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Drug treatment

Ophthalmology. 2013 Nov 28. pii: S0161-6420(13)00898-1. doi: 10.1016/j.ophtha.2013.09.050. [Epub ahead of print]

Comparison of Outcomes from a Phase 3 Study of Age-Related Macular Degeneration with a Matched, Observational Cohort.

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OBJECTIVE: To compare outcomes of intravitreal therapy from an observational study cohort with those of participants receiving treatment in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab (MARINA) for the treatment of neovascular age-related macular degeneration (wet AMD).

DESIGN: Database observational study. Participants in the observational cohort were chosen to match demographic features and entry criteria of the treatment group from MARINA. Outcomes over 12 months were compared.

PARTICIPANTS: Eight hundred twenty-one anti-vascular endothelial growth factor (anti-VEGF)-naïve eyes treated with ranibizumab with 12 months or more of follow-up were included in the total Fight Retinal Blindness! (FRB-All) cohort, whereas a subset of this cohort of 401 eyes who were matched to the MARINA treatment group were included as the FRB-MARINA cohort.

INTERVENTION: Intravitreal ranibizumab therapy of 0.5 mg for wet AMD.

METHODS: Visual acuity (VA) in logarithm of the minimum angle of resolution (logMAR) letters and treatments given were recorded continuously and anonymously in an electronic database for 12 months. Locally weighted scatterplot smoothing (LOESS) regression was used to plot change in visual acuity data over the course of 12 months for both the FRB-All cohort and the FRB-MARINA cohort, whereas results from the MARINA trial were taken from the published study report.

MAIN OUTCOME MEASURES: Change in VA in logMAR letters over 12 months, treatment, and visit intensity.

RESULTS: Mean visual acuity improvement after 12 months in FRB-MARINA (+5.5 letters) was similar to that of the 0.5-mg group from MARINA (+7.2 letters). Improvement in FRB-ALL was slightly less (+4.9 letters). Mean treatment effect compared with the MARINA control group was similar for the MARINA treated group (+17.6 letters) and the FRB-MARINA cohort (+15.9 letters). A mean of 7.3 injections in 12

months was received by the observational cohorts.

CONCLUSIONS: Similarity of mean VA improvement in the matched observational cohort with that of the phase 3 clinical trial suggests that these results can be achieved in real-world clinical practice with a modified treatment regimen.

PMID: 24290801 [PubMed - as supplied by publisher]

Int J Technol Assess Health Care. 2013 Oct;29(4):392-401. doi: 10.1017/S0266462313000500.

Comparative effectiveness of anti-VEGF agents for diabetic macular edema.

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Institute for Clinical and Economic Review.

Objectives: The aim of this study was to evaluate the comparative effectiveness of anti-vascular endothelial growth factor therapy in the treatment of diabetic macular edema (DME).

Methods: Searches focused on reports concerning treatment of DME with aflibercept, bevacizumab, pegaptanib, or ranibizumab published between January 2000 and June 30, 2012, with comparisons to laser photocoagulation, sham injection, or other control (e.g., triamcinolone). Effectiveness was based on best-corrected visual acuity (BCVA), in terms of letters gained. Direct meta-analyses were conducted on BCVA for each anti-vascular endothelial growth factor (VEGF) agent; indirect comparisons also were performed for each anti-VEGF pair.

Results: A total of fifteen randomized controlled trials (eleven fair- or good-quality) and eight observational studies were included. No direct comparative studies were identified. Improvement in visual acuity versus control was seen with all agents (range: 4-9 letters); outcomes were consistent across multiple timepoints. Meta-analyses showed no statistically significant and/or consistent differences between agents in BCVA changes or the percentage of patients gaining more than ten letters. No discernible differences in the potential harms of anti-VEGFs, including ocular events, MI, stroke, and other cardiovascular events, as well as death, were noted between aflibercept, pegaptanib, and ranibizumab. Data on harms for bevacizumab were underreported.

Conclusions: All anti-VEGF agents are effective in improving visual acuity in comparison to laser photocoagulation. Evidence is insufficient to distinguish the performance of any single anti-VEGF agent over others. The safety of bevacizumab remains the greatest element of uncertainty.

PMID: 24290332 [PubMed - in process]

Hellenic J Cardiol. 2013 Nov-Dec;54(6):435-40.

Influence of intravitreal injection of bevacizumab on systemic blood pressure changes in patients with exudative form of age-related macular degeneration.

Risimic D, Milenkovic S, Nikolic D, Simeunovic D, Jaksic V, Stojkovic M, Stefanovic I, Jakovic N, Prostran M.

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INTRODUCTION: The aim of our study was to examine blood pressure (BP) changes in hypertensive and nonhypertensive patients after intravitreal bevacizumab injections and to assess whether intravitreal bevacizumab carries an associated vascular risk in patients with exudative ocular disease. We also aimed to estimate the influence of gender.

METHODS: The study included 57 patients with age-related macular degeneration who received an intravitreal injection of 1.25 mg (0.1 mL) of bevacizumab. We analyzed systolic and diastolic BP values separately. Patients were divided into males and females, and into hypertensives and normotensives based on their BP values. BP was measured before bevacizumab administration, and 10 minutes, 1 hour, 2 days, 7 days and 6 weeks after the injection.

RESULTS: Males had a statistically significant decline in systolic BP values 1 hour and 6 weeks after drug administration ($p<0.05$). The most notable significant decline in diastolic BP values was for males and for normotensive participants 1 hour after drug administration ($p<0.05$), while the most notable decline in diastolic BP values for females and for hypertensive participants was 7 days after drug administration, with statistical significance only for hypertensive patients ($p<0.01$). For males it was noticed that a statistically significant decline in diastolic BP persisted after 6 weeks ($p<0.05$).

CONCLUSIONS: An intravitreal bevacizumab injection is safe as regards BP changes over 6 weeks post administration. Regular follow up for 6 weeks should be mandatory in order to promptly recognize individuals who have changes in BP values and include them in BP treatment in order to prevent complications.

PMID: 24305579 [PubMed - in process]

Adv Ther. 2013 Dec 6. [Epub ahead of print]

Retrospective Analysis of First-Line Anti-Vascular Endothelial Growth Factor Treatment Patterns in Wet Age-Related Macular Degeneration.

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INTRODUCTION: This study compared the number of, and expenditures on, first-line intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections between patients who were treated with aflibercept or ranibizumab for wet age-related macular degeneration (AMD).

METHODS: This was a retrospective cohort study based on U.S. administrative claims data. Selected patients had initiated first-line intravitreal anti-VEGF treatment with ranibizumab or aflibercept (index date) between November 18, 2011 and April 30, 2013, were aged ≥18 years on the index date, had 12 months of continuous insurance enrollment prior to the index date (baseline period), were diagnosed with wet AMD during the baseline period or on the index date, and had at least 6 or 12 months of follow-up enrollment after the index date without switching to a different anti-VEGF agent (follow-up periods). Outcomes measured within the 6 and 12 month follow-up periods included the number of, and healthcare expenditures on, intravitreal anti-VEGF injections. Multivariable regressions compared the outcomes between aflibercept and ranibizumab.

RESULTS: The 6 months analyses included 319 aflibercept patients and 1,054 ranibizumab patients (12 month analyses: 57 and 374, respectively). Over the first 6 months after the index date, neither the number of injections (aflibercept mean = 3.8 ± 1.6; ranibizumab mean = 3.9 ± 1.9) nor the expenditures on injections (aflibercept mean = $7 468 ± $4 211; ranibizumab mean = $7 816 ± $4 834) differed significantly between aflibercept patients and ranibizumab patients (in multivariable regression treating ranibizumab as reference: incidence rate ratio = 0.97, 95% confidence interval [CI] 0.91-1.03, P = 0.277; cost ratio = 0.96, 95% CI 0.89-1.04, P = 0.338). Differences were also insignificant in the 12 month analyses. The overall mean days between injections differed by only 1.8 (95% CI 1.3-2.3) days between the aflibercept patients and ranibizumab patients (42.4 and 40.6, respectively).

CONCLUSION: Aflibercept and ranibizumab were used at a similar frequency resulting in similar intravitreal

anti-VEGF injection healthcare expenditures among wet AMD patients initiating first-line intravitreal anti-VEGF treatment.

PMID: 24310208 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2013 Dec;27(6):425-32. doi: 10.3341/kjo.2013.27.6.425. Epub 2013 Nov 15.

Anti-VEGF-refractory Exudative Age-related Macular Degeneration: Differential Response According to Features on Optical Coherence Tomography.

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PURPOSE: To describe optical coherence tomography (OCT) characteristics of neovascular age-related macular degeneration (AMD) patients refractory to intravitreal anti-vascular endothelial growth factor (VEGF) injections (ranibizumab, bevacizumab) and their responses to alternative anti-VEGF agents or photodynamic therapy (PDT).

METHODS: A retrospective review of 267 neovascular AMD patients treated with intravitreal anti-VEGF injections.

RESULTS: Twenty patients (7.5%) were refractory to anti-VEGF injections (stationary or increased retinal exudation despite three or more monthly injections). They were grouped into either the extensive intraretinal fluid group (IRF group, 9 patients) or the subretinal fluid only group (SRF group, 11 patients) according to OCT findings. In the IRF group, response rates to subsequent treatment were 0% (0 / 7) for bevacizumab, 50% (3 / 6) for ranibizumab and 50% (3 / 6) for PDT ± anti-VEGF. Three out of four bevacizumab-refractory patients showed response to ranibizumab as a secondary treatment. In the SRF group, response rates were lower with 0% (0 / 7) for bevacizumab, 22.2% (2 / 9) for ranibizumab and 28.6% (2 / 7) for PDT ± anti-VEGF. One out of four bevacizumab-refractory patients responded to ranibizumab. The visual outcome was worse in the IRF group (median 20 / 1,000) than in the SRF group (median 20 / 100).

CONCLUSIONS: In anti-VEGF-refractory neovascular AMD, patients with extensive IRF refractory to bevacizumab can be responsive to ranibizumab while patients with SRF may be refractory to both, suggesting a different pathophysiology and intraocular pharmacokinetics.

PMID: 24311928 [PubMed - in process]

Retina. 2013 Nov 27. [Epub ahead of print]

PIGMENT EPITHELIAL TEARS ASSOCIATED WITH ANTI-VEGF THERAPY: Incidence, Long-term Visual Outcome, and Relationship with Pigment Epithelial Detachment in Age-related Macular Degeneration.

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PURPOSE: To evaluate the prevalence of retinal pigment epithelium (RPE) tears associated with anti-VEGF therapy and its relation with retinal pigment epithelial detachment (PED).

METHODS: A total of 226 patients with exudative age-related macular degeneration treated with intravitreal

anti-VEGF were included retrospectively in the study. The presence of RPE tears; the effect of the presence, height, and duration of PED on the rate of RPE tears; and change in visual acuity during follow-up were recorded.

RESULTS: Among 226 study patients, 28 (12.3%) had RPE tears. The RPE tear rate was significantly higher in patients with vascularized PED (vPED) than in those without PED (19.7% vs. 2.1%; P < 0.001). The change in visual acuity after the formation of RPE tear was not statistically significant (on logMAR scale: 0.92 ± 0.49 initially, 0.89 ± 0.41 after the RPE tear, 0.96 ± 0.45 at the last follow-up; P = 0.613). Pigment epithelial detachment height >580 μm (odds ratio = 69.4; 95% confidence interval = 16.7-288.1) and PED duration ≤4.5 months (odds ratio = 166.7; 95% confidence interval = 15.2-1000) were found to be significant risk factors for RPE tear formation.

CONCLUSION: The RPE tears are not infrequent among eyes treated with intravitreal anti-VEGFs. The presence, increased height, and shorter duration of vPED are potential risk factors for RPE tears associated with anti-VEGF therapy.

PMID: 24296398 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Nov 26. pii: S0161-6420(13)00889-0. doi: 10.1016/j.ophtha.2013.09.044. [Epub ahead of print]

Systemic Complement Inhibition with Eculizumab for Geographic Atrophy in Age-Related Macular Degeneration: The COMPLETE Study.

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PURPOSE: To evaluate the effect of eculizumab, a systemic inhibitor of complement component (C5), on the growth of geographic atrophy (GA) in patients with age-related macular degeneration (AMD).

DESIGN: Prospective, double-masked, randomized clinical trial.

PARTICIPANTS: Patients with GA measuring from 1.25 to 18 mm2 based on spectral-domain optical coherence tomography imaging.

METHODS: Patients were randomized 2:1 to receive intravenous eculizumab or placebo over 6 months. In the eculizumab treatment arm, the first 10 patients received a low-dose regimen of 600 mg weekly for 4 weeks followed by 900 mg every 2 weeks until week 24, and the next 10 patients received a high-dose regimen of 900 mg weekly for 4 weeks followed by 1200 mg every 2 weeks until week 24. The placebo group was infused with saline. Patients were observed off treatment for an additional 26 weeks. Both normal-luminance and low-luminance visual acuities were measured throughout the study, and the low-luminance deficits were calculated as the difference between the letter scores.

MAIN OUTCOME MEASURES: Change in area of GA at 26 weeks.

RESULTS: Thirty eyes of 30 patients were enrolled. Eighteen fellow eyes also met inclusion criteria and were analyzed as a secondary endpoint. For the 30 study eyes, mean square root of GA area measurements ± standard deviation at baseline were 2.55±0.94 and 2.02±0.74 mm in the eculizumab and placebo groups, respectively (P = 0.13). At 26 weeks, GA enlarged by a mean of 0.19±0.12 and 0.18±0.15 mm in the eculizumab and placebo groups, respectively (P = 0.96). At 52 weeks of follow-up, GA enlarged by a mean of 0.37±0.22 mm in the eculizumab-treated eyes and by a mean of 0.37±0.21 mm in the placebo group (P = 0.93, 2 sample t test). None of the eyes converted to wet AMD. No drug-related adverse events were identified.

CONCLUSIONS: Systemic complement inhibition with eculizumab was well tolerated through 6 months but did not decrease the growth rate of GA significantly. However, there was a statistically significant correlation between the low-luminance deficit at baseline and the progression of GA over 6 months.

PMID: 24289920 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Methods Mol Biol. 2013 Dec 4. [Epub ahead of print]

Efficient Production of Photoreceptor Precursor Cells from Human Embryonic Stem Cells.

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Abstract: Transplantation of photoreceptor precursor cells (PPCs) differentiated from human embryonic stem cells (hESCs) is a promising approach to treat common blinding diseases such as age-related macular degeneration and retinitis pigmentosa. However, existing PPC generation methods are inefficient. To enhance differentiation protocols for rapid and high-yield production of PPCs, we focused on optimizing the handling of the cells by including feeder-independent growth of hESCs, using size-controlled embryoid bodies (EBs), and addition of triiodothyronine (T3) and taurine to the differentiation medium, with subsequent removal of undifferentiated cells via negative cell-selection. Our novel protocol produces higher yields of PPCs than previously reported while reducing the time required for differentiation, which will help understand retinal diseases and facilitate large-scale preclinical trials.

PMID: 24301073 [PubMed - as supplied by publisher]

Rossi EA, Rangel-Fonseca P, Parkins K, Fischer W, Latchney LR, Folwell MA, Williams DR, Dubra A, Chung MM.

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Abstract: Morgan and colleagues demonstrated that the RPE cell mosaic can be resolved in the living human eye non-invasively by imaging the short-wavelength autofluorescence using an adaptive optics (AO) ophthalmoscope. This method, based on the assumption that all subjects have the same longitudinal chromatic aberration (LCA) correction, has proved difficult to use in diseased eyes, and in particular those affected by age-related macular degeneration (AMD). In this work, we improve Morgan's method by accounting for chromatic aberration variations by optimizing the confocal aperture axial and transverse placement through an automated iterative maximization of image intensity. The increase in image intensity after algorithmic aperture placement varied depending upon patient and aperture position prior to optimization but increases as large as a factor of 10 were observed. When using a confocal aperture of 3.4 Airy disks in diameter, images were obtained using retinal radiant exposures of less than 2.44 J/cm2, which is ~22 times below the current ANSI maximum permissible exposure. RPE cell morphologies that were strikingly similar to those seen in postmortem histological studies were observed in AMD eyes, even in areas where the pattern of fluorescence appeared normal in commercial fundus autofluorescence (FAF) images. This new method can be used to study RPE morphology in AMD and other diseases, providing a powerful tool for understanding disease pathogenesis and progression, and offering a new means to assess the efficacy of treatments designed to restore RPE health.

PMID: 24298413 [PubMed - as supplied by publisher] PMCID: PMC3829547

Yakugaku Zasshi. 2013;133(12):1269-76.

Application of Ultrasound-enhanced Gene and Drug Delivery to the Ocular Tissue.

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Abstract: Visual images provide an immensely rich source of information about the external world. Eye has characteristic structure sensory cells are arranged along the eye wall, and is filled inside with vitreous body. In recent years, intravitreal injection of anti-vascular endothelial growth factor (VEGF) agent had widely spread, and numerous number of patients who suffered ocular angiogenic disease such as diabetic retinopathy, age-related macular degeneration and retinal vascular occlusion for the disease, were treated and spared the blindness. Vitreous cavity was regarded as reservoir of drug, intravitreal injection is thought a sort of drug delivery. However, with regard to the administration of a selective drug deliver, it has not yet been solved. Our aim is to establish a new method of gene transfer, drug delivery using low-energy ultrasound to the eye, to date, we confirmed drug and gene deliver to the ocular tissue such as cornea, conjunctiva and retina with high efficiency. In addition, tissue damage was minimal. We have also shown that ultrasound irradiation with combination of a microbubbles or bubble liposome could be introduced drug and gene more effectively. Based on these knowledge, we will focus on development of a new device for intraocular ultrasound exposure and potential for therapeutic application of ultrasound to humans retinal disease such as retinal artery obstruction.

PMID: 24292171 [PubMed - in process]

Prog Retin Eye Res. 2013 Nov 28. pii: S1350-9462(13)00070-0. doi: 10.1016/j.preteyeres.2013.11.001. [Epub ahead of print]

Macular dystrophies mimicking age-related macular degeneration.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population in the Western world. AMD is a clinically heterogeneous disease presenting with drusen, pigmentary changes, geographic atrophy and/or choroidal neovascularization. Due to its heterogeneous presentation, it can be challenging to distinguish AMD from several macular diseases that can mimic the features of AMD. This clinical overlap may potentially lead to misdiagnosis. In this review, we discuss the characteristics of AMD and the macular dystrophies that can mimic AMD. The appropriate use of clinical and genetic analysis can aid the clinician to establish the correct diagnosis, and to provide the patient with the appropriate prognostic information. An overview is presented of overlapping and distinguishing clinical features.

PMID: 24291520 [PubMed - as supplied by publisher]

Transl Res. 2013 Nov 8. pii: S1931-5244(13)00381-2. doi: 10.1016/j.trsl.2013.11.002. [Epub ahead of print]

Retinal repair with induced pluripotent stem cells.

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Abstract: Retinal degeneration such as age-related macular degeneration and other inherited forms, such as Stargardt's disease and retinitis pigmentosa, and optic neuropathies including glaucoma and ischemic optic neuropathy are major causes of vision loss and blindness worldwide. Damage to retinal pigment epithelial cells and photoreceptors in the former, and to retinal ganglion cell axons in the optic nerve and their cell bodies in the retina in the latter diseases lead to the eventual death of these retinal cells, and in humans there is no endogenous replacement or repair. Cell replacement therapies provide 1 avenue to restore function in these diseases, particularly in the case of retinal repair, although there are considerable issues to overcome, including the differentiation and integration of the transplanted cells. What stem cell sources could be used for such therapies? One promising source is induced pluripotent stem cells (iPSCs), which could be drawn from an individual patient needing therapy, or generated and banked from select donors. We review developing research in the use of iPSCs for retinal cell replacement therapy.

PMID: 24291154 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Nov 28. pii: S0161-6420(13)00906-8. doi: 10.1016/j.ophtha.2013.10.006. [Epub ahead of print]

Appearance of Regressing Drusen on Adaptive Optics in Age-Related Macular Degeneration.

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PMID: 24290975 [PubMed - as supplied by publisher]

Pathogenesis

Mol Ther. 2013 Oct 17. doi: 10.1038/mt.2013.243. [Epub ahead of print]

Repression of Choroidal Neovascularization Through Actin Cytoskeleton Pathways by MicroRNA-24.

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Abstract: Actin cytoskeleton is critical for cell motility and division, both of which are important for angiogenesis. MicroRNAs (miRNA/miR) are emerging as pivotal modulators of vascular development and disease. How miRNAs regulate actin cytoskeleton dynamics in endothelial cells (EC) and neovascularization is still unclear. Here, we report that miR-24 regulates actin dynamics in ECs through targeting multiple members downstream of Rho signaling, including Pak4, Limk2, and Diaph1 proteins. Overexpression of miR-24 in ECs blocks stress fiber and lamellipodia formation, represses EC migration, proliferation, and tube formation in vitro, as well as angiogenesis in an ex vivo aortic ring assay. Moreover, subretinal delivery of miR-24 mimics represses laser-induced choroidal neovascularization (CNV) in vivo. Mechanistically, knockdown of miR-24 target protein LIMK2 or PAK4 inhibits stress fiber formation and tube formation in vitro, mimicking miR-24 overexpression phenotype in angiogenesis, while overexpression of LIMK2 and PAK4 by adenoviruses partially rescued the tube formation defects in miR-24 overexpressing ECs. Taken together, these findings suggest that miR-24 represses angiogenesis by simultaneously regulating multiple components in the actin cytoskeleton pathways. Manipulation of actin cytoskeleton pathways by miR-24 may represent an attractive therapeutic solution for the treatment of wet age-related

macular degeneration (AMD) and other vascular diseases.Molecular Therapy (2013); doi:10.1038/mt.2013.243.

PMID: 24297048 [PubMed - as supplied by publisher]

Photochem Photobiol. 2013 Oct 29. doi: 10.1111/php.12200. [Epub ahead of print]

A2E Mediated Photochemical Modification to Fibronectin and its Implications to Age Related Changes in Bruch's Membrane;

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Abstract: Lipofuscin accumulates normally with age and is more pronounced in retinal dystrophies such as Age-related macular degeneration. The major bis-retinoid component of lipofuscin is A2E. In addition to cell damage effects by A2E, we have previously demonstrated that blue light mediated A2E leads to modifications of the basement membrane protein laminin. Therefore, the purpose of this study is to advance the understanding of A2E photo-oxidation effects on fibronectin, the major glycoprotein of Bruch's membrane. In this study, A2E was irradiated with blue light in the presence of a fibronectin peptide consisting of amino acids from the integrin binding region. The modification sites were identified via LC/MS. Our research indicated that blue light irradiation caused cleavage throughout the A2E molecule closest to the pyridinium ring, and attached to the fibronectin peptide preferentially at lysine and arginine residues. All of these reactions are similar to the Maillard reaction. Altogether this study suggests that blue light irradiated A2E modifies peptides and forms advance glycation endproducts. Furthermore these results can be used to identify modifications that occur in Bruch's membrane in vivo.

PMID: 24303925 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2013 Nov 28. pii: S0161-6420(13)00942-1. doi: 10.1016/j.ophtha.2013.10.017. [Epub ahead of print]

Genetic Susceptibility, Dietary Antioxidants, and Long-term Incidence of Age-related Macular Degeneration in Two Populations.

Wang JJ, Buitendijk GH, Rochtchina E, Lee KE, Klein BE, van Duijn CM, Flood VM, Meuer SM, Attia J, Myers C, Holliday EG, Tan AG, Smith WT, Iyengar SK, de Jong PT, Hofman A, Vingerling JR, Mitchell P, Klein R, Klaver CC.

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OBJECTIVE: To examine effect modification between genetic susceptibility to age-related macular degeneration (AMD) and dietary antioxidant or fish consumption on AMD risk.

DESIGN: Pooled data analysis of population-based cohorts.

PARTICIPANTS: Participants from the Blue Mountains Eye Study (BMES) and Rotterdam Study (RS).

METHODS: Dietary intakes of antioxidants (lutein/zeaxanthin [LZ], β-carotene, and vitamin C), long-chain omega-3 polyunsaturated fatty acids, and zinc were estimated from food frequency questionnaires. The AMD genetic risk was classified according to the number of risk alleles of CFH (rs1061170) or ARMS2

(rs10490924) as low (no or 1 risk allele) or high (≥2 risk alleles). Interactions between dietary intake and genetic risk levels were assessed. Associations between dietary intake and AMD risk were assessed comparing the highest with the 2 lower intake tertiles by genetic risk subgroups using discrete logistic regression, conducted in each study separately and then using pooled data. Participants without AMD lesions at any visit were controls. We adjusted for age and sex in analyses of each cohort sample and for smoking status and study site in pooled-data analyses.

MAIN OUTCOME MEASURES: All 15-year incident late AMD cases were confirmed by chief investigators of the Beaver Dam Eye Study, BMES, and RS. Intergrader reproducibility was assessed in an early AMD subsample, with 86.4% agreement between BMES and RS graders, allowing for a 1-step difference on a 5-step AMD severity scale.

RESULTS: In pooled data analyses, we found significant interaction between AMD genetic risk status and LZ intake (P = 0.0009) but nonsignificant interactions between genetic risk status and weekly fish consumption (P = 0.05) for risk of any AMD. Among participants with high genetic risk, the highest intake tertile of LZ was associated with a >20% reduced risk of early AMD, and weekly consumption of fish was associated with a 40% reduced risk of late AMD. No similar association was evident among participants with low genetic risk. No interaction was detected between β-carotene or vitamin C and genetic risk status.

CONCLUSIONS: Protection against AMD from greater LZ and fish consumption in persons with high genetic risk based on 2 major AMD genes raises the possibility of personalized preventive interventions.

PMID: 24290803 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2013 Dec 4;13(1):74. [Epub ahead of print]

Health state utilities in patients with diabetic retinopathy, diabetic macular oedema and age-related macular degeneration: a systematic review.

Poku E, Brazier J, Carlton J, Ferreira A.

BACKGROUND: Health state utility values (HSUVs) are important in the assessment of the cost effectiveness of new interventions. In the case of visual conditions, models generally tend have tended to be built around a set of health states defined by visual acuity (VA). The aim of this review was to assess the impact of VA on HSUVs in patients with diabetic retinopathy, diabetic macular oedema or age-related macular degeneration.

METHODS: A systematic literature search was undertaken in major bibliographic databases to identify articles reporting on the relationship between HSUVs and vision. Data were extracted for population characteristics, visual levels and estimated utilities. Evidence from reported statistical models, where available, was considered in the evaluation of vision in the better-seeing eye and the worse-seeing eye. Due to the heterogeneity of included studies, a narrative synthesis was undertaken.

RESULTS: Of the 17 relevant studies, 9 studies had data that could be used in the analysis of the impact of vision on HSUVs. Visual loss was associated with a marked impact on health utilities. However, the relationship was not comparable between conditions or by measure of HSUVs. Key results included the finding that overall, self-rated time-trade off estimates were more likely to discriminate between different VA levels than EQ-5D values. Additionally, a stronger correlation was observed between HSUVs and better-seeing eye VA compared to worse-seeing eye VA.

CONCLUSIONS: Visual acuity has a significant impact on HSUVs. Nevertheless, care must be taken in the interpretation and use of estimates in cost-effectiveness models due to differences in measures and population diversity.

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Genetics

Ophthalmic Genet. 2013 Dec 4. [Epub ahead of print]

Three Variants of or near VEGF-A Gene are not Associated with Neovascular Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy in a Han Chinese Population.

Su Y, Zhang X, Zuo C, Li M, Wu K, Ji Y, Wen F.

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Abstract Purpose: To investigate whether three previously identified variants for age-related macular degeneration (AMD), the single nucleotide polymorphism (SNP) variants of or near the vascular endothelial growth factor A gene (VEGFA), were associated with neovascular AMD or polypoidal choroidal vasculopathy (PCV) in a Han Chinese cohort.

Methods: This was a case-control study comprising 251 PCV patients, 157 neovascular AMD patients, and 204 control participants in a Han Chinese population. The rs833069, rs943080 and rs4711751 SNP were genotyped using the Multiplex SNaPshot system. Genotypes and allele frequencies of patients and controls were evaluated for the SNPs using PLINK software.

Results: None of the allelic or genotypic effects of these three variants was significantly associated with PCV, neovascular AMD or combined both patient categories.

Conclusions: No association was found to support the role for the rs833069, rs943080 and rs4711751 variants of or near VEGFA gene in susceptibility to either PCV or neovascular AMD in Han Chinese population. Further replication is necessary to validate these results.

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Chromosome 10q26 locus and age-related macular degeneration: A progress update.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of late-onset central vision loss in developed countries. Both genetic and environmental factors contribute to the onset of AMD. Variation at a locus on chromosome 10q26 has been consistently associated with this disease and represents one of the two strongest genetic effects being identified in AMD. At least three genes are located within the bounds of the locus: pleckstrin homology domain containing family A member 1 (PLEKHA1), age-related maculopathy susceptibility 2 (ARMS2) and high-temperature requirement A serine peptidase 1 (HTRA1), all of which are associated with AMD. Due to the strong linkage disequilibrium (LD) across this region, statistical genetic analysis alone is incapable of distinguishing the effect of an individual gene in the locus. Uncertainty remains, however, in regards to which gene is responsible for the linkage and association of the locus with AMD. Investigating functional consequences of the associated variants and related genes tends to be essential to identifying the biologically responsible gene(s) underlying AMD. This review examines the recent progress and current uncertainty on the genetic and functional analyses of the 10q26 locus in AMD with a focus on ARMS2 and HTRA1. A discussion, which entails the possible multi-faceted approaches for pinpointing the gene(s) in the locus underlying the pathogenesis of AMD, is also included.

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Diet & lifestyle

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Living together with age-related macular degeneration: An interpretative phenomenological analysis of sense-making within a dyadic relationship.

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Abstract: In this article, we present an idiographic analysis of a couple's experience of living and coming to terms with age-related macular degeneration. Interpretative phenomenological analysis was used to explore three joint interviews, conducted over an 18-month period, with a married couple (aged 82 and 77 years) both living with age-related macular degeneration. Three themes are discussed: the disruption of vision impairment, managing mutual deterioration and resilience through togetherness. We discuss the existential challenges of vision impairment and consider the applicability of Galvin and Todres' typology of well-being as a means of understanding well-being in older adults.

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Antioxidants and vision health: facts and fiction.

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Abstract: A number of nutritional supplements containing antioxidants are advertised for better vision health. Do they benefit the average consumer? The literature was examined for the effectiveness of antioxidants for human eye health, and for the intricacies in collection of such evidence. The following diseases were considered: cataract, glaucoma, age-related macular degeneration (AMD), retinopathy, retinitis pigmentosa, eye infections, and uveitis. The literature indicates that antioxidant supplements plus lutein have a reasonable probability of retarding AMD. For glaucoma, such supplements were ineffectual in some studies but useful in others. In some studies, antioxidant rich fruits and vegetables were also useful for protection against glaucoma. For diabetic retinopathy, antioxidant supplements may have a small benefit, if any, but only as an adjunct to glycemic control. In very high-risk premature retinopathy and retinitis pigmentosa, antioxidant supplements may be beneficial but those with excess Vitamin E should be avoided. For cataract, there is no evidence for an advantage of such nutritional supplements. However, lubricant drops containing N-acetylcarnosine may be helpful in initial stages of the disease. For eye infections and other causes of uveitis, antioxidants have not been found useful. We recommend that a diet high in antioxidant rich foods should be developed as a habit from an early age. However, when initial signs of vision health deterioration are observed, the appropriate nutritional supplement products may be recommended but only to augment the primary medical treatments.

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Secondary Analyses of the Effects of Lutein/Zeaxanthin on Age-Related Macular Degeneration Progression: AREDS2 Report No. 3.

The Age-Related Eye Disease Study 2 (AREDS2) Research Group, Chew EY, Clemons TE, Sangiovanni JP, Danis RP, Ferris FL 3rd, Elman MJ, Antoszyk AN, Ruby AJ, Orth D, Bressler SB, Fish GE, Hubbard

GB, Klein ML, Chandra SR, Blodi BA, Domalpally A, Friberg T, Wong WT, Rosenfeld PJ, Agrón E, Toth CA, Bernstein PS, Sperduto RD.

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IMPORTANCE: The Age-Related Eye Disease Study (AREDS) formulation for the treatment of age-related macular degeneration (AMD) contains vitamin C, vitamin E, beta carotene, and zinc with copper. The Age-Related Eye Disease Study 2 (AREDS2) assessed the value of substituting lutein/zeaxanthin in the AREDS formulation because of the demonstrated risk for lung cancer from beta carotene in smokers and former smokers and because lutein and zeaxanthin are important components in the retina.

OBJECTIVE: To further examine the effect of lutein/zeaxanthin supplementation on progression to late AMD.

DESIGN, SETTING, PARTICIPANTS: The Age-Related Eye Disease Study 2 is a multicenter, double-masked randomized trial of 4203 participants, aged 50 to 85 years, at risk for developing late AMD; 66% of patients had bilateral large drusen and 34% had large drusen and late AMD in 1 eye.

INTERVENTIONS: In addition to taking the original or a variation of the AREDS supplement, participants were randomly assigned in a factorial design to 1 of the following 4 groups: placebo; lutein/zeaxanthin, 10 mg/2 mg; omega-3 long-chain polyunsaturated fatty 3 acids, 1.0 g; or the combination. MAIN OUTCOMES AND MEASURES Documented development of late AMD by central, masked grading of annual retinal photographs or by treatment history.

RESULTS: In exploratory analysis of lutein/zeaxanthin vs no lutein/zeaxanthin, the hazard ratio of the development of late AMD was 0.90 (95% CI, 0.82-0.99; P = .04). Exploratory analyses of direct comparison of lutein/zeaxanthin vs beta carotene showed hazard ratios of 0.82 (95% CI, 0.69-0.96; P = .02) for development of late AMD, 0.78 (95% CI, 0.64-0.94; P = .01) for development of neovascular AMD, and 0.94 (95% CI, 0.70-1.26; P = .67) for development of central geographic atrophy. In analyses restricted to eyes with bilateral large drusen at baseline, the direct comparison of lutein/zeaxanthin vs beta carotene showed hazard ratios of 0.76 (95% CI, 0.61-0.96; P = .02) for progression to late AMD, 0.65 (95% CI, 0.49-0.85; P = .002) for neovascular AMD, and 0.98 (95% CI, 0.69-1.39; P = .91) for central geographic atrophy.

CONCLUSION AND RELEVANCE: The totality of evidence on beneficial and adverse effects from AREDS2 and other studies suggests that lutein/zeaxanthin could be more appropriate than beta carotene in the AREDS-type supplements.

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Evidence for Including Lutein and Zeaxanthin in Oral Supplements for Age-Related Macular Degeneration.

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Resveratrol protects RPE cells from sodium iodate by modulating PPARα and PPARδ

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Abstract: Selective killing of RPE cells in vivo by sodium iodate develops cardinal phenotypes of atrophic age-related macular degeneration. However, the molecular mechanisms are elusive. We tried to search for small cyto-protective molecules against sodium iodate and explore their mechanisms of action. Sodium iodate-mediated RPE cell death was associated with increased levels of reactive oxygen species (ROS) and IL-8. Resveratrol, a natural occurring polyphenol compound, was found to strongly protect RPE cells from sodium iodate with inhibition of production of ROS and IL-8. Resveratrol activated all isoforms of PPARs. Treatment with PPARα and PPARδ agonists inhibited sodium iodate-induced ROS production and protected RPE cells from sodium iodate. A PPARα antagonist significantly reduced resveratrol's protection of RPE cells from sodium iodate. Paradoxically, knocking down PPARδ also rendered RPE cells resistant to sodium iodate. Moreover, PPAR agonists reversed sodium iodate-induced production of IL-8. However, neutralizing extracellular IL-8 failed to protect RPE cells from sodium iodate. Taken together, these observations show that resveratrol protects RPE cells from sodium iodate injury through the activation of PPARα and alteration of PPARδ conformation. PPARα and δ modulators might ameliorate stress-induced RPE degeneration in vivo.

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Driving Habits in Older Patients with Central Vision Loss.

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OBJECTIVE: To determine if central visual loss is associated with driving cessation, driving restriction, or other-driver preference.

DESIGN: Cross-sectional study.

PARTICIPANTS: Sixty-four subjects with bilateral visual loss (<20/32 in better eye) or severe unilateral visual loss (<20/200) from age-related macular degeneration (AMD) and 58 normally sighted controls between 60 and 80 years of age.

METHODS: Participants self-reported driving habits. Other-driver preference was defined as preferring that another drive when there is more than 1 driver in the car. Subjects reporting 2 or more driving limitations were considered to have restricted their driving.

MAIN OUTCOME MEASURES: Self-reported driving cessation, other-driver preference, and driving restriction.

RESULTS: Age-related macular degeneration subjects were older (74.7 vs. 69.7 years), had worse visual acuity (VA; mean better-eye VA, 0.43 vs. 0.08 logarithm of minimum angle of resolution [logMAR]) and contrast sensitivity (CS; 1.4 vs. 1.9 log units of CS [logCS]), and were more likely to be white when compared with controls (P <0.001 for all). Drivers with AMD-related vision loss were more likely to avoid driving over longer distances, beyond 1 hour, at night, and in unfamiliar conditions (P < 0.05 for all). In multivariate models, driving cessation was associated with worse better-eye VA (odds ratio [OR], 1.5 per 1-line decrement in VA; P <0.001) and worse binocular CS (OR, 1.36 per 0.1 logCS increment; P = 0.005); however, AMD group status was not associated with driving cessation (OR, 1.9; P = 0.35). Factors predicting driving restriction were AMD (OR, 9.0; P = 0.004), worse vision (OR, 2.5 per line of VA loss; P

<0.001), lower CS (OR, 2.2 per 0.1-logCS increment; P <0.001), and female gender (OR, 27.9; P = 0.002). Other-driver preference was more common with worse vision (OR, 1.6 per 0.1-logMAR increment; P = 0.003), female gender (OR, 4.5; P = 0.02), and being married (OR, 3.8; P = 0.04).

CONCLUSIONS: Most patients with AMD-related central vision loss continue to drive, but demonstrate significant driving restrictions, especially with more severe VA and CS loss. Future work should determine which driving adaptations the visually impaired best balance safety and independence.

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