atypical hemolytic uremic syndrome and dense deposit disease and the eye disorder: age-related macular degeneration. In addition, factor H binds to receptors on host cells and is involved in adhesion, phagocytosis and modulation of cell activation. In this review we discuss current concepts on the physiological and pathophysiological roles of factor H in light of new data and recent developments in our understanding of the versatile roles of factor H as an inhibitor of complement activation and inflammation, as well as a mediator of cellular interactions. A detailed knowledge of the functions of factor H in health and disease is expected to unravel novel therapeutic intervention possibilities and to facilitate the development or improvement of therapies.

PMID: 24970127 [PubMed]

BMC Ophthalmol. 2014 Jun 25;14(1):83. [Epub ahead of print]

Associations of complement factor B and complement component 2 genotypes with subtypes of polypoidal choroidal vasculopathy.

Tanaka K, Nakayama T, Mori R, Sato N, Kawamura A, Yuzawa M.

BACKGROUND: We previously reported on subtypes of polypoidal choroidal vasculopathy (PCV), and categorized PCV as polypoidal choroidal neovascularization (CNV) and typical PCV. The aim of this study was to clarify whether complement component 2 (C2) and complement factor B (CFB) genotypes are associated with subtypes of polypoidal choroidal vasculopathy, such as polypoidal CNV and typical PCV.

METHODS: First, we categorized 677 patients into typical age-related macular degeneration (tAMD; 250 patients), PCV (376) and retinal angiomatous proliferation (RAP; 51). Second, we categorized 282 patients with PCV as having polypoidal CNV (84 patients) or typical PCV (198) based on indocyanine green angiographic findings. In total, 274 subjects without AMD, such as PCV and CNV, served as controls. A SNP (rs547154) in the C2 gene and three SNPs (rs541862, rs2072633, rs4151667) in the CFB gene were genotyped, and case-control studies were performed in subjects with these PCV subtypes.

RESULTS: In tAMD, no SNPs were associated with allele distributions. In PCV, rs547154 and rs2072633 were associated with allele distributions. RAP was only associated with rs2072633. After logistic regression analysis with adjustment for confounding factors, tAMD, PCV and RAP were found to be associated with rs2072633.As to PCV subtypes, there were significant differences in the distributions of rs547154, rs541862 and rs2072633 in the case-control studies for polypoidal CNV, but not between the typical PCV and control groups. Logistic regression analysis with adjustment for confounding factors showed the distributions of rs547154, rs541862 and rs2072633 to differ significantly between the controls and polypoidal CNV cases and that these SNPs were protective. The A/A genotype of rs2072633 was significantly more common in the polypoidal CNV than in the typical PCV group ($p = 0.03$), even with adjustment for polyp number and greatest linear dimension.

CONCLUSIONS: PCV might be genetically divisible into polypoidal CNV and typical PCV. The C2 and CFB gene variants were shown to be associated with polypoidal CNV. Typical PCV was not associated with variants in these genes.

PMID: 24965207 [PubMed - as supplied by publisher]

Curr Eye Res. 2014 Jun 23:1-8. [Epub ahead of print]

Oxidized LDL Induces Apoptosis of Human Retinal Pigment Epithelium Through Activation of ERK-Bax/Bcl-2 Signaling Pathways.

Yating Q, Yuan Y, Wei Z, Qing G, Xingwei W, Qiu Q, Lili Y.

Purpose: Retinal pigment epithelium (RPE) cell dysfunction and death play a vital role in the pathogenesis of age-related macular degeneration (AMD). We previously reported that oxidized low-density lipoprotein (OX-LDL) induces retinal degeneration in vivo. In this study, we investigated the role of the ERK-Bax/Bcl-2 signaling pathways in OX-LDL-induced apoptosis in human RPE.

Methods: ARPE-19 cells were incubated with 10-100 mg/mL n-LDL or OX-LDL for 24 h. Cell viability was assessed using the Cell Titer 96 Aqueous One Solution cell proliferation assay. RPE apoptosis was measured with a flow cytometer. Reverse transcription polymerase chain reaction was used to detect Bcl-2 and Bax mRNA levels in RPE cells. Bcl-2 and Bax protein expression was measured by western blotting. Activation of extracellular signal-regulated kinase (ERK) protein was evaluated by western blot analysis. One-way analysis of variance was used to compare differences.

Results: OX-LDL treatment decreased ARPE-19 cell viability in a dose-dependent manner, whereas n-LDL

had no effect. Compared with the control group, OX-LDL significantly increased the apoptosis of RPE, 10 mg/mL, 50 mg/mL, 100 mg/mL apoptosis rate was 6.43 ± 0.19%, 5.12 ± 0.27%, 5.53 ± 0.35%, respectively. OX-LDL also increased Bcl-2 expression and decreased Bax expression significantly. The Bcl-2 to Bax ratio was elevated after OX-LDL treatment. Inhibition of ERK downregulated Bax and was associated with RPE apoptosis.

Conclusions: Our data suggest that apoptosis induced by OX-LDL in RPE partly depends on Erk-Bax/Bcl-2 signaling pathway activation. These results may provide further information regarding the effects of OX-LDL in human RPE and their potential role in AMD pathogenesis.

PMID: 24956392 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2014 Jun 19. pii: S0161-6420(14)00394-7. doi: 10.1016/j.ophtha.2014.04.040. [Epub ahead of print]

Cigarette Smoking and the Natural History of Age-related Macular Degeneration: The Beaver Dam Eye Study.

Myers CE, Klein BE, Gangnon R, Sivakumaran TA, Iyengar SK, Klein R.

PURPOSE: To examine the association of current cigarette smoking and pack-years smoked with the incidence and progression of age-related macular degeneration (AMD) and to examine the interactions of current smoking and pack-years smoked with complement factor H (CFH, rs1061170) and age-related maculopathy susceptibility 2 (ARMS2, rs10490924) genotype.

DESIGN: A longitudinal population-based study of AMD in a representative American community. Examinations were performed every 5 years over a 20-year period.

PARTICIPANTS: A total of 4439 participants in the population-based Beaver Dam Eye Study (BDES).

METHODS: Age-related macular degeneration status was determined from grading retinal photographs. Multi-state models were used to model the relationship of current smoking and pack-years smoked and interactions with CFH and ARMS2 with the incidence and progression of AMD over the entire age range.

MAIN OUTCOME MEASURES: Incidence and progression of AMD over a 20-year period and interactions between current smoking and pack-years smoked with CFH and ARMS2 genotype.

RESULTS: The incidence of early AMD over the 20-year period was 24.4%, and the incidence of late AMD was 4.5%. Current smoking was associated with an increased risk of transitioning from minimal to moderate early AMD. A greater number of pack-years smoked was associated with an increased risk of transitioning from no AMD to minimal early AMD and from severe early AMD to late AMD. Current smoking and a greater number of pack-years smoked were associated with an increased risk of death. There were no statistically significant multiplicative interactions between current smoking or pack-years smoked and CFH or ARMS2 genotype.

CONCLUSIONS: Current smoking and a greater number of pack-years smoked increase the risk of the progression of AMD. This has important health care implications because smoking is a modifiable behavior.

PMID: 24953792 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Jun 25. pii: S0002-9394(14)00359-6. doi: 10.1016/j.ajo.2014.06.012. [Epub ahead of print]

Visual Impairment and Blindness Due to Macular Diseases Globally: A Systematic Review and Meta-

Analysis.

Jonas JB, Bourne RR, White RA, Flaxman SR, Keeffe J, Leasher J, Naidoo K, Pesudovs K, Price H, Wong TY, Resnikoff S, Taylor HR; Vision Loss Expert Group of the Global Burden of Disease Study.

PURPOSE: To estimate the number of people visually impaired or blind due to macular diseases except of diabetic maculopathy.

DESIGN: Meta-analysis.

METHODS: Based on the Global Burden of Disease Study 2010 and ongoing literature research, we examined how many people were affected by vision impairment (presenting visual acuity <6/18, ≥3/60) and blindness (presenting visual acuity <3/60) due to macular diseases, with diabetic maculopathy excluded.

RESULTS: In 2010, out of 32.4 million blind and 191 million vision impaired, 2.1 million (95% uncertainty interval (UI):1.9,2.7) people were blind, and 6.0 million (95%UI:5.2,8.1) million were visually impaired due to macular diseases. In 2010, macular diseases caused 6.6% (95%UI:6.0,7.9) of all blindness and 3.1% (95% UI:2.7,4.0) of all vision impairment, worldwide. These figures were lower in regions with young populations than in high-income regions. From 1990 to 2010, number of blind or visually impaired due to macular diseases increased by 36% or 0.6 million people (95%UI:0.5,0.8) and by 81% or 2.7 million (95%UI:2.6,3.9) people respectively, while the global population increased by 30%. Age-standardized global prevalence of macula related blindness and vision impairment in adults aged 50+ years decreased from 0.2% (95% UI:0.2,0.2) in 1990 to 0.1% (95%UI:0.1, 0.2) in 2010, and remained unchanged from 0.4% (95%UI:0.3,0.5) to 0.4% (95%UI:0.4,0.6), respectively.

CONCLUSIONS: In 2010, 2.1 million people were blind and 6.0 million people were visually impaired due to macular diseases, except of diabetic maculopathy. One out 15 blind people was blind, and one out of 32 visually impaired people was visually impaired due to macular diseases.

PMID: 24973605 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jun 26. pii: IOVS-14-14476. doi: 10.1167/iovs.14-14476. [Epub ahead of print]

Ethnic Variation in Early Age-related Macular Degeneration Lesions between White Australians and Singaporean Asians.

Joachim N, Mitchell P, Younan C, Burlutsky G, Cheng CY, Cheung GC, Zheng Y, Moffitt M, Wong TY, Wang JJ.

Purpose: To compare early age-related macular degeneration (AMD) lesion characteristics between white Australians and Singaporean Asians.

Methods: Participants of the Blue Mountains Eye Study (BMES; whites, n=3508) and the Singapore Epidemiology of Eye Disease Study (SEED, Malay, n=3280, Indian, n=3400 and Chinese, n=3353) underwent examinations including retinal photography. AMD lesions were assessed following the Wisconsin AMD grading protocol by the same photographic grader. Prevalence and characteristics of early AMD lesions were compared between the BMES and the SEED. The associations between ethnicity and early AMD lesion types were analyzed using logistic regression models adjusting for age, sex, smoking status, lipids and genetic polymorphisms associated with AMD.

Results: After age-standardization to the BMES population, the prevalence of distinct soft drusen was significantly higher in Singaporeans compared to Australians (23.9%, 95% confidence interval (CI) 22.9-25.0 versus 6.2%, 95% CI 5.3-7.0), with an adjusted odds ratio (OR) 4.6 (95% CI 3.4-6.0). In contrast, the prevalence of indistinct soft or reticular drusen was significantly lower in Singaporeans compared to Australians (6.5%, 95% CI 5.9-7.1 versus 8.3%, 95% CI 7.4-9.3, with non-significant adjusted OR 1.2, 95%

CI 0.8-1.7). Soft drusen of any type were frequently present at the inner and outer macula (within a zone ≥500µm to <3000µm radius from the foveal centre) among Singaporeans, while among Australians soft drusen were more frequently present at the central macula (<500µm radius).

Conclusion: Singaporean Asians had a milder spectrum of early AMD lesions and lesion characteristics (predominantly distinct soft drusen and non-central location) compared to white Australians.

PMID: 24970259 [PubMed - as supplied by publisher]

Environ Res. 2014 Jun 21;133C:178-184. doi: 10.1016/j.envres.2014.05.023. [Epub ahead of print]

Environmental cadmium and lead exposures and age-related macular degeneration in U.S. adults: The National Health and Nutrition Examination Survey 2005 to 2008.

Wu EW, Schaumberg DA, Park SK.

Abstract: Age-related macular degeneration (AMD) is a complex disease resulting from the interplay of genetic predisposition and environmental exposures, and has been linked to oxidative stress and inflammatory mechanisms. Lead and cadmium can accumulate in human retinal tissues and may damage the retina through oxidative stress, and may thereby play a role in the development of AMD. We examined associations between blood lead, blood cadmium, and urinary cadmium concentrations and the presence of AMD in 5390 participants aged 40 years and older with blood lead and blood cadmium measures and a subsample of 1548 with urinary cadmium measures in the 2005-2008 National Health and Nutrition Examination Surveys. AMD was identified by grading retinal photographs with a modification of the Wisconsin Age-Related Maculopathy Grading System. The weighted prevalence of AMD was 6.6% (n=426). Controlling for age, gender, race/ethnicity, education and body mass index, adults in the highest blood cadmium quartile had higher odds of AMD compared to the lowest quartile (odds ratio [OR], 1.56; 95% CI, 1.02-2.40), with a significant trend across quartiles (p-trend=0.02). After further adjustment for pack -years of cigarette smoking, estimates were somewhat attenuated (OR, 1.43; 95% CI, 0.91-2.27; p-trend=0.08). Similar associations were found with urinary cadmium. The association between urinary cadmium and AMD was stronger in non-Hispanic whites (NHW) than in non-Hispanic blacks (NHB) (OR, 3.31; 95% CI, 1.37-8.01 for levels above versus below the median among NHW; OR,1.45; 95% CI, 0.40-5.32 for levels above versus below the median among NHB; p-interaction=0.03). We found no association between blood lead levels and AMD. Higher cadmium body burden may increase risk of AMD, particularly among non-Hispanic white individuals; however, additional studies are needed before firm conclusions can be drawn.

PMID: 24959985 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jun 26. pii: IOVS-14-14379. doi: 10.1167/iovs.14-14379. [Epub ahead of print]

Epidemiological Association between Systemic Diseases and Age-Related Macular Degeneration: the Korea National Health and Nutrition Examination Survey.

Cho BJ, Heo JW, Shin JP, Ahn J, Kim TW, Chung H.

Purpose: To examine the epidemiological association between systemic diseases and age-related macular degeneration (AMD) in the general population.

Methods: This cross-sectional study involved nationally representative data obtained from the 2008-2011 Korea National Health and Nutrition Examination Surveys. A total of 14,352 subjects aged ≥40 years participated in standardized health interviews regarding physician-diagnosis of several systemic diseases as well as physical examinations including fundus photography for the evaluation of AMD.

Results: The overall prevalence rates of early, late, and any AMD were 6.0%, 0.6%, and 6.6%, respectively. In univariate logistic regression analyses adjusted for age and sex as well as smoking in late AMD, both any AMD and late AMD were less prevalent among diabetic patients and more prevalent in participants with a history of liver cancer. A history of liver cirrhosis was associated with a higher prevalence of any AMD. In the final multivariate model, the associated factors for any AMD included age (OR, 1.09), the presence of diabetes mellitus (DM) (OR, 0.74), and a history of liver cancer (OR, 4.32). Factors associated with late AMD included age (OR 1.09), ever-smoking history (OR, 2.45), the presence of DM (OR, 0.22), and a history of liver cancer (OR, 12.51). The presence of diabetic retinopathy was associated with a lower prevalence of any AMD (OR, 0.35).

Conclusion: When adjusted for confounders, any AMD and late AMD were less prevalent in diabetic patients. In contrast, a history of liver cancer was associated with a higher prevalence of any AMD and late AMD.

PMID: 24970257 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jun 23;55(6):3955-6. doi: 10.1167/iovs.14-14322.

Author response: aspirin use and risk of age-related macular degeneration.

Ye J, Xu YF.

PMID: 24958805 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2014 Jun 23;55(6):3954. doi: 10.1167/iovs.14-14203.

Aspirin use and risk of age-related macular degeneration.

Wang W, Zhang X.

PMID: 24958804 [PubMed - in process]

Genetics

Graefes Arch Clin Exp Ophthalmol. 2014 Jun 28. [Epub ahead of print]

The contribution of genetic factors to phenotype and progression of drusen in early age-related macular degeneration.

Dietzel M, Pauleikhoff D, Arning A, Heimes B, Lommatzsch A, Stoll M, Hense HW.

PURPOSE: Genetic factors contribute to the development and progression of age-related macular degeneration (AMD). We aimed to assess the association of drusen as phenotypic characteristics of early AMD and their progression with polymorphisms in the CFH, ABCA1, and ARMS2 genes.

METHODS: In the Münster Aging and Retina Study (MARS), drusen were detected in 406 patients with early AMD and 170 healthy controls according to the International Classification using fundus photographs, with a follow-up examination after 2.6 years (median). Six drusen features were assessed: drusen number (</≥20); confluence of drusen (</≥50 %), largest drusen size (</≥175 µm); area occupied by drusen (</≥10 %); most frequent drusen size (</≥175 µm), and presence of soft, indistinct drusen (no/yes). Based on these features, an unweighted summary drusen severity score (DSS; categorized in "low", "intermediate" and "high") was calculated. The relationship of each drusen feature and the DSS with CFH rs1061170, ABCA1 rs1883025, and ARMS2 rs10490924 at baseline and after 2.6 years was analyzed using

multivariate logistic regression models.

RESULTS: Cross-sectionally, each drusen feature was associated with a higher frequency of the CFH and ARMS2 risk variants. Compared to healthy eyes, the CFH risk variant was more common in eyes with early as well as advanced drusen features, while the ARMS2 variant was only associated with advanced drusen. After 2.6 years, 43 % of the eyes showed a progression of at least 1 unit in the DSS. The progression from low to higher DSS was inversely associated with ABCA1 (OR = 0.54), and the progression from intermediate to high DSS was positively related to CFH rs1061170 (OR = 2.3; $p < 0.05$ for each).

CONCLUSIONS: Variants in CFH, ABCA1, and ARMS2 genes are related to the presence and progression of drusen in early AMD. CFH and, inversely, ABCA1 seem to be involved in early drusen development, while the role of ARMS2 is more pronounced in advanced stages of early AMD.

PMID: 24970616 [PubMed - as supplied by publisher]

Diet & lifestyle

Food Chem Toxicol. 2014 Jun 22. pii: S0278-6915(14)00290-7. doi: 10.1016/j.fct.2014.06.015. [Epub ahead of print]

Safety evaluation of zeaxanthin concentrate (OmniXan™): Acute, subchronic toxicity and mutagenicity studies.

Ravi KB, Raghunatha Reddy KR, Shankaranarayanan J, Deshpande JV, Juturu V, Soni MG.

Abstract: The available evidence suggests a beneficial effect of zeaxanthin against the progression of age-related macular degeneration (AMD). The objective of the present study was to investigate potential adverse effects of OmniXan™, a RR-zeaxanthin (65%) enriched product obtained from paprika (Capsicum annum fruits) in subchronic toxicity and mutagenicity studies. The oral LD50 of OmniXanTM in rats was greater than 2000 mg/kg body weight (bw)/day. For the subchronic toxicity study, Wistar rats (10/sex/group) were gavaged daily with zeaxanthin concentrate at doses of 0, 4, 40 and 400 mg/kg bw/day for 90-days. No treatment related clinical signs and mortalities observed. Similarly, no treatment related toxicologically significant changes in body weight, feed consumption; ophthalmoscopic examination, neurological examination, hematology, urine analysis and organ weights were observed. Statistically significant changes observed in some clinical chemistry parameters were considered toxicologically and biologically insignificant and non adverse. Macroscopic and microscopic examinations did not reveal treatment-related abnormalities. The results of mutagenicity testing using Salmonella typhimurium did not reveal any genotoxicity. The no observed-adverse-effect level (NOAEL) for zeaxanthin concentrate (OmniXanTM) was determined as 400 mg/kg bw/day, the highest dose tested. The findings of this subchronic toxicity and mutagenicity studies support safety of zeaxanthin concentrate.

PMID: 24964014 [PubMed - as supplied by publisher]

PLoS One. 2014 Jun 23;9(6):e100389. doi: 10.1371/journal.pone.0100389. eCollection 2014.

Combining neuroprotectants in a model of retinal degeneration: no additive benefit.

Di Marco F, Di Paolo M, Romeo S, Colecchi L, Fiorani L, Spana S, Stone J, Bisti S.

Abstract: The central nervous system undergoing degeneration can be stabilized, and in some models can be restored to function, by neuroprotective treatments. Photobiomodulation (PBM) and dietary saffron are distinctive as neuroprotectants in that they upregulate protective mechanisms, without causing measurable tissue damage. This study reports a first attempt to combine the actions of PBM and saffron. Our working hypothesis was that the actions of PBM and saffron in protecting retinal photoreceptors, in a rat light

damage model, would be additive. Results confirmed the neuroprotective potential of each used separately, but gave no evidence that their effects are additive. Detailed analysis suggests that there is actually a negative interaction between PBM and saffron when given simultaneously, with a consequent reduction of the neuroprotection. Specific testing will be required to understand the mechanisms involved and to establish whether there is clinical potential in combining neuroprotectants, to improve the quality of life of people affected by retinal pathology, such as age-related macular degeneration, the major cause of blindness and visual impairment in older adults.

PMID: 24955576 [PubMed - in process] PMCID: PMC4067315