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MD Research News

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Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2016 Nov 23. [Epub ahead of print]

High-frequency aflibercept injections in persistent neovascular age-related macular degeneration.

Muftuoglu IK, Tsai FF, Gaber R, Alam M, Meshi A, Freeman WR.

PURPOSE: To report the 1-year outcomes of every-4-weeks (Q4W) as-needed aflibercept treatment in resistant neovascular age-related macular degeneration (nAMD) patients who had been treated and failed prior bevacizumab or ranibizumab injections, and who also responded poorly to every-8-weeks (Q8W) aflibercept treatment.

METHODS: Forty-three eyes of 39 patients with persistent nAMD despite monthly bevacizumab and/or ranibizumab injections and who were switched to Q8W 2-mg aflibercept injections, but showed persistence of fluid were included. Patients were treated with as-needed Q4W aflibercept injections with monthly monitoring. Maximum retinal thickness (MRT), central macular thickness (CMT), maximum pigment epithelial detachment height (PED) and best-corrected visual acuity (BCVA) were assessed and compared to baseline when high-frequency aflibercept was initiated.

RESULTS: A mean of 8 (interquartile range, 4-11) Q4W injections were given during the follow-up. MRT and CMT significantly decreased at all follow-up visits ($p < 0.05$); however, there was no significant change in maximum PED height ($p > 0.05$) at any visit. Mean BCVA was 0.38 ± 0.28 (logMAR) (≈20/63, Snellen) at baseline, and 0.4 ± 0.34 (logMAR) (≈20/76, Snellen) at 1 year ($p = 0.76$). Seventy-two percent of eyes maintained a final BCVA of 20/63 or better. Twelve eyes (28 %) had some subretinal scar tissue formation and 5 eyes (11.6 %) had evidence of atrophy at 1 year.

CONCLUSION: A stepwise algorithm with Q4W as-needed aflibercept treatment led to anatomic improvement in previously treated eyes which failed other therapies, including aflibercept every 8 weeks. Lack of visual improvement may be due to a ceiling effect as our eyes generally had good visual acuity.

PMID: 27878592

Ophthalmology. 2016 Nov 15. [Epub ahead of print]

Macular Atrophy in Neovascular Age-Related Macular Degeneration with Monthly versus Treat-and-Extend Ranibizumab: Findings from the TREX-AMD Trial.

Abdelfattah NS, Al-Sheikh M, Pitetta S, Mousa A, Sadda SR, Wykoff CC; Treat-and-Extend Age-Related Macular Degeneration Study Group.

PURPOSE: To compare the enlargement rate of macular atrophy (ERMA) in eyes treated with ranibizumab monthly or using a treat-and-extend (TREX) regimen for neovascular age-related macular degeneration (AMD) or fellow control eyes, as well as analyze risk factors for macular atrophy (MA) development and

progression.

DESIGN: Eighteen-month, multicenter, randomized, controlled clinical trial.

PARTICIPANTS: Sixty patients with treatment-naïve neovascular AMD in 1 eye randomized 1:2 to monthly or TREX ranibizumab.

METHODS: Patients' study and fellow eyes were followed for 18 months using spectral-domain optical coherence tomography (SD OCT) and fundus autofluorescence (FAF) imaging. The MA was quantified on FAF images using Heidelberg Region Finder software (Heidelberg Engineering, Heidelberg, Germany), with suspected areas of atrophy confirmed by SD OCT and infrared reflectance imaging. For eyes without baseline MA yet developed MA by 18 months, intervening visits were assessed to determine the first visit at which MA appeared to define progression rates. Foveal choroidal thickness (FCT), subretinal hyperreflective material (SHRM), and pigment epithelial detachment (PED), were assessed at baseline to determine whether they influenced MA progression.

MAIN OUTCOME MEASURES: Mean ERMA at 18 months. Relationship between visual acuity and MA, and the baseline risk factors for ERMA were also assessed.

RESULTS: The final analysis cohort included 88 eyes in 3 groups: monthly (n = 19), TREX (n = 30), and control fellow eyes (n = 39). Mean ERMA over 18 months was 0.39±0.67 (monthly), 1.1±1.9 (TREX), and 0.49±1 mm2 (control, P = 0.12). Mean ERMA per group among the 40.9% (n = 36) of baseline patients with MA was 0.9±1, 1.9±2.2, and 1±1.3 mm2, respectively (P = 0.31). The incidence rate of MA in the 3 groups was 40%, 0%, and 8.3%, respectively. Mann-Whitney U test revealed a statistically significant association between baseline FCT (127±46 vs. 155±55 μm, P = 0.01) and SHRM thickness (106±131 vs. 50±85 μm, P = 0.02) on MA. In eyes with no baseline MA, presence of SHRM, SHRM, and PED thickness, and presence of baseline hemorrhage were all significant predictors of new MA development (P = 0.04, 0.01, 0.04, 0.004, 0.01, respectively).

CONCLUSIONS: Ranibizumab did not show a statistically significant influence on new MA development in eyes with neovascular AMD, whether dosed monthly or per TREX regimen. The FCT, SHRM thickness, and hemorrhage at baseline were all significant predictors of new MA.

PMID: 27863845

Ophthalmology. 2016 Nov 15. [Epub ahead of print]

SCORE2 Report 2: Study Design and Baseline Characteristics.

Scott IU, VanVeldhuisen PC, Ip MS, Blodi BA, Oden NL, Figueroa M, Dugel PU; SCORE2 Investigator Group.

PURPOSE: To describe the design and baseline characteristics of participants in the Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2) and to compare with cohorts from other retinal vein occlusion trials.

DESIGN: Phase III prospective, multicenter, randomized clinical trial designed to assess whether intravitreal bevacizumab is noninferior to intravitreal aflibercept for treatment of decreased vision attributable to macular edema associated with central retinal vein occlusion (CRVO) or hemiretinal vein occlusion (HRVO).

PARTICIPANTS: Total of 362 participants: 307 with CRVO and 55 with HRVO.

METHODS: Demographic and study eye characteristics are summarized and compared between CRVO and HRVO study participants.

MAIN OUTCOME MEASURES: Baseline ophthalmic characteristics, including visual acuity and retinal thickness, and medical history characteristics, including hypertension, diabetes mellitus, and coronary

artery disease.

RESULTS: The mean age of participants was 69 years, 76% of participants were white, and 90% were non-Hispanic. There was a racial disparity with respect to disease type, with 38% of HRVO patients being black compared with 11% of CRVO patients (P value adjusted for multiple testing = 0.0001). This is similar to findings from the previous SCORE Study. Comorbidities included hypertension (77%), diabetes mellitus (31%), and coronary artery disease (15%). At baseline, mean visual acuity letter score was 50 (20/100) (range, 19-73 [20/400 to 20/40]), mean optical coherence tomography (OCT)-measured central subfield thickness was 678 µm (range, 300-1203 µm), and mean number of months from diagnosis of macular edema to randomization was 6 (range, 0-104 months). One hundred twenty (33%) SCORE2 participants had been treated previously with anti-vascular endothelial growth factor (anti-VEGF) therapy, with these participants having baseline visual acuity letter score and OCT-measured central subfield thickness similar to those without prior anti-VEGF treatment, but longer mean duration of macular edema before randomization (18 months vs. 1 month for those without prior anti-VEGF treatment; P < 0.0001).

CONCLUSIONS: The SCORE2 cohort is a heterogeneous population, including both CRVO and HRVO eyes and both treatment-naïve eyes and eyes treated previously with anti-VEGF, which will allow study results to have broad applicability to CRVO and HRVO patients receiving treatment for macular edema. Similarities of the baseline characteristics of the SCORE2 population to other CRVO trial cohorts will allow meaningful comparisons of outcome results across trials.

PMID: 27863843

J Ocul Pharmacol Ther. 2016 Nov 18. [Epub ahead of print]

Retinal Nerve Fiber Layer Thickness Changes in Age-Related Macular Degeneration Treated with Multiple Intravitreal Ranibizumab.

Sengul EA, Artunay O, Turkseven Kumral E, Yenerel M, Rasier R, Kockar A, Yuzbasioglu E.

PURPOSE: The objective of this study was to investigate the effect of multiple intravitreal ranibizumab (IVR) injections on the retinal nerve fiber layer (RNFL) in neovascular age-related macular degeneration (nAMD).

METHODS: One hundred sixty-eight eyes of 168 patients with nAMD who received an IVR at least 3 times were included in this prospective interventional case series. The RNFL thickness data on 80 healthy eyes, used as the control group, were obtained. The patients were grouped as follows: 3-10 injections (group 1, 62 eyes, 37%), 10-20 injections (group 2, 62 eyes, 37%), and ≥20 injections (group 3, 44 eyes, 26%). The RNFL thickness was measured by spectral domain optical coherence tomography.

RESULTS: The mean baseline measurement of the RNFL thickness was 97.4 ± 6.4 µm in the control group, 96.4 ± 5.6 µm in group 1, 93.8 ± 4.6 µm in group 2, and 93.2 ± 5.3 µm in group 3. At the last follow-up, it was 95.1 ± 2.4 µm in the control group, 93.4 ± 7.3 µm in group 1, 90.5 ± 3.6 µm in group 2, and 89.2 ± 4.9 µm in group 3 (all P values >0.050). A statistically significant difference was not found between the mean total RNFL thickness of the eyes that received injections and that of the eyes in the healthy control group (P value >0.050). A statistically significant difference was not found in all the treatment groups between the intraocular pressure level taken 1 day after the administration of the injections and that recorded preintervention (all P values >0.050).

CONCLUSION: Repeated IVR did not lead to a significant change in RNFL thickness in patients with nAMD.

PMID: 27860530

J Ophthalmol. 2016;2016:6538192. Epub 2016 Nov 3.

Effects of Intravitreal Ranibizumab Injection on Chinese Patients with Wet Age-Related Macular Degeneration: 5-Year Follow-Up Results.

Lu Y, Huang J, Zhao J, Yu X, Long L, Dai H.

Purpose: To observe the effect of intravitreal ranibizumab injection on wet age-related macular degeneration (wAMD) over 5 years in Chinese patients.

Methods: Thirty-seven patients who were diagnosed with wAMD in our hospital from June 2007 to June 2014 were retrospectively reviewed. The PRN regimen and the treatment and extend regimen were applied. Best corrected visual acuity (BCVA), number of ranibizumab injections, and changes in the choroidal neovascularization (CNV) lesion over 5 years were analyzed.

Results: The mean BCVA measured by the ETDRS chart at baseline was 47.4 and 5 years after the treatment it was 34.89 letters, which was significantly different ($p = 0.013$). Fourteen eyes (37.8%) had improved visual acuity after 5 years. The number of injections in 5 years was 11.53, and most of the injections were in the first two years. Seventeen (45.9%) cases developed fibrous lesions, and 2 (5.4%) cases had atrophic lesions after 5 years. The fibrosis/atrophy was significantly correlated with the injection numbers (Pearson, $r = 0.663$, and $p = 0.000$).

Conclusion: Most of the patients can maintain visual acuity treated by ranibizumab in the first 3 years. After 5 years, some patients can still improve or maintain visual acuity. Fibrous scarring of the lesion is the main reason for a decrease in vision of wAMD patients.

PMID: 27885338 PMCID: PMC5112299

J Fr Ophtalmol. 2016 Nov 16. [Epub ahead of print]

Retinal oximetry during treatment of retinal vein occlusion by ranibizumab in patients with high blood pressure and dyslipidemia.

Keilani C, Halalchi A, Wakpi Djeugue D, Regis A, Abada S.

INTRODUCTION: In the present study, we examined retinal vascular oxygen saturation in patients with retinal vein occlusion (RVO), high blood pressure (HBP) and dyslipidemia, before and during intravitreal vascular endothelial growth factor (VEGF) injection (ranibizumab).

METHODS: We retrospectively reviewed the medical records of six patients with visual acuity (VA) reduced by macular edema (ME) secondary to RVO with HBP and dyslipidemia, who underwent intravitreal anti-VEGF injection between October 2014 and February 2015 in the department of ophthalmology of François-Quesnay Hospital at Mantes-la-Jolie (France). The main inclusion criterion was the presence of RVO with ME and decreased VA. The primary endpoint was improvement of retinal venous oxygen saturation in patients with RVO before and 3 months after intravitreal ranibizumab injection. Secondary outcomes were improvement of retinal arterial oxygen saturation, improvement of best-corrected visual acuity (BCVA) on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, regression of ME measured by the central macular thickness (CMT) in nm and studying the correlation between blood pressure (BP) and retinal venous oxygen saturation before and after ranibizumab.

RESULTS: Six eyes of six patients were included. Before treatment, the mean (standard deviation [SD]) of the retinal venous saturation (%) was 38.1±14.2. Three months after the injections, the mean (SD) of the retinal venous saturation (%) increased statistically significantly 49.2±11 ($P=0.03$).

CONCLUSION: In this study, retinal venous oxygen saturation in patients with RVO, HBP and dyslipidemia was partially normalized during intravitreal ranibizumab treatment.

PMID: 27865689

Other treatment & diagnosis

Am J Ophthalmol. 2016 Nov 15. [Epub ahead of print]

En face Optical Coherence Tomography Imaging for the Detection of Nascent Geographic Atrophy.

Schaal KB, Gregori G, Rosenfeld PJ.

PURPOSE: To determine if en face optical coherence tomography (OCT) imaging can identify nascent geographic atrophy (nGA) in eyes with intermediate age-related macular degeneration (iAMD).

DESIGN: Retrospective observational case series.

METHODS: Patients with iAMD from the COMPLETE study at the Bascom Palmer Eye Institute were evaluated to determine if nGA was present at baseline and at follow-up using high density Spectralis OCT B-scans and en face OCT images from the Cirrus OCT instrument. If available, additional en face OCT images and B-scans were analyzed at follow-up times beyond the 52-week period.

RESULTS: A total of 37 eyes (27 patients) were evaluated for at least one year using both B-scans and en face images. Two drusen suspicious for nGA at baseline were identified, but neither druse developed GA after 24 and 62 months of follow-up, respectively. Another druse displayed hypertransmission into the choroid at week 52 on B-scan imaging and was classified as nGA. En face OCT imaging identified this druse as a focal bright area. This druse did progress to GA during a follow-up of 38 months.

CONCLUSIONS: En face OCT imaging appeared to be as useful as routine B-scan imaging for identifying areas suspicious for nGA in this population from the COMPLETE Study. Additional longitudinal follow-up of eyes with drusen is needed to determine if en face OCT imaging can replace the evaluation of individual B-scans for the detection of nGA.

PMID: 27864062

EBioMedicine. 2016 Nov 10. [Epub ahead of print]

Phase 2a Randomized Clinical Trial: Safety and Post Hoc Analysis of Subretinal rAAV.sFLT-1 for Wet Age-related Macular Degeneration.

Constable IJ, Pierce CM, Lai CM, Magno AL, Degli-Esposti MA, French MA, McAllister IL, Butler S, Barone SB, Schwartz SD, Blumenkranz MS, Rakoczy EP.

BACKGROUND: We present the results of a Phase 2a randomized controlled trial investigating the safety, and secondary endpoints of subretinal rAAV.sFLT-1 gene therapy in patients with active wet age-related macular degeneration (wAMD).

METHODS: All patients (n=32), (ClinicalTrials.gov; NCT01494805), received ranibizumab injections at baseline and week 4, and thereafter according to prespecified criteria. Patients in the gene therapy group (n=21) received rAAV.sFLT-1 (1×1011vg). All patients were assessed every 4weeks to the week 52 primary endpoint.

FINDINGS: Ocular adverse events (AEs) in the rAAV.sFLT-1 group were mainly procedure related and self-resolved. All 11 phakic patients in the rAAV.sFLT-1 group showed progression of cataract following vitrectomy. No systemic safety signals were observed and none of the serious AEs were associated with rAAV.sFLT-1. AAV2 capsid was not detected and rAAV.sFLT-1 DNA was detected transiently in the tears of 13 patients. ELISPOT analysis did not identify any notable changes in T-cell response. In the rAAV.sFLT -1 group 12 patients had neutralizing antibodies (nAb) to AAV2. There was no change in sFLT-1 levels in bodily fluids. In the rAAV.sFLT-1 group, Best Corrected Visual Acuity (BCVA) improved by a median of 1.0 (IQR: -3.0 to 9.0) Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline compared to a median of -5.0 (IQR: -17.5 to 1.0) ETDRS letters change in the control group. Twelve (57%) patients in the rAAV.sFLT-1 group maintained or improved vision compared to 4 (36%) in the control group. The median

number of ranibizumab retreatments was 2.0 (IQR: 1.0 to 6.0) for the gene therapy group compared to 4.0 (IQR: 3.5 to 4.0) for the control group. Interpretation rAAV.sFLT-1 combined with the option for co-treatment appears to be a safe and promising approach to the treatment of wAMD.

PMID: 27865764

Ophthalmology. 2016 Nov 14. [Epub ahead of print]

Comparison between Widefield En Face Swept-Source OCT and Conventional Multimodal Imaging for the Detection of Reticular Pseudodrusen.

Schaal KB, Legarreta AD, Feuer WJ, Gregori G, Cheng Q, Legarreta JE, Durbin MK, Stetson PF, Kubach S, Rosenfeld PJ.

PURPOSE: The ability to detect reticular pseudodrusen (RPD)/subretinal drusenoid deposits (SDDs) using 12×12-mm widefield en face swept-source optical coherence tomography (SS-OCT) imaging was compared with conventional multimodal imaging (color, fundus autofluorescence (FAF), and infrared reflectance [IR] imaging) in eyes with nonexudative age-related macular degeneration (AMD).

DESIGN: Cross-sectional study.

PARTICIPANTS: Patients with nonexudative AMD were prospectively enrolled in an SS-OCT imaging study at the Bascom Palmer Eye Institute.

METHODS: On the same day, all participants underwent color, FAF, and IR fundus imaging, as well as imaging with a prototype Zeiss 100 kHz SS-OCT instrument (Carl Zeiss Meditec Inc, Dublin, CA). Two masked graders assessed the presence, absence, or uncertainty of RPD/SDDs on conventional multimodal images and separately on 4 different SS-OCT en face images derived from the same volumetric dataset. The results from grading the conventional images and the SS-OCT en face images were compared.

MAIN OUTCOME MEASURES: Agreement in the detection of RPD/SDDs using different imaging modalities.

RESULTS: A total of 307 eyes (209 patients) were graded for the presence or absence of RPD/SDDs. The agreement between SS-OCT and multimodal imaging was 83%. The difference in RPD/SDD detection with either image modality was not statistically significant (P = 0.21). The sensitivity of SS-OCT in RPD/SDD detection was 83%, and when using conventional imaging, the sensitivity was 75%. When using SS-OCT imaging alone, 10% of RPD/SDD cases would be missed, and when using conventional imaging alone, 14% of RPD/SDD cases would be missed. The presence of RPD/SDD was confirmed retrospectively in 48 of 52 cases once the overall grading was unmasked and the graders reevaluated the conventional multimodal images and the widefield SS-OCT en face images.

CONCLUSIONS: All 4 imaging modalities used together provided the best strategy for the detection of RPD/SDDs. However, when using widefield en face SS-OCT slab imaging alone, the detection of RPD/SDDs was at least as good as conventional imaging.

PMID: 27856030

Eye (Lond). 2016 Nov 25. [Epub ahead of print]

A view of the current and future role of optical coherence tomography in the management of age-related macular degeneration.

Schmidt-Erfurth U, Klimscha S, Waldstein SM, Bogunović H.

Abstract: Optical coherence tomography (OCT) has become an established diagnostic technology in the clinical management of age-related macular degeneration (AMD). OCT is being used for primary diagnosis,

evaluation of therapeutic efficacy, and long-term monitoring. Computer-based advances in image analysis provide complementary imaging tools such as OCT angiography, further novel automated analysis methods as well as feature detection and prediction of prognosis in disease and therapy by machine learning. In early AMD, pathognomonic features such as drusen, pseudodrusen, and abnormalities of the retinal pigment epithelium (RPE) can be imaged in a qualitative and quantitative way to identify early signs of disease activity and define the risk of progression. In advanced AMD, disease activity can be monitored clearly by qualitative and quantified analyses of fluid pooling, such as intraretinal cystoid fluid, subretinal fluid, and pigment epithelial detachment (PED). Moreover, machine learning methods detect a large spectrum of new biomarkers. Evaluation of treatment efficacy and definition of optimal therapeutic regimens are an important aim in managing neovascular AMD. In atrophic AMD hallmarked by geographic atrophy (GA), advanced spectral domain (SD)-OCT imaging largely replaces conventional fundus autofluorescence (FAF) as it adds insight into the condition of the neurosensory layers and associated alterations at the level of the RPE and choroid. Exploration of imaging features by computerized methods has just begun but has already opened relevant and reliable horizons for the optimal use of OCT imaging for individualized and population-based management of AMD-the leading retinal epidemic of modern times.

PMID: 27886184

PLoS One. 2016 Nov 23;11(11):e0166968. eCollection 2016.

Choroidal Round Hyporeflectivities in Geographic Atrophy.

Corbelli E, Sacconi R, De Vitis LA, Carnevali A, Rabiolo A, Querques L, Bandello F, Querques G.

PURPOSE: In geographic atrophy (GA), choroidal vessels typically appear on structural optical coherence tomography (OCT) as hyperreflective round areas with highly reflective borders. We observed that some GA eyes show choroidal round hyporeflectivities with highly reflective borders beneath the atrophy, and futher investigated the charcteristcs by comparing structural OCT, indocyanine green angiography (ICGA) and OCT angiography (OCT-A).

METHODS: Round hyporeflectivities were individuated from a pool of patients with GA secondary to non-neovascular age-related macular degeneration consecutively presenting between October 2015 and March 2016 at the Medical Retina & Imaging Unit of the University Vita-Salute San Raffaele. Patients underwent a complete ophthalmologic examination including ICGA, structural OCT and OCT-A. The correspondence between choroidal round hyporeflectivities beneath GA on structural OCT and ICGA and OCT-A imaging were analyzed.

RESULTS: Fifty eyes of 26 consecutive patients (17 females and 9 males; mean age 76.8±6.2 years) with GA were included. Twenty-nine round hyporeflectivities have been found by OCT in choroidal layers in 21 eyes of 21 patients (42.0%; estimated prevalence of 57.7%). All 29 round hyporeflectivities showed constantly a hyperreflective border and a backscattering on structural OCT, and appeared as hypofluorescent in late phase ICGA and as dark foci with non detectable flow in the choroidal segmentation of OCT-A. Interestingly, the GA area was greater in eyes with compared to eyes without round hyporeflectivities (9.30±5.74 and 5.57±4.48mm2, respectively; p = 0.01).

CONCLUSIONS: Our results suggest that most round hyporeflectivities beneath GA may represent non-perfused or hypo-perfused choroidal vessels with non-detectable flow.

PMID: 27880806

Retina. 2016 Dec;36(12):2274-2281.

RETINAL ANGIOMATOUS PROLIFERATION DIAGNOSIS: A Multiimaging Approach.

Ravera V, Bottoni F, Giani A, Cigada M, Staurenghi G.

PURPOSE: To identify signs occurring more frequently in retinal angiomatous proliferation (RAP) lesions compared with other types of choroidal neovascularization (CNV) in age-related macular degeneration.

METHODS: In this cross-sectional retrospective study, 30 patients were evaluated. These signs were correlated with the type of CNV: shunting of blood flow to the lesion by fluorescein angiography, late leakage by indocyanine green angiography, intraretinal cysts and retinal pigmented epithelium interruption along the retinal pigmented epithelium detachment with a hyperreflective oval area by spectral domain optical coherence tomography, and presence of reticular pseudodrusen by infrared light.

RESULTS: Shunting of blood flow was found in 56% of RAP, whereas it was absent in 100% of other CNVs. Late leakage in indocyanine green angiography occurred in all RAP cases, while it was found in 7% of other CNVs. Intraretinal cysts were detected in 100% of RAP cases and in 14% of other CNVs. Retinal pigmented epithelium interruption along the retinal pigmented epithelium detachment was evident in 93% of RAP cases and in 15% of other CNVs. Reticular pseudodrusen were present in 87% of RAP cases and in 21% of other CNVs.

CONCLUSION: All the signs investigated were strongly associated to RAP lesions. A multimodal imaging approach may help differentiating subtypes of neovascularization.

PMID: 27870798

Trials. 2016 Nov 24;17(1):560.

StereoTactic radiotherapy for wet Age-Related macular degeneration (STAR): study protocol for a randomised controlled clinical trial.

Neffendorf JE, Desai R, Wang Y, Kelly J, Murphy C, Reeves BC, Chakravarthy U, Wordsworth S, Lewis C, Peacock J, Uddin S, O'Sullivan JM, Jackson TL.

BACKGROUND: The standard of care for neovascular age-related macular degeneration (nAMD) involves ongoing intravitreal injections of anti-angiogenic drugs targeting vascular endothelial growth factor (VEGF). The most commonly used anti-VEGF drugs are ranibizumab, bevacizumab and aflibercept. The main objective of the STAR trial is to determine if stereotactic radiotherapy can reduce the number of anti-VEGF injections that patients with nAMD require.

METHODS/DESIGN: STAR is a multicentre, double-masked, randomised, sham-controlled clinical trial. It evaluates a new device (manufactured by Oraya, Newark, CA, USA) designed to deliver stereotactic radiotherapy (SRT) to nAMD lesions. The trial enrols participants with chronic, active nAMD. Participants receive a single SRT treatment (16 Gy or sham) with a concomitant baseline intravitreal injection of 0.5 mg ranibizumab. Thereafter, they attend every month for 24 months, and ranibizumab is administered at the visit if retreatment criteria are met. The primary outcome is the number of pro re nata ranibizumab injections during the first 24 months. Secondary outcomes include visual acuity, lesion morphology, quality of life and safety. Additional visits occur at 36 and 48 months to inspect for radiation retinopathy. The target sample size of 411 participants (randomised 2:1 in favour of radiation) is designed to detect a reduction of 2.5 injections against ranibizumab monotherapy, at 90% power, and a significance level (alpha) of 0.025 (one-sided two-sample t test). This gives 97% power to detect non-inferiority of visual acuity at a five-letter margin. The primary analyses will be by intention to treat.

DISCUSSION: The safety and efficacy outcomes will help determine the role of SRT in the management of chronic, active nAMD.

PMID: 27881184

Med Hypotheses. 2016 Dec;97:98-101. Epub 2016 Oct 29.

Retinal pigment epithelium cell-derived exosomes: Possible relevance to CNV in wet-age related

macular degeneration.

Tong Y, Zhou YL, Wang YX, Zhao PQ, Wang ZY.

Abstract: Exosomes are small vesicles that are released by almost every cell type and play a crucial role in many physiological and pathological processes associated with different diseases. Specifically, they promote angiogenesis in the pathogenesis of some diseases. According to previous research, the proteins of exosomes taken from the aqueous humor (AH) of patients with wet-age related macular degeneration (AMD) may function as a new diagnostic biomarker of AMD, suggesting that exosomes may play an important role in the occurrence and development of choroidal neovascularization (CNV). Moreover, additional research has revealed that the levels of some protein makers of exosomes are up-regulated in aged retinal pigment epithelium (RPE) and that drusen and oxidative stress may promote the secretion of exosomes derived from RPE cells. Consequently, we hypothesize that RPE cell-derived exosomes may be relevant to CNV in wet AMD. If this hypothesis is proven correct, future studies based on this link may also help to elucidate the molecular mechanisms of wet AMD and to find new therapeutic targets for the treatment of AMD.

PMID: 27876140

J Biol Chem. 2016 Nov 14. [Epub ahead of print]

Receptor tyrosine kinase MERTK is not required for transfer of bis-retinoids to the retinal pigmented epithelium.

Palczewska G, Maeda A, Golczak M, Arai E, Dong Z, Perusek L, Kevany B, Palczewski K.

Abstract: Accumulation of bis-retinoids in the retinal pigmented epithelium (RPE) is a hallmark of aging and retinal disorders such as Stargardt disease and age-related macular degeneration. These aberrant fluorescent condensation products including A2E are thought to be transferred to RPE cells primarily through phagocytosis of the photoreceptor outer segments. However, we observed by two-photon microscopy that mouse retinas incapable of phagocytosis due to a deficiency of the c-mer proto-oncogene tyrosine kinase (Mertk) nonetheless contained fluorescent retinoid condensation material in their RPE. Primary RPE cells from Mertk -/- mice also accumulated fluorescent products in vitro Finally, quantification of A2E demonstrated the acquisition of retinal condensation products in Mertk-/- mouse RPE prior to retinal degeneration. In these mice, we identified activated microglia cells that likely were recruited to transport A2E-like condensation products to the RPE and dispose of the dying photoreceptor cells. These observations demonstrate a novel transport mechanism between photoreceptor cells and RPE that does not involve canonical Mertk-dependent phagocytosis.

PMID: 27875314

Acta Ophthalmol. 2016 Nov 22. [Epub ahead of print]

Placental growth factor and its potential role in diabetic retinopathy and other ocular neovascular diseases.

Nguyen QD, De Falco S, Behar-Cohen F, Lam WC, Li X, Reichhart N, Ricci F, Pluim J, Li WW.

Abstract: The role of vascular endothelial growth factor (VEGF), including in retinal vascular diseases, has been well studied, and pharmacological blockade of VEGF is the gold standard of treatment for neovascular age-related macular degeneration, retinal vein occlusion and diabetic macular oedema. Placental growth factor (PGF, previously known as PlGF), a homologue of VEGF, is a multifunctional peptide associated with angiogenesis-dependent pathologies in the eye and non-ocular conditions. Animal studies using genetic modification and pharmacological treatment have demonstrated a mechanistic role for PGF in pathological angiogenesis. Inhibition decreases neovascularization and microvascular abnormalities across different models, including oxygen-induced retinopathy, laser-induced choroidal neovascularization

and in diabetic mice exhibiting retinopathies. High levels of PGF have been found in the vitreous of patients with diabetic retinopathy. Despite these strong animal data, the exact role of PGF in pathological angiogenesis in retinal vascular diseases remains to be defined, and the benefits of PGF-specific inhibition in humans with retinal neovascular diseases and macular oedema remain controversial. Comparative effectiveness research studies in patients with diabetic retinal disease have shown that treatment that inhibits both VEGF and PGF may provide superior outcomes in certain patients compared with treatment that inhibits only VEGF. This review summarizes current knowledge of PGF, including its relationship to VEGF and its role in pathological angiogenesis in retinal diseases, and identifies some key unanswered questions about PGF that can serve as a pathway for future basic, translational and clinical research.

PMID: 27874278

Sci Rep. 2016 Nov 22;6:37391.

Lymphocytic Microparticles Modulate Angiogenic Properties of Macrophages in Laser-induced Choroidal Neovascularization.

Tahiri H, Omri S, Yang C, et al

Abstract: Pathological choroidal neovascularization (CNV) is the common cause of vision loss in patients with age-related macular degeneration (AMD). Macrophages possess potential angiogenic function in CNV. We have demonstrated that human T lymphocyte-derived microparticles (LMPs) exert a potent antiangiogenic effect in several pathological neovascularization models. In this study, we investigated the alteration of proangiogenic properties of macrophages by LMPs treatment in vitro and in vivo models. LMPs regulated the expression of several angiogenesis-related factors in macrophages and consequently stimulated their antiangiogenic effects evidenced by the suppression of the proliferation of human retinal endothelial cells in co-culture experiments. The involvement of CD36 receptor in LMPs uptake by macrophages was demonstrated by in vitro assays and by immunostaining of choroidal flat mounts. In addition, ex vivo experiments showed that CD36 mediates the antiangiogenic effect of LMPs in murine and human choroidal explants. Furthermore, intravitreal injection of LMPs in the mouse model of laser-induced CNV significantly suppressed CNV in CD36 dependent manner. The results of this study suggested an ability of LMPs to alter the gene expression pattern of angiogenesis-related factors in macrophages, which provide important information for a new therapeutic approach for efficiently interfering with both vascular and extravascular components of CNV.

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Pathogenesis

Int J Biol Sci. 2016 Oct 25;12(11):1332-1340. eCollection 2016.

The Evolving Functions of Autophagy in Ocular Health: A Double-edged Sword.

Chai P, Ni H, Zhang H, Fan X.

Abstract: Autophagy plays an adaptive role in cell survival, development, differentiation and intracellular homeostasis. Autophagy is recognized as a 'self-cannibalizing' process that is active during stresses such as starvation, chemotherapy, infection, ageing, and oxygen shortage to protect organisms from various irritants and to regenerate materials and energy. However, autophagy can also lead to a form of programmed cell death distinct from apoptosis. Components of the autophagic pathway are constitutively expressed at a high level in the eye, including in the cornea, lens, retina, and orbit. In addition, the activation of autophagy is directly linked to the development of eye diseases such as age-related macular degeneration (ARMD), cataracts, diabetic retinopathy (DR), glaucoma, photoreceptor degeneration, ocular tumours, ocular infections and thyroid-associated ophthalmopathy (TAO). A high level of autophagy defends against external stress; however, excessive autophagy can result in deterioration, as observed in

ocular diseases such as ARMD and DR. This review summarizes recent developments elucidating the relationship between autophagy and ocular diseases and the potential roles of autophagy in the pathogenesis and treatment of these diseases.

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Mol Vis. 2016 Nov 10;22:1332-1341. eCollection 2016.

Retinal safety of intravitreal rtPA in healthy rats and under excitotoxic conditions.

Daruich A, Parcq J, Delaunay K, Naud MC, Le Rouzic Q, Picard E, Crisanti P, Vivien D, Berdugo M, Behar-Cohen F.

PURPOSE: Intravitreal recombinant tissue plasminogen activator (rtPA) is used off-label for the surgical management of submacular hemorrhage, a severe complication of neovascular age-related macular degeneration. rtPA is approved for coronary and cerebral thrombolysis. However, in ischemic stroke rtPA is known to increase excitotoxic neural cell death by interacting with the N-methyl-D-aspartate (NMDA) receptor. We therefore investigated the retinal toxicity of rtPA in healthy rats and in a model of NMDA-induced retinal excitotoxicity.

METHODS: First, rtPA at three different doses (2.16 µg/5 µl, 0.54 µg/5 µl, and 0.27 µg/5 µl) or vehicle (NaCl 0.9%) was injected intravitreally in healthy rat eyes. Electroretinograms (ERGs) were performed at 24 h or 7 days. Annexin V-fluorescein isothiocyanate (FITC)-labeled apoptotic retinal ganglion cells (RGCs) were counted on flatmounted retinas at 24 h or 7 days. Next, NMDA + vehicle or NMDA + rtPA (0.27 µg/5 µl) was injected intravitreally to generate excitotoxic conditions. Apoptotic annexin V-FITC-labeled RGCs and surviving Brn3a-labeled RGCs were quantified on flatmounted retinas and radial sections, 18 h after treatment.

RESULTS: In healthy rat eyes, the number of apoptotic RGCs was statistically significantly increased 24 h after the administration of rtPA at the highest dose (2.16 µg/5 µl; p = 0.0250) but not at the lower doses of 0.54 and 0.27 µg/5 µl (p = 0.36 and p = 0.20), compared to vehicle. At day 7, there was no difference in the apoptotic RGC count between the rtPA- and vehicle-injected eyes (p = 0.70, p = 0.52, p = 0.11). ERG amplitudes and implicit times were not modified at 24 h or 7 days after injection of any tested rtPA doses, compared to the baseline. Intravitreal administration of NMDA induced RGC death, but under these excitotoxic conditions, coadministration of rtPA did not increase the number of dead RGCs (p = 0.70). Similarly, the number of surviving RGCs on the flatmounted retinas and retinal sections did not differ between the eyes injected with NMDA + vehicle and NMDA + rtPA (p = 0.59 and p = 0.67).

CONCLUSIONS: At low clinical equivalent doses corresponding to 25 µg/0.1 ml in humans, intravitreal rtPA is not toxic for healthy rat retinas and does not enhance NMDA-induced excitotoxicity. Vitreal equivalent doses ≥200 µg/0.1 ml should be avoided in patients, due to potential RGC toxicity.

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Acta Ophthalmol. 2016 Nov 18. [Epub ahead of print]

New neovascular age-related macular degeneration is associated with systemic leucocyte activity.

Subhi Y, Lykke Sørensen T.

PURPOSE: To investigate systemic leucocyte activity in subtypes of age-related macular degeneration (AMD) and onset of neovascular AMD.

METHODS: Patients with early and late AMD and age-matched control individuals were recruited consecutively, and venous blood was sampled for differential leucocyte counts. Patients with neovascular AMD were grouped based on time of blood sampling in relation to diagnosis of neovascular AMD: diagnosis

of new neovascular AMD more than 30 days before blood sampling, within 30 days of blood sampling and more than 30 days after blood sampling.

RESULTS: Of 347 recruited participants, 330 fulfilled the eligibility criteria (77 age-matched controls, 33 with early AMD, 56 with geographic atrophy and 164 with neovascular AMD). We did not find any differences in the differential counts between patients at different stages of AMD and age-matched control individuals. However, lymphocyte and monocytes-basophils-eosinophils mixed (MXD) counts were both significantly increased in patients with new neovascular AMD. Among these patients; higher MXD correlated with lower BCVA, larger central foveal thickness and larger total lesion size; higher lymphocytes correlated with smaller total lesion size; higher neutrophils correlated with CNV lesion size; and higher neutrophil-to-lymphocyte ratio correlated with larger lesion size.

CONCLUSIONS: Systemic leucocyte activity is associated with onset of CNV in patients with AMD and correlate with lesion size and BCVA, which suggest that acute systemic immune activity may play a role in neovascular flaring of AMD.

PMID: 27860298

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CD93 as a Potential Target in Neovascular Age-Related Macular Degeneration.

Tosi GM, Caldi E, Parolini B, Toti P, Neri G, Nardi F, Traversi C, Cevenini G, Marigliani D, Nuti E, Bacci T, Galvagni F, Orlandini M.

Abstract: In patients with age-related macular degeneration (AMD), choroidal neovascularization is the major cause of severe visual loss. In these patients, the persistence of neovascular growth despite vascular endothelial growth factor-A blockage needs the discovery of new endothelial cell targets. The glycoprotein CD93, highly expressed in activated endothelial cells, has been recently involved in the regulation of the angiogenic process both as transmembrane and soluble protein. Choroidal neovascular membranes from patients affected by AMD were examined by immunofluorescence using anti-CD93 and anti-von Willebrand factor antibodies. Blood vessels within intraocular and extraocular neoplasias were used as controls for CD93 expression. All choroidal neovascular membranes displayed strong CD93 staining in the von Willebrand factor-positive endothelial cells, consistently with the analyses showing a high colocalization coefficient in the blood vessels. Intraocular and extraocular tumor vessels showed similar results, whereas the normal choroid displayed blood vessels with only faint CD93 staining. Additionally, the concentration of soluble CD93 was determined in the aqueous humor of patients affected by naïve neovascular AMD by enzyme-linked immunosorbent assays. Age-matched cataract patients served as controls. Soluble CD93 was significantly increased in the aqueous humor of naïve neovascular AMD patients and tended to decrease after treatment with an antiangiogenic drug. In conclusion, both transmembrane and soluble CD93 are overexpressed in patients with neovascular AMD, indicating that CD93 may represent a potential new antiangiogenic target in the treatment of choroidal neovascularization.

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Biochem Biophys Res Commun. 2016 Nov 14. [Epub ahead of print]

Potential suppression of the high glucose and insulin-induced retinal neovascularization by Sirtuin 3 in the human retinal endothelial cells.

Mao XB, You ZP, Wu C, Huang J.

Abstract: Retinal neovascularization generally play roles in the formation of various severe eye diseases, such as age-related macular degeneration and diabetic retinopathy. The regulation of neovascularization-related pathways by Sirtuin 3 (Sirt3), a major mitochondrial NAD+-dependent deacetylase, give us a cue that Sirt3 may participate in the retinal neovascularization. However, the mechanism remains unclear. Here,

we established a retinal neovascularization model by using human retinal endothelial cells (HRECs) under the induction of high glucose and insulin (HGI). With this model, Sirt3-expressing lentivirus was constructed and then used to investigate the effect of Sirt3 overexpression on the expression of migration-, neovascularization- and autophagy-related genes. After the treatment of HGI on HRECs, the mRNA and protein levels of migration-related genes, including matrix metalloproteinase-2 (MMP-2) and MMP-9, were significantly upregulated. Meanwhile, angiogenesis-related genes, including vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1α (HIF-1α), and insulin-like growth factor-1 (IGF-1) were promoted at both mRNA and protein levels. However, HGI had no clear effect on the mRNA and protein levels of microtubule associated protein 1 light chain 3 (LC3), an autophagy-related gene. When Sirt3 was overexpressed by lentivirus infection after HGI, the upregulation of MMP-2, MMP-9, VEGF, HIF-1α, and IGF-1 were suppressed at both transcription and translation levels. At the same time, LC3 mRNA and LC3-II protein increased. These results suggest that Sirt3 may inhibit retinal neovascularization by regulating the migration-, neovascularization- and autophagy-related factors expression. Thus we argue that Sirt3 may be a potential candidate drug for curing various eye diseases induced by retinal neovascularization.

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Genetics

Mol Vis. 2016 Nov 10;22:1318-1331. eCollection 2016.

Genetic and immunohistochemical analysis of HSPA5 in mouse and human retinas.

Chintalapudi SR, Wang X, Li H, Lau YH, Williams RW, Jablonski MM.

PURPOSE: Photoreceptor degenerative diseases are among the leading causes of vision loss. Although the causative genetic mutations are often known, mechanisms leading to photoreceptor degeneration remain poorly defined. We have previously demonstrated that the photoreceptor membrane-associated protein XAP-1 antigen is a product of the HSPA5 gene. In this study, we used systems genetic methods, statistical modeling, and immunostaining to identify and analyze candidate genes that modulate Hspa5 expression in the retina.

METHODS: Quantitative trait locus (QTL) mapping was used to map the genomic region that regulates Hspa5 in the cross between C57BL/6J X DBA/2J mice (BXD) genetic reference panel. The stepwise refinement of candidate genes was based on expression QTL mapping, gene expression correlation analyses (direct and partial), and analysis of regional sequence variants. The subcellular localization of candidate proteins and HSPA5 in mouse and human retinas was evaluated by immunohistochemistry. Differences in the localization of extracellular HSPA5 were assessed between healthy human donor and atrophic age-related macular degeneration (AMD) donor eyes.

RESULTS: In the eyes of healthy mice, extracellular HSPA5 was confined to the area around the cone photoreceptor outer segments. Mapping variation in Hspa5 mRNA expression levels in the retina revealed a statistically significant trans-acting expression QTL (eQTL) on Chromosome 2 (Chr 2) and a suggestive locus on Chr 15. Sulf2 on Chr 2 was the strongest candidate gene based on partial correlation analysis, Pearson correlation with Hspa5, expression levels in the retina, a missense variant in exon 14, and its reported function in the extracellular matrix and interphotoreceptor matrix. SULF2 is localized to the rod and cone photoreceptors in both human and mouse retinas. In human retinas with no pathology, extracellular HSPA5 was localized around many cones within the macular area. In contrast, fewer HSPA5-immunopositive cones were observed in the retinas from AMD donors.

CONCLUSIONS: We identified Sulf2 as a candidate gene modulating the Hspa5 expression in the retina. The preferential loss of HSPA5 in the interphotoreceptor matrix around cone photoreceptors in atrophic AMD retinas opens up new avenues for exploring the changes in interphotoreceptor matrix (IPM) that are associated with macular disease.

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Genetics. 2016 Nov 22. [Epub ahead of print]

Recombinant Haplotypes Narrow the ARMS2/HTRA1 Association Signal for Age-Related Macular Degeneration.

Grassmann F, Heid IM, Weber BH.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in ageing societies and is caused by both environmental and genetic factors. The strongest genetic signal for AMD with odds ratios of up to 2.8 per adverse allele was found previously to center over two genes, ARMS2 and HTRA1 on 10q26, although with little knowledge as to the true functionally relevant gene or genetic variation. Due to extensive linkage disequilibrium (LD) at this locus, it was long assumed that the broad association signal cannot be dissected by statistical means. In this report, we have now separated the 10q26 region by analyzing imputed haplotypes with the help of a large case/control association data set. Rare recombinant haplotypes identified in 16,144 cases and 17,832 controls from the International AMD Genomics Consortium (IAMDGC), revealed genetic variants in ARMS2 but not HTRA1 to exclusively carry the AMD disease load with p values between 1.0x10-773 and 6.7x10-5 This study is a proof-of-concept and universally applicable to refine extended association signals providing the means to prioritize genes of interest for subsequent biological studies.

PMID: 27879347

Diet, lifestyle and low vision

EMBO Mol Med. 2016 Nov 15. [Epub ahead of print]

Gut microbiota influences pathological angiogenesis in obesity-driven choroidal neovascularization.

Andriessen EM, Wilson AM, Mawambo G, Dejda A, Miloudi K, Sennlaub F, Sapieha P.

Abstract: Age-related macular degeneration in its neovascular form (NV AMD) is the leading cause of vision loss among adults above the age of 60. Epidemiological data suggest that in men, overall abdominal obesity is the second most important environmental risk factor after smoking for progression to late-stage NV AMD To date, the mechanisms that underscore this observation remain ill-defined. Given the impact of high-fat diets on gut microbiota, we investigated whether commensal microbes influence the evolution of AMD Using mouse models of NV AMD, microbiotal transplants, and other paradigms that modify the gut microbiome, we uncoupled weight gain from confounding factors and demonstrate that high-fat diets exacerbate choroidal neovascularization (CNV) by altering gut microbiota. Gut dysbiosis leads to heightened intestinal permeability and chronic low-grade inflammation characteristic of inflammaging with elevated production of IL-6, IL-1β, TNF-α, and VEGF-A that ultimately aggravate pathological angiogenesis.

PMID: 27861126

Nutr Res Rev. 2016 Nov 21:1-14. [Epub ahead of print]

Dietary DHA and health: cognitive function ageing.

Cardoso C, Afonso C, Bandarra NM.

Abstract: DHA is a key nutritional n-3 PUFA and needs to be supplied by the human diet. DHA is found in significant amounts in the retinal and neuronal cell membranes due to its high fluidity. Indeed, DHA is selectively concentrated in the synaptic and retinal membranes. DHA is deemed to display anti-inflammatory properties and to reduce the risk of CVD. Consumption of larger amounts of DHA appears to reduce the risk of depression, bipolar disorder, schizophrenia and mood disorders. Conversely, it has been shown that loss of DHA from the nerve cell membrane leads to dysfunction of the central nervous system in

the form of anxiety, irritability, susceptibility to stress, dyslexia, impaired memory and cognitive functions, and extended reaction times. DHA plays an important role in ensuring a healthy ageing, by thwarting macular degeneration, Alzheimer's disease, and other brain disorders at the same time as enhancing memory and strengthening neuroprotection in general. A reduced level of DHA is associated with cognitive decline during ageing. Different mechanisms for this fundamental DHA role have been put forward. Namely, neuroprotectin D1, a DHA derivative, may support brain cell survival and repair through neurotrophic, anti-apoptotic, and anti-inflammatory signalling. Many of the effects of DHA on the neurological system may be related to signalling connections, thus leading to the study of the related signalolipidomics. Therefore, the present review will focus on the influence of DHA deficiency upon ageing, with specific emphasis upon neurological disorders related to cognitive function and mental health.

PMID: 27866493

Nutrients. 2016 Nov 22;8(11).

Fish Consumption and Age-Related Macular Degeneration Incidence: A Meta-Analysis and Systematic Review of Prospective Cohort Studies.

Zhu W, Wu Y, Meng YF, Xing Q, Tao JJ, Lu J.

Abstract: The association between fish consumption and risk of age-related macular degeneration (AMD) is still unclear. The aim of the current meta-analysis and systematic review was to quantitatively evaluate findings from observational studies on fish consumption and the risk of AMD. Relevant studies were identified by searching electronic databases (Medline and EMBASE) and reviewing the reference lists of relevant articles up to August, 2016. Prospective cohort studies that reported relative risks (RRs) and 95% confidence intervals (CIs) for the link between fish consumption and risk of AMD were included. A total of 4202 cases with 128,988 individuals from eight cohort studies were identified in the current meta-analysis. The meta-analyzed RR was 0.76 (95% CI, 0.65-0.90) when any AMD was considered. Subgroup analyses by AMD stages showed that fish consumption would reduce the risk of both early (RR, 0.83; 95% CI, 0.72-0.96) and late (RR; 0.76; 95% CI, 0.60-0.97) AMD. When stratified by the follow-up duration, fish consumption was a protective factor of AMD in both over 10 years (n = 5; RR, 0.81; 95% CI, 0.67-0.97) and less than 10 years (n = 3; RR, 0.70; 95% CI, 0.51 to 0.97) follow-up duration. Stratified analyses by fish type demonstrated that dark meat fish (RR, 0.68, 95% CI, 0.46-0.99), especially tuna fish (RR, 0.58; 95% CI, 95% CI, 0.47-0.71) intake was associated with reduced AMD risk. Evidence of a linear association between dose of fish consumption and risk of AMD was demonstrated. The results of this meta-analysis demonstrated that fish consumption can reduce AMD risk. Advanced, well-designed, randomized clinical trials are required in order to validate the conclusions in this study.

PMID: 27879656

Ophthalmic Res. 2016 Nov 24. [Epub ahead of print]

The Protective Effect of Brown-, Gray-, and Blue-Tinted Lenses against Blue LED Light-Induced Cell Death in A2E-Laden Human Retinal Pigment Epithelial Cells.

Park SI, Jang YP.

Abstract: A2E-laden ARPE-19 cells were exposed to a blue light to induce cytotoxicity, in order to investigate the protective effects of various tinted ophthalmic lenses against photo-induced cytotoxicity in human retinal pigment epithelial (RPE) cells laden with A2E, known to be among the etiologies of age-related macular degeneration (AMD). Different-colored tinted lenses with varying levels of tint and different filtering characteristics, such as polarized, blue-cut, and photochromatic lenses, were placed over the cells, and the protective efficacies thereof were evaluated by lactate dehydrogenase assay. When tinted lenses were placed over ARPE-19 cells, there were different reductions in cytotoxicity according to the colors and tint levels. The level of protection afforded by brown-tinted lenses was 6.9, 36.1, and 49% with a tint level of

15, 50, and 80%, respectively. For gray-tinted lenses, the protective effect was 16.3, 35, and 43.4% for the corresponding degree of tint, respectively. In the case of blue-tinted lenses, a protective effect of 20% was observed with 80% tinted lenses, but 15 and 50% tinted lenses provided no significant protection. In addition, photochromic lenses showed a protective effect but blue-cut lenses and polarized lenses provided no significant protection. Tinted lenses significantly reduced cytotoxicity in RPE cells irradiated with blue light. The protection was more efficient in lenses with a brown or gray tint than in blue-tinted lenses. Tinted glasses may provide significant protection against potential blue-light-induced photochemical and photo-oxidative damage in RPE cells.

PMID: 27880954

Vision Res. 2016 Nov 19. [Epub ahead of print]

Scene perception in age-related macular degeneration: Effect of spatial frequencies and contrast in residual vision.

Peyrin C, Ramanoël S, Roux-Sibilon A, Chokron S, Hera R.

Abstract: Age-related macular degeneration (AMD) is characterized by a central vision loss. Here, we investigated the ability of AMD patients to process the spatial frequency content of scenes in their residual vision, depending of the luminance contrast level. AMD patients and normally-sighted elderly participants (controls) performed a categorization task involving large scenes (outdoors vs. indoors) filtered in low spatial frequencies (LSF), high spatial frequencies (HSF), and non-filtered scenes (NF). Luminance contrast of scenes was equalized between stimuli using a root-mean square (RMS) contrast normalization. In Experiment 1, we applied an RMS contrast of 0.1 (for luminance values between 0 and 1), a value situated between the mean contrast of LSF and HSF scenes in natural conditions. In Experiment 2, we applied an RMS contrast of 0.3, corresponding to the mean contrast of HSF scenes in natural conditions. In Experiment 3, we manipulated four levels of linearly-increasing RMS contrasts (0.05, 0.10, 0.15, and 0.20) for HSF scenes only. Compared to controls, AMD patients gave more non-responses in the categorization of HSF than NF or LSF scenes, irrespective of the contrast level of scenes. Performances improved as contrast increased in HSF scenes. Controls were not differentially affected by the spatial frequency content of scenes. Overall, results suggest that LSF processing is well preserved in AMD patients and allows efficient scene categorization in their parafoveal residual vision. The HSF processing deficit could be partially restored by enhancing luminance contrast.

PMID: 27876510

Ann Pharmacother. 2016 Nov 19. [Epub ahead of print]

Benefits, Potential Harms, and Optimal Use of Nutritional Supplementation for Preventing Progression of Age-Related Macular Degeneration.

Rojas-Fernandez CH, Tyber K.

OBJECTIVE: To briefly review age-related macular degeneration (AMD), the main findings from the Age Related Eye Disease Study (AREDS) report number 8 on the use of nutritional supplements for AMD, and to focus on data suggesting that supplement use should be guided using genetic testing of AMD risk genes.

DATA SOURCES: A literature search (January 2001 through October 26, 2016) was conducted using MEDLINE and the following MeSH terms: Antioxidants/therapeutic use, Genotype, Macular Degeneration/drug therapy, Macular degeneration/genetics, Dietary Supplements, Proteins/genetics, and Zinc Compounds/therapeutic use Bibliographies of publications identified were also reviewed.

STUDY SELECTION AND DATA EXTRACTION: English-language studies assessing AREDS supplement response in patients with AMD in relation to complement factor H gene (CFH) and age-related maculopathy susceptibility 2 gene (ARMS2) risk alleles were evaluated.

DATA SYNTHESIS: Three of the 4 studies demonstrated a treatment interaction between ARMS2 and CFH genotypes and a differential response to supplements. The fourth study documented an interaction for the CFH genotype only. Reported response interactions included attenuated response, no response, and good response, whereas a subset showed increased progression of AMD. Conversely, one study reported no interactions between CFH and ARMS2 risk alleles and response to supplements.

CONCLUSIONS: The weight of the evidence supports using genetic testing to guide selection of ocular vitamin use. This approach will avoid using supplements that could speed the progression of AMD in vulnerable patients, avoid using supplements that will have little to no effect in others, and result in appropriately using supplements in those that are likely to derive meaningful benefits.

PMID: 27866147

Trials. 2016 Nov 3;17(1):531.

Evaluation of efficacy and efficiency of a pragmatic intervention by a social worker to support informal caregivers of elderly patients (The ICE Study): study protocol for a randomized controlled trial.

Pozet A, Lejeune C, Bonnet M, Dabakuyo S, Dion M, Fagnoni P, Gaimard M, Imbert G, Nerich V, Foubert A, Chotard M, Bonin M, Anota A, Bonnetain F.

BACKGROUND: Medical progress and the lifestyle modification have prolonged life expectancy, despite the development of chronic diseases. Support and care for older subjects are often provided by a network of informal caregivers composed of family, friends and neighbors, who are essential in helping older persons to continue living at home. It has been shown that the extent and diversity of informal tasks may jeopardize the physical, mental and social wellbeing of caregivers.

METHODS/DESIGN: The aim of the Informal Carers of Elderly cohort is to define, through a longitudinal study, profiles of caregivers of older patients with a diagnosis of one of the following diseases: cancer (breast, prostate, colorectal), neurodegenerative diseases (Parkinson's disease, Alzheimer's disease and similar diseases), neurovascular diseases (stroke), sensory diseases (age-related macular degeneration (AMD)) and heart disease (heart failure). Patients must be at least 60 years old and living in the region of Burgundy-Franche-Comte (France). By following the different phases of the caregiving relationship from the announcement of the diagnosis, it will be possible to assess the quality of life of caregivers, coping strategies, levels of anxiety and depression, social support and the extent of their burden. We will also evaluate the efficacy and efficiency of the implementation of a pragmatic intervention by a social worker to help informal caregivers, through a randomized interventional trial nested in the cohort. Qualitative approaches aimed at studying the caregiver/patient relationship, and situations leading to breakdown of the caregiver relationship will be also undertaken.

DISCUSSION: Through an analytical and longitudinal definition of profiles of informal caregivers, this study will gather detailed information on their life courses and their health trajectory by identifying consequences associated with the concept of their role as carers. In addition, the randomized interventional trial will explore the relevance of the implementation of a supportive intervention by a social worker to help caregivers. These data will help to identify strategies that could be used to improve the existing sources of aid and to propose new approaches to help caregivers. This study will provide the opportunity to identify the most relevant means of support adapted to caregivers, and provide an impulse for new health care policies.

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Corrigendum to "Nutritional Risk Factors for Age-Related Macular Degeneration".

Ersoy L, Ristau T, Lechanteur YT, Hahn M, Hoyng CB, Kirchhof B, den Hollander AI, Fauser S.

Abstract:[This corrects the article DOI: 10.1155/2014/413150.].

Erratum for

Nutritional risk factors for age-related macular degeneration. [Biomed Res Int. 2014]

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