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MD Research News

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Drug treatment

Retina. 2014 Mar 14. [Epub ahead of print]

ANTI-VEGF TREATMENT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: A Treat-and-Extend Protocol Over 2 Years.

Abedi F, Wickremasinghe S, Islam AF, Inglis KM, Guymer RH.

PURPOSE: To evaluate 2-year visual acuity outcome of a treat-and-extend protocol of anti-vascular endothelial growth factor treatment in age-related macular degeneration.

METHODS: In this prospective cohort study, 120 age-related macular degeneration patients with choroidal neovascularization received 3 initial monthly ranibizumab or bevacizumab injections; monthly injections were continued until there was no choroidal neovascularization activity (subretinal/intraretinal fluid, loss of >5 letters, or persistent/recurrent retinal hemorrhage). When there was no choroidal neovascularization activity, the interval to the next visit/injection was extended by 2 weeks to a maximum of 12 weeks. In the presence of choroidal neovascularization activity, this interval was shortened by 2 weeks. Main outcome measures included the percentage losing <15 letters and the mean visual acuity change after 12 months and 24 months.

RESULTS: Mean baseline visual acuity was 51.2 ± 12.1 Early Treatment Diabetic Retinopathy Study scores. Mean visual acuity change from baseline was +9.5 ± 10.9 and +8.0 ± 12.9 letters after 12 months and 24 months, respectively, with, on average, 8.6 ± 1.1 visits/injections in the first year and 5.6 ± 2.0 in the second year. After 12 months and 24 months, 97.5% and 95.0% of patients, respectively, lost <15 letters.

CONCLUSION: The "inject-and-extend" protocol-with fewer injections and visits-delivered outcomes comparable to those of the pivotal clinical trials of monthly ranibizumab.

PMID: 24637667 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Mar 11. pii: S0014-4835(14)00069-4. doi: 10.1016/j.exer.2014.02.024. [Epub ahead of print]

Capacity of aflibercept to counteract VEGF-stimulated abnormal behavior of retinal microvascular endothelial cells.

Deissler HL1, Lang GK2, Lang GE2.

Abstract: Members of the vascular endothelial growth factor (VEGF) family differently regulate processes in

retinal endothelial cells (REC) which are crucially involved in the pathogenesis of diabetic retinopathy: Both, VEGF-A and placenta growth factor (PlGF), stimulate proliferation of primary and immortalized bovine REC ((i)BREC) but only VEGF-A165 stimulates their migration. Diabetic macular edema is most likely a consequence of an elevated permeability of REC which can be induced by VEGF-A, but not by PlGF. Binding of VEGF-A by the antibody fragment ranibizumab is sufficient to completely restore or prevent VEGF-A-induced disturbance of the iBREC barrier or migration of these cells without affecting the basal processes. This was observed even in the presence of other growth factors when surplus proliferation was only partly blocked. The recombinant protein aflibercept (VEGF-trap) not only binds very strongly to VEGF-A, but - in contrast to ranibizumab - also recognizes PlGF. In this study, we investigated whether this additional targeting of PlGF also results in better inhibition of growth factor-induced proliferation and migration, and disturbance of the iBREC barrier. In addition, uptake of aflibercept by iBREC and potential functional consequences were examined. In accordance with its binding specificity, aflibercept strongly and specifically inhibited iBREC proliferation stimulated with VEGF-A, PlGF or a combination of these factors. By treatment with aflibercept at therapeutically achievable concentrations, VEGF-A-stimulated iBREC migration was reduced not only to normal values but driven below the basal level. However, the VEGF-A binding humanized antibody bevacizumab as well as the unrelated control antibody rituximab also inhibited basal or VEGF-A stimulated migration at clinically relevant concentrations, suggesting an effect of high amounts of IgG domain-containing proteins which does not depend on their binding specificity. However, aflibercept specifically blocked VEGF-A stimulated migration at lower concentration without influencing basal processes. Effects on permeability were determined by measuring transendothelial resistance (TER) of iBREC (±VEGF-A165) and their expression of the tight junction protein claudin-1.

The VEGF-A-disturbed barrier was completely restored by treatment with ≤25 µg/ml aflibercept of which even much higher concentrations did not interfere with normal barrier function. Uptake of aflibercept by iBREC - analyzed by Western blot - was observed after 1 h of treatment and the amount further increased during prolonged incubation. Most of the internalized aflibercept was present in subcellular fractions of proteins assigned to the membranes and organelles, but it was also detected in the fraction consisting of cytoskeletal proteins. Co-immunofluorescence staining showed aflibercept absorbed by iBREC to be localized in or close to the Golgi apparatus. Aflibercept at high concentrations interferes with an important normal iBREC function, but prevents and restores VEGF-A-induced disturbances at considerably lower concentrations. Therefore, reduction of the doses administered in DR and DME therapy might be considered.

PMID: 24631334 [PubMed - as supplied by publisher]

J Ophthalmic Vis Res. 2013 Oct;8(4):359-371.

Polypoidal Choroidal Vasculopathy: An Update on Therapeutic Approaches.

Wong RL, Lai TY.

Abstract: Polypoidal choroidal vasculopathy (PCV) is a retinal disease involving the choroidal vasculature characterized by the presence of polypoidal lesions with or without branching vascular network best seen on indocyanine green angiography (ICGA). Clinical features of PCV include recurrent subretinal hemorrhage; serosanguineous pigment epithelial detachment, subretinal exudation and serous retinal detachment. PCV is more prevalent among Asians and Blacks as compared to Caucasians and has been found to account for 25 to 50% of cases of presumed neovascular age-related macular degeneration in Asian patients. Treatment is indicated in patients with symptomatic PCV due to potentially irreversible visual loss. Various treatment modalities for symptomatic PCV have been described in the literature, including thermal laser photocoagulation, ICGA-guided photodynamic therapy (PDT) with verteporfin, anti-vascular endothelial growth factor (VEGF) therapy, and combined PDT and anti-VEGF therapy. This review aims to provide an update on the therapeutic options for PCV, with particular reference to recent studies published in the past two years.

PMID: 24653824 [PubMed - as supplied by publisher]

Diabetes Care. 2014 Apr;37(4):900-5. doi: 10.2337/dc13-1990.

Ocular Anti-VEGF Therapy for Diabetic Retinopathy: Overview of Clinical Efficacy and Evolving Applications.

Cheung N, Wong IY, Wong TY.

Abstract: Ocular anti-vascular endothelial growth factor (VEGF) therapy represents one of the most significant advances in modern medicine. The introduction and widespread use of ocular anti-VEGF therapy for age-related macular degeneration heralded a new era in the treatment of vascular and exudative diseases of the retina. Its expanding indications now include diabetic macular edema and proliferative diabetic retinopathy, two vision-threatening forms of diabetic retinopathy. It is widely anticipated that ocular anti-VEGF therapy could spark a dramatic shift in the treatment paradigm for diabetic retinopathy. However, despite its clear efficacy shown in clinical trials, the dynamic landscape of evolving medical, ethical, and economic issues related to this new treatment suggests significant challenges ahead. In this article, we provide a discussion of this topic as part of this two-part Bench to Clinic narrative. Here, our Clinic contribution provides an overview of the current evidence from clinical trials on anti-VEGF therapy for diabetic retinopathy, and highlights the hopes and fears of this new treatment from clinical and public health standpoints. In the Bench narrative that precedes this contribution, Simó et al. provide an overview of the role of VEGF in the pathogenesis of diabetic retinopathy.

PMID: 24652721 [PubMed - in process]

JAMA Ophthalmol. 2014 Mar 20. doi: 10.1001/jamaophthalmol.2014.109. [Epub ahead of print]

VEGFA and VEGFR2 Gene Polymorphisms and Response to Anti-Vascular Endothelial Growth Factor Therapy: Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Hagstrom SA, Ying GS, Pauer GJ, Sturgill-Short GM, Huang J, Maguire MG, Martin DF; for the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) Research Group.

IMPORTANCE: Individual variation in response and duration of anti-vascular endothelial growth factor (VEGF) therapy is seen among patients with neovascular age-related macular degeneration. Identification of genetic markers that affect clinical response may result in optimization of anti-VEGF therapy. OBJECTIVE To evaluate the pharmacogenetic relationship between genotypes of single-nucleotide polymorphisms (SNPs) in the VEGF signaling pathway and response to treatment with ranibizumab or bevacizumab for neovascular age-related macular degeneration.

DESIGN, SETTING, AND PARTICIPANTS: In total, 835 of 1149 patients (72.7%) participating in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) at 43 CATT clinical centers. INTERVENTION Each patient was genotyped for 7 SNPs in VEGFA (rs699946, rs699947, rs833069, rs833070, rs1413711, rs2010963, and rs2146323) and 1 SNP in VEGFR2 (rs2071559) using TaqMan SNP genotyping assays.

MAIN OUTCOMES AND MEASURES: Genotypic frequencies were compared with clinical measures of response to therapy at 1 year, including the mean visual acuity, mean change in visual acuity, at least a 15-letter increase, retinal thickness, mean change in total foveal thickness, presence of fluid on optical coherence tomography, presence of leakage on fluorescein angiography, mean change in lesion size, and mean number of injections administered. Differences in response by genotype were evaluated with tests of linear trend calculated from logistic regression models for categorical outcomes and linear regression models for continuous outcomes. The method of controlling the false discovery rate was used to adjust for multiple comparisons.

RESULTS: For each of the measures of visual acuity evaluated, no association was observed with any of the genotypes or with the number of risk alleles. Four VEGFA SNPs demonstrated an association with

retinal thickness: rs699947 (P = .03), rs833070 (P = .04), rs1413711 (P = .045), and rs2146323 (P = .006). However, adjusted P values for these associations were all statistically nonsignificant (range, P = .24 to P = .45). Among the participants in 2 as-needed groups, no association was found in the number of injections among the different genotypes or for the total number of risk alleles. The effect of risk alleles on each clinical measure did not differ by treatment group, drug, or dosing regimen (P > .01 for all).

CONCLUSIONS AND RELEVANCE: This study provides evidence that no pharmacogenetic associations exist between the studied VEGFA and VEGFR2 SNPs and response to anti-VEGF therapy.

PMID: 24652518 [PubMed - as supplied by publisher]

Curr Opin Ophthalmol. 2014 Mar 14. [Epub ahead of print]

Financial return-on-investment of ophthalmic interventions: a new paradigm.

Brown MM, Brown GC, Lieske HB, Lieske PA.

PURPOSE OF REVIEW: Although the patient value gain (improvement in quality-of-life and/or length-of-life) has been highlighted in Value-based Medicine cost-utility analyses, the financial value gain associated with healthcare interventions has received less emphasis. It is important for professional healthcare providers to realize their interventions often confer a large financial return-on-investment (ROI) to society.

RECENT FINDINGS: The societal costs associated with vitreoretinal and other ophthalmic interventions include: direct ophthalmic medical costs expended (hospital, physician, drug, diagnostic testing and so forth), direct medical costs saved (decreased costs for depression, injury, skilled nursing facility, nursing home and others), direct nonmedical costs saved (decreased costs for caregivers, transportation, residence costs, moving costs, and others), and indirect medical costs saved (improving employment incidence and wages). The financial ROI for direct ophthalmic medical costs expended for ranibizumab therapy for neovascular age-related macular degeneration is 450%, whereas that for cataract surgery is 4500% and for medical open-angle glaucoma therapy is 4000%. Many costs gained add to the Gross Domestic Product and increase the wealth of the nation.

SUMMARY: Many vitreoretinal and other ophthalmologic interventions confer considerable patient value, but also result in a large financial ROI to society. This financial ROI increases the wealth of the nation.

PMID: 24638114 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2014 Feb 18;7(1):86-91. doi: 10.3980/j.issn.2222-3959.2014.01.15. eCollection 2014.

Comparison of intravitreal ranibizumab and bevacizumab for the treatment of macular edema secondary to retinal vein occlusion.

Yuan A, Ahmad BU, Xu D, Singh RP, Kaiser PK, Martin DF, Sears JE, Schachat AP, Ehlers JP.

AIM: To compare the efficacy of ranibizumab and bevacizumab for macular edema due to retinal vein occlusion (RVO).

METHODS: A retrospective study was conducted at a single academic institution. Eighty-one patients naïve to anti-VEGF therapy with RVO and macular edema were identified. Twenty-six eyes were treated with ranibizumab, 33 eyes with bevacizumab, and 22 eyes with bevacizumab then switched to ranibizumab (crossover). The main outcome was change in visual acuity at 3 months, 6 months, and final visit.

RESULTS: The mean visual acuity improved from 20/80 to 20/40 in the ranibizumab (R) group and from 20/125 to 20/60 in the bevacizumab (B) group (P=0.66). The mean change in central subfield thickness (CST) was -186 and -212μm, respectively (P=0.69). Mean time between injections was 94±21.1d in the R

group and 103.8±10.5d in the B group (P=0.78). In the crossover group, mean initial visual acuity was 20/125, reached 20/60 at crossover, and remained 20/60 at conclusion (P=0.91).

CONCLUSION: Both ranibizumab and bevacizumab are effective for the treatment of RVO and appear to have similar visual and anatomic outcomes. Changing treatments from bevacizumab to ranibizumab did not result in further gains in visual acuity.

PMID: 24634869 [PubMed] PMCID: PMC3949464

Curr Eye Res. 2014 Mar 17. [Epub ahead of print]

Comparison of Clinical Efficacy of Intravitreal Ranibizumab with and without Triamcinolone Acetonide in Macular Edema Secondary to Central Retinal Vein Occlusion.

Fan C, Wang Y, Ji Q, Zhao B, Xie J.

Abstract Purpose: To compare visual outcomes and spectral-domain optical coherence tomography results following treatment with intravitreal ranibizumab (IVR) or IVR combined with intravitreal triamcinolone acetonide (IVTA) for macular edema (ME) secondary to central retinal vein occlusion (CRVO).

Methods: This prospective, case-controlled study examined 57 eyes (57 patients) with ME secondary to CRVO, which were treated with IVR (0.5 mg, n = 30 eyes) or IVR (0.5 mg) and IVTA (1 mg, n = 27 eyes) as the initial therapy. Further intravitreal treatment was administered as necessary.

Results: All 57 patients completed at least 6 months of follow-up. At baseline, mean (± standard error) best-corrected visual acuity (BCVA) was 45.8 ± 23.2 letters in the IVR group and 47.3 ± 19.3 letters in the IVR + IVTA group (p = 0.790). Significant improvement in BCVA over baseline was observed in both groups at all six study visits (IVR group: p = 0.0003, 0.0001, 0.0018, 0.0145, 0.0107, 0.005; IVR + IVTA group: p = 0.0001, 0.0001, 0.0004, 0.0068, 0.0007, 0.0002), with no significant BCVA differences between groups. Significant reduction in mean central subfield thickness, compared with baseline, was also observed in both groups at all six study visits (IVR group, p = 0.0001; IVR + IVTA group, p = 0.0001), with no significant difference between groups in the magnitude of macular thickness reduction. The mean number of injections was significantly higher (p = 0.0001) in the IVR group (4.23 ± 0.56) than in the IVR + IVTA group (3.42 ± 0.41).

Conclusions: Treating ME secondary to CRVO with IVR or IVR + IVTA had similar effects on central macular thickness and BCVA in patients with ME secondary to CRVO over a 6-month follow-up period. The mean number of intravitreal injections was higher in the IVR group than in the IVR + IVTA group.

PMID: 24635755 [PubMed - as supplied by publisher]

J Clin Pharm Ther. 2014 Mar 17. doi: 10.1111/jcpt.12146. [Epub ahead of print]

Ranibizumab for age-related macular degeneration: a meta-analysis of dose effects and comparison with no anti-VEGF treatment and bevacizumab.

Jiang S, Park C, Barner JC.

WHAT IS KNOWN AND OBJECTIVES: Ranibizumab is used monthly or as-needed (PRN) for the treatment of age-related macular degeneration. However, which treatment regimen is more effective remains unknown. The objectives of this study are to: (i) compare the efficacy of monthly versus as-needed quarterly treatment; and (ii) compare the efficacy of ranibizumab 0·5 mg treatment with: (a) no anti-vascular endothelial growth factor (VEGF); (b) ranibizumab 0·3 mg; and (c) bevacizumab.

METHOD: This is a systematic meta-analytic review of randomized-controlled clinical trials of ranibizumab

in neovascular AMD. Weighted multiple regression analyses were used to compare the monthly vs. PRN/quarterly treatment.

RESULTS: Eight randomized controlled trials met our inclusion criteria. Patients on the monthly ranibizumab treatment had higher visual acuity letter gains (β = 0·441, P < 0·05) compared with patients on as-needed/quarterly treatment. More patients on the monthly treatment gained ≥15 letters than as-needed/quarterly treatment (β = 0·582, P < 0·05). Ranibizumab produced significantly higher improvement in visual acuity (d = 1·20, z = 7·14, P < 0·05) and led to a higher proportion of patients gaining ≥15 letters (OR: 6·67; 95% CI 3·16-14·06; P < 0·05) when compared with non-anti-VEGF. Ranibizumab did not show any advantage in visual acuity compared with bevacizumab. No significant differences were found between ranibizumab 0·3 mg and 0·5 mg.

WHAT IS NEW AND CONCLUSION: This is the first meta-analysis to systematically evaluate the efficacy of different treatment regimens for anti-VEGF therapy. Ranibizumab 0·3 or 0·5 mg monthly treatment was more effective for neovascular AMD than non-anti-VEGF treatments but is no better than bevacizumab.

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Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2014 Mar 20. pii: iovs.13-13338v1. doi: 10.1167/iovs.13-13338. [Epub ahead of print]

Choroidal thickness in patients with reticular pseudodrusen using 3D-1060nm OCT maps.

Haas P, Esmaeelpour M, Ansari-Shahrezaei S, Drexler W, Binder S.

Purpose: To map and analyze choroidal thickness (ChT) in age-related macular degeneration patients with reticular pseudodrusen (RPD) using 3-dimensional (3D) 1060nm optical coherence tomography (OCT).

Methods: Fifty eyes from twenty-five patients with RPD were grouped according to the severity of age-related macular degeneration (AMD) and the presence of RPD. All patients were imaged by high speed (60.000 A-scans/s) 3D-1060nm OCT over a 36x36° field of view. ChT-maps were automatically generated and compared to RPD areas visualized by fundus autofluorescence and infra-red imaging. Retinal thickness maps, ChT maps, Haller's and Sattler's layer thickness were statistically analyzed between groups.

Results: The mean±SD (µm) subfoveal ChT was 201±88 and 145±48, and 271±130 for dry AMD with RPD, wet AMD with RPD and eyes with wet AMD and no RPD, respectively. ChT maps demonstrated the most significant choroidal thinning within eyes with wet AMD and RPD. Sattler's and Haller's layer thickness differed across the Early Treatment Diabetic Retinopathy Study grid when compared between eyes with and without RPD. Within eyes with RPD, ChT maps visualized that ChT was thicker below RDP areas than non RPD areas.

Conclusion: The 3D-1060nm OCT choroidal maps over a large field of view offer non-invasive visualization for demonstrating local thickening correlation with RPD within each eye and overall thinning due to AMD severity and RPD. This choroidal thinning was most striking in Sattler's layer, suggesting a choroidopathy of this vascular layer.

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JAMA Ophthalmol. 2014 Mar 1;132(3):338-45. doi: 10.1001/jamaophthalmol.2013.5799.

Geographic atrophy: a histopathological assessment.

Bird AC, Phillips RL, Hageman GS.

IMPORTANCE: Geographic atrophy (GA) is the major cause of blind registration in Western communities, although, with few exceptions, it is less common than choroidal neovascular disease. The variation of phenotype implies that age-related macular degeneration (AMD) does not follow the same course from one case to another and that phenotyping may be important before initiating a therapeutic trial.

OBJECTIVE: To document photoreceptor and retinal pigment epithelium (RPE) cell loss and other changes at the RPE-choroid interface in donated human eyes in which visual loss was deemed to be due to GA.

DESIGN, SETTING, AND PARTICIPANTS: Histological study of a consecutive series of eyes donated by individuals previously diagnosed clinically as having GA. Donors were chosen on the basis of available clinical records (from MidAmerica Transplant Services, St Louis, Missouri; the Iowa Lions Eye Bank, Iowa City; and the Utah Lions Eye Bank, Salt Lake City) and selected were those considered to have GA due to AMD. Tissues in the regions of atrophy were examined with light, electron, and autofluorescence microscopy.

RESULTS: In most of the 37 donors examined, there was marked loss of photoreceptor cells for variable distances distal from the edge of the GA. Rod loss was greater than cone loss. An inverse relationship existed between the quantity of autofluorescent inclusions in the RPE and the thickness of sub-RPE basal laminar deposit. Integrity of the choroid varied from one eye to another and was not related strictly to photoreceptor survival. In some eyes, photoreceptor loss existed in the absence of obvious morphological changes in the Bruch membrane or RPE.

CONCLUSIONS AND RELEVANCE: The findings support the view that photoreceptor loss occurs early in AMD in a proportion of cases and imply that photoreceptor-cell loss may contribute to the functional loss recorded in early stages of AMD at least in part. The variation of changes from one eye to another implies that patients selected for a specific prophylactic therapy for early AMD should be chosen on the basis of the characteristics of their disease.

PMID: 24626824 [PubMed - in process]

Ophthalmology. 2014 Mar 13. pii: S0161-6420(14)00069-4. doi: 10.1016/j.ophtha.2014.01.025. [Epub ahead of print]

Relationship between Retinal Microstructures on Optical Coherence Tomography and Microperimetry in Age-Related Macular Degeneration.

Wu Z, Ayton LN, Luu CD, Guymer RH.

PURPOSE: To determine the relationship between structural parameters of the outer retina on spectral-domain optical coherence tomography (SD-OCT) and microperimetric retinal sensitivity in early stages of age-related macular degeneration (AMD).

DESIGN: Prospective, observational study.

PARTICIPANTS: Seventy-five eyes of 75 participants with early stages of AMD (drusen ≥125 μm, with/without pigmentary abnormalities) and 25 control participants of a similar age.

METHODS: Participants underwent microperimetry testing and high-resolution SD-OCT scans. Structural parameters at 5 central points (0°, 1°, and 2.33° nasal and temporal to the fovea along the horizontal axis) corresponding to areas tested by microperimetry were compared. Structural parameters included outer segment (OS) length, thickness and elevation of the retinal pigment epithelium (RPE) band, grading of the inner-segment ellipsoid (ISe) band integrity, and presence of hyperreflective foci (HF).

MAIN OUTCOME MEASURES: Relationship between structural parameters and retinal sensitivity.

RESULTS: Retinal sensitivity was significantly correlated with RPE elevation ($P < 0.001$), ISe grading ($P < 0.001$), and presence of HF ($P \leq 0.018$) at all test points, but not with OS length ($P \geq 0.093$) or RPE thickness ($P \geq 0.125$). However, multiple linear regression analyses revealed that only ISe grading ($P \leq 0.011$) and RPE elevation ($P \leq 0.030$) remained significantly associated with retinal sensitivity at all points. By using a simple linear model incorporating ISe grading and RPE elevation to predict values of retinal sensitivity, the 95% limits of agreement between the predicted and the actual value was ±3.83 dB.

CONCLUSIONS: The integrity of the ISe band and drusen-associated RPE elevation are significant independent predictors of microperimetric retinal sensitivity. Our findings imply that these 2 structural parameters may be surrogate markers of retinal function in the early stages of AMD.

PMID: 24629618 [PubMed - as supplied by publisher]

Hum Mol Genet. 2014 Mar 18. [Epub ahead of print]

Stem Cells for Investigation and Treatment of Inherited Retinal Disease.

Tucker BA, Mullins RF, Stone EM.

Abstract: Vision is the most important human sense. It facilitates every major activity of daily living ranging from basic communication, mobility and independence to an appreciation of art and nature. Heritable diseases of the retina, such as age-related macular degeneration and retinitis pigmentosa, are the leading cause of blindness in the developed world, collectively affecting as many as one-third of all people over the age of 75, to some degree. For decades, scientists have dreamed of preventing vision loss or of restoring the vision of patients affected with retinal degeneration through some type of drug, gene or cell-based transplantation approach. In this review we will discuss the current literature pertaining to retinal transplantation. We will focus on the use of iPSCs for interrogation of disease pathophysiology, analysis of drug and gene therapeutics and as a source of autologous cells for cell replacement.

PMID: 24647603 [PubMed - as supplied by publisher]

J Vis Exp. 2014 Feb 19;(84). doi: 10.3791/51061.

Detecting Abnormalities in Choroidal Vasculature in a Mouse Model of Age-related Macular Degeneration by Time-course Indocyanine Green Angiography.

Kumar S, Berriochoa Z, Jones AD, Fu Y.

Abstract:Indocyanine Green Angiography (or ICGA) is a technique performed by ophthalmologists to diagnose abnormalities of the choroidal and retinal vasculature of various eye diseases such as age-related macular degeneration (AMD). ICGA is especially useful to image the posterior choroidal vasculature of the eye due to its capability of penetrating through the pigmented layer with its infrared spectrum. ICGA time course can be divided into early, middle, and late phases. The three phases provide valuable information on the pathology of eye problems. Although time-course ICGA by intravenous (IV) injection is widely used in the clinic for the diagnosis and management of choroid problems, ICGA by intraperitoneal injection (IP) is commonly used in animal research. Here we demonstrated the technique to obtain high-resolution ICGA time-course images in mice by tail-vein injection and confocal scanning laser ophthalmoscopy. We used this technique to image the choroidal lesions in a mouse model of age-related macular degeneration. Although it is much easier to introduce ICG to the mouse vasculature by IP, our data indicate that it is difficult to obtain reproducible ICGA time course images by IP-ICGA. In contrast, ICGA via tail vein injection provides high quality ICGA time-course images comparable to human studies. In addition, we showed that ICGA performed on albino mice gives clearer pictures of choroidal vessels than that performed on

pigmented mice. We suggest that time-course IV-ICGA should become a standard practice in AMD research based on animal models.

PMID: 24637497 [PubMed - in process]

PLoS One. 2014 Mar 14;9(3):e91873. doi: 10.1371/journal.pone.0091873. eCollection 2014.

Quantitative analysis of cone photoreceptor distribution and its relationship with axial length, age, and early age-related macular degeneration.

Obata R, Yanagi Y.

PURPOSE: It has not been clarified whether early age-related macular degeneration (AMD) is associated with cone photoreceptor distribution. We used adaptive optics fundus camera to examine cone photoreceptors in the macular area of aged patients and quantitatively analyzed its relationship between the presence of early AMD and cone distribution.

METHODS: Sixty cases aged 50 or older were studied. The eyes were examined with funduscopy and spectral-domain optical coherence tomography to exclude the eyes with any abnormalities at two sites of measurement, 2° superior and 5° temporal to the fovea. High-resolution retinal images with cone photoreceptor mosaic were obtained with adaptive optics fundus camera (rtx1, Imagine Eyes, France). After adjusting for axial length, cone packing density was calculated and the relationship with age, axial length, or severity of early AMD based on the age-related eye disease study (AREDS) classification was analyzed.

RESULTS: Patient's age ranged from 50 to 77, and axial length from 21.7 to 27.5 mm. Mean density in metric units and that in angular units were 24,900 cells/mm2, 2,170 cells/deg2 at 2° superior, and 18,500 cells/mm2, 1,570 cels/deg2 at 5° temporal, respectively. Axial length was significantly correlated with the density calculated in metric units, but not with that in angular units. Age was significantly correlated with the density both in metric and angular units at 2° superior. There was no significant difference in the density in metric and angular units between the eyes with AREDS category one and those with categories two or three.

CONCLUSION: Axial length and age were significantly correlated with parafoveal cone photoreceptor distribution. The results do not support that early AMD might influence cone photoreceptor density in the area without drusen or pigment abnormalities.

PMID: 24632778 [PubMed - in process] PMCID: PMC3954804

Am J Ophthalmol. 2014 Mar 11. pii: S0002-9394(14)00141-X. doi: 10.1016/j.ajo.2014.03.003. [Epub ahead of print]

Ghost Maculopathy: An Artifact on Near-Infrared Reflectance and MultiColor™ Imaging Masquerading as Chorioretinal Pathology.

Pang CE, Freund KB.

PURPOSE: To describe the features of an artifact on near-infrared reflectance and MultiColor™ imaging termed as 'ghost maculopathy' and to illustrate how it may masquerade as true chorioretinal pathology.

DESIGN: This was a retrospective, observational case series.

METHODS: We studied 144 eyes of 72 consecutive patients in a vitreoretinal clinical practice, reviewing multimodal imaging including color and red-free fundus photography, fundus autofluorescence (FAF), near-infrared reflectance, MultiColor™ imaging and spectral-domain optical coherence tomography (SD-OCT).

RESULTS: In 36 of 144 (25%) eyes, there was an appearance of a hyper-reflective spot on near-infrared reflectance and MultiColor™ imaging, located at the macula, nasal or superonasal to the fovea, which did not correspond to any apparent lesion on color and red-free fundus photography, FAF or SD-OCT. This spot was termed the 'ghost image' in this phenomenon of 'ghost maculopathy'. The ghost image was present consistently on near-infrared reflectance and MultiColor™ imaging in all 36 eyes at every imaging encounter, showed minimal and subtle variability in its shape and location within each eye, however, showed large inter-individual variability in size, shape, location and reflectivity between different eyes. Nine eyes were found to have a similar hyper-reflective spot resembling that in ghost maculopathy but corresponding SD-OCT images were consistent with diagnoses of choroidal nevus, age-related macular degeneration and multifocal choroiditis. All eyes with ghost maculopathy were found to be pseudophakic with a posterior chamber intraocular lens.

CONCLUSION: Ghost maculopathy is the phenomenon of an imaging artifact appearing at the macula on near-infrared reflectance and MultiColor™ imaging that occurs predominantly in pseudophakic patients and may be mistaken for true chorioretinal pathology. Awareness of this artifact is prudent to avoid misinterpretation of clinical findings and possible unnecessary over-investigations.

PMID: 24631479 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2014 Mar 1;45(2):132-7. doi: 10.3928/23258160-20140306-06.

Outcomes and complications of pneumatic retinopexy over a 12-year period.

Modi YS, Epstein A, Flynn HW Jr, Shi W, Smiddy WE.

BACKGROUND AND OBJECTIVE: To evaluate anatomic and clinical outcomes of pneumatic retinopexy for treatment of primary retinal detachment.

PATIENTS AND METHODS: Noncomparative, single-center, consecutive, interventional case series evaluating all patients treated between 2000 and 2012. Patients with less than 1 month of follow-up or coexisting neovascular age-related macular degeneration, uveitis, endophthalmitis, or prior posterior segment surgery were excluded.

RESULTS: Sixty-three eyes of 63 patients with primary retinal detachment treated with pneumatic retinopexy were included. Median follow-up was 10.3 months. Single-operation success (SOS), defined as anatomic reattachment with pneumatic retinopexy alone, occurred in 40 eyes (63%). The retina was successfully reattached in 21 of the other 23 eyes (91%) with one additional surgery. There was no difference in visual acuity outcomes between SOS and additional surgical intervention (P = .85). New or missed breaks were identified in 19 of 63 eyes (30%). Postoperative subretinal fluid was observed in 22 of 63 eyes (35%) and persisted at last follow-up in two of 63 eyes (3%). At final follow-up, the retina was fully attached in 97% of eyes.

CONCLUSION: Pneumatic retinopexy remains a reasonably successful option in the management of primary retinal detachment. No difference in best corrected visual acuity outcomes in eyes achieving SOS versus those requiring additional surgery was demonstrated.

PMID: 24635154 [PubMed - in process]

Pathogenesis

Onco Targets Ther. 2014 Feb 14;7:263-267. eCollection 2014.

The relationship between intervention in the CD40 signal pathway and choroidal

neovascularization.

Zhang P, Su Y, Liu F.

Abstract: Age-related macular degeneration, pathologic myopia, ocular trauma, and other eye diseases can cause choroidal neovascularization (CNV). In recent years, photodynamic therapy (PDT), anti-vascular endothelial growth factor (anti-VEGF) medications, laser treatment, and other measures against CNV have been gradually applied in the clinical setting and in some cases have achieved good results. However, the pathogenesis of CNV has not been fully elucidated. The costimulatory system made up of cluster of differentiation 40 protein (CD40) and its ligand (CD40L) is an important signal transduction pathway among immune cells. The activation of CD40 can also stimulate the secretion of a variety of angiogenic growth factors (eg, VEGF) and basic fibroblast growth factors that might lead to CNV. The high level expression of CD40 and CD40L has been detected in CNV diseases. Interference with the CD40 signaling pathway may become a new target for CNV treatment. We review the relationship between CD40, CD40L, and CNV.

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J Comp Neurol. 2014 Feb 12. doi: 10.1002/cne.23558. [Epub ahead of print]

Adenosine tri-phosphate induced photoreceptor death and retinal remodelling in rats.

Vessey KA, Greferath U, Aplin FP, Jobling AI, Phipps JA, Ho T, de Iongh RU, Fletcher EL.

Abstract: Many common causes of blindness involve the death of retinal photoreceptors followed by progressive inner retinal cell remodelling. For an inducible model of retinal degeneration to be useful, it must recapitulate these changes. Intravitreal administration of adenosine tri-phosphate (ATP) has recently been found to induce acute photoreceptor death. The aim of this study was to characterise the chronic effects of ATP on retinal integrity. Five week old, dark agouti rats were administered 50mM ATP into the vitreous of one eye and saline into the other. Vision was assessed using the electroretinogram and optokinetic response and retinal morphology investigated via histology. ATP caused significant loss of visual function within one day and loss of 50% of the photoreceptors within 1 week. At three months, 80% of photoreceptor nuclei were lost, while total photoreceptor loss occurred by six months. The degeneration and remodelling was similar to that found in heritable retinal dystrophies and age-related macular degeneration and included inner retinal neuronal loss, migration and formation of new synapses; Müller cell gliosis, migration and scarring; blood vessel loss and; retinal pigment epithelium migration. In addition, extreme degeneration and remodelling events such as neuronal and glial migration outside the neural retina and proliferative changes in glial cells were observed. These extreme changes were also observed in the two year old P23H Rhodopsin transgenic rat model of retinitis pigmentosa. This ATP-induced model of retinal degeneration may provide a valuable tool for the development of pharmaceutical therapies or for the testing of electronic implants aimed at restoring vision.

PMID: 24639102 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2014 Mar 17. pii: S0161-6420(14)00047-5. doi: 10.1016/j.ophtha.2014.01.016. [Epub ahead of print]

A Risk Score for the Prediction of Advanced Age-Related Macular Degeneration: Development and Validation in 2 Prospective Cohorts.

Chiu CJ, Mitchell P, Klein R, Klein BE, Chang ML, Gensler G, Taylor A.

PURPOSE: To develop a clinical eye-specific prediction model for advanced age-related macular

degeneration (AMD).

DESIGN: The Age-Related Eye Disease Study (AREDS) cohort followed up for 8 years served as the training dataset, and the Blue Mountains Eye Study (BMES) cohort followed up for 10 years served as the validation dataset.

PARTICIPANTS: A total of 4507 AREDS participants (contributing 1185 affected vs. 6992 unaffected eyes) and 2169 BMES participants (contributing 69 affected vs. 3694 unaffected eyes).

METHODS: Using Bayes' theorem in a logistic model, we used 8 baseline predictors-age, sex, education level, race, smoking status, and presence of pigment abnormality, soft drusen, and maximum drusen size-to devise and validate a macular risk scoring system (MRSS). We assessed the performance of the MRSS by calculating sensitivity, specificity, and the area under the receiver operating characteristic curve (i.e., c-index).

MAIN OUTCOME MEASURES: Advanced AMD.

RESULTS: The internally validated c-indexAREDS (0.88; 95% confidence interval, 0.87-0.89) and the externally validated c-indexBMES (0.91; 95% confidence interval, 0.88-0.95) suggested excellent performance of the MRSS. The sensitivity and specificity at the optimal macular risk score cutoff point of 0 were 87.6% and 73.6%, respectively. An application for the iPhone and iPad also was developed as a practical tool for the MRSS.

CONCLUSIONS: The MRSS was developed and validated to provide satisfactory accuracy and generalizability. It may be used to screen patients at risk of developing advanced AMD.

PMID: 24650555 [PubMed - as supplied by publisher]

Eye (Lond). 2014 Mar 14. doi: 10.1038/eye.2014.55. [Epub ahead of print]

Prevalence and risk factors for age-related macular degeneration in the elderly Chinese population in south-western Taiwan: the Puzih eye study.

Huang EJ, Wu SH, Lai CH, Kuo CN, Wu PL, Chen CL, Chen CY, King YC, Wu PC.

Aim: This study aimed to ascertain the prevalence of and the risk factors associated with early and late age -related macular degeneration (AMD) among Chinese individuals aged ≥65 years residing in Puzih, Taiwan.

Methods: This population-based cross-sectional study graded digital colour photographs of the ocular fundus of 673 individuals using the Wisconsin Age-Related Maculopathy Grading System. We compared the characteristics of individuals with early and late AMD using χ2-analyses and described risk factors for early and late AMD using odds ratios and 95% confidence intervals.

Results: Individuals with late AMD were significantly older and more likely to have hypertension. Further, their sunlight exposure time was longer than that of those with early AMD, only drusen, or no AMD lesions ($P<0.01$). A history of hyperlipidaemia for >10 years was a significant risk factor for early AMD, while old age, hypertension for >10 years, and exposure to sunlight for >8 h per day were associated with late AMD.

Conclusions: The prevalence rate of early AMD in the present study was 15.0%, which is similar to that reported for Caucasians and Japanese included in the European Eye Study and the Hisayama Study, respectively. The late AMD prevalence rate of 7.3% found among our study participants was comparable to that reported by the Greenland Inuit Eye Study and Reykjavik Study, but considerably lower than that reported for Caucasians, indicating that late AMD might be less prevalent among Asians than Caucasians.

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Int J Ophthalmol. 2014 Feb 18;7(1):145-51. doi: 10.3980/j.issn.2222-3959.2014.01.27. eCollection 2014.

Health resource utilization and the economic burden of patients with wet age-related macular degeneration in Thailand.

Dilokthornsakul P, Chaiyakunapruk N, Ruamviboonsuk P, Ratanasukon M, Ausayakhun S, Tungsomeroengwong A, Pokawattana N, Chanatittarat C.

AIM: To determine healthcare resource utilization and the economic burden associated with wet age-related macular degeneration (AMD) in Thailand.

METHODS: This study included patients diagnosed with wet AMD that were 60 years old or older, and had best corrected visual acuity (BCVA) measured at least two times during the follow-up period. We excluded patients having other eye diseases. Two separate sub-studies were conducted. The first sub-study was a retrospective cohort study; electronic medical charts were reviewed to estimate the direct medical costs. The second sub-study was a cross-sectional survey estimating the direct non-medical costs based on face-to-face interviews using a structured questionnaire. For the first sub-study, direct medical costs, including the cost of drugs, laboratory, procedures, and other treatments were obtained. For the second sub-study, direct non-medical costs, e.g. transportation, food, accessories, home renovation, and caregiver costs, were obtained from face-to-face interviews with patients and/or caregivers.

RESULTS: For the first sub-study, sixty-four medical records were reviewed. The annual average number of medical visits was 11.1±6.0. The average direct medical costs were $3 604±4 530 per year. No statistically-significant differences of the average direct medical costs among the BCVA groups were detected (P=0.98). Drug costs accounted for 77% of total direct medical costs. For direct non-medical costs, 67 patients were included. Forty-eight patients (71.6%) required the accompaniment of a person during the out-patient visit. Seventeen patients (25.4%) required a caregiver at home. The average direct non-medical cost was $2 927±6 560 per year. There were no statistically-significant differences in the average costs among the BCVA groups (P=0.74). Care-giver cost accounted for 87% of direct non-medical costs.

CONCLUSION: Our study indicates that wet AMD is associated with a substantial economic burden, especially concerning drug and care-giver costs.

PMID: 24634881 [PubMed] PMCID: PMC3949476

Invest Ophthalmol Vis Sci. 2014 Mar 13. pii: iovs.13-13470v1. doi: 10.1167/iovs.13-13470. [Epub ahead of print]

The Spatial Profile of Macular Pigment in Subjects from a Singapore Chinese Population.

Neelam K, Ho H, Yip CC, Li W, Au Eong KG.

Purpose: To examine the spatial profile of macular pigment (MP) and its relationship with serum concentrations of lutein (L) and zeaxanthin (Z) in subjects from a Singapore Chinese population.

Methods: In this cross-sectional study, the following details were recorded in 95 healthy subjects: sociodemographic, life style information, body mass index (BMI), visual acuity, MP spatial profile using the Macular Metrics DensitometerTM, and serum L and Z.

Results: The mean (standard deviation, SD) age of the population was 42.40 (±13) years, ranging from 21 to 68 years. Females demonstrated significantly lower MP optical density (MPOD) than males (MPOD: females =0.52 ± 0.17; males = 0.61± 0.21, p = 0.03). MP spatial profile was typical and atypical with central dip in 68 (85%) and 12 (15%) subjects, respectively. Age and BMI were found to be significant predictors for atypical MP spatial profile (age: odds ratio, OR = 1.06, 95% confidence interval, CI = 1.01-1.13, p =

0.04; BMI: OR = 1.17, 95% CI = 1.01-1.34, p = 0.03). A positive relationship was observed between MPOD and serum concentrations of L and Z but only the latter relationship reached statistical significance (serum L: r = 0.12, p = 0.30; serum Z: r = 0.26, p = 0.02).

Conclusion: A central dip in MP spatial profile was observed with older age and higher BMI, the two known risk factors for age-related macular degeneration (AMD) suggesting that atypical MP spatial profile may be associated with an increased risk of AMD. Further studies with larger sample sizes are required to confirm these observations.

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Genetics

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In vivo effect of mutant ELOVL4 on the expression and function of wild type ELOVL4.

Mandal NA, Tran JT, Zheng L, Wilkerson JL, Brush RS, McRae J, Agbaga MP, Zhang K, Petrukhin K, Ayyagari R, Anderson RE.

Purpose: Mutations in the ELOVL4 gene cause human Stargardt's Macular Dystrophy 3 (STGD3), a juvenile onset dominant form of macular degeneration. To understand the role of the ELOVL4 protein in retinal function, several mouse models have been developed by using transgenic (TG), knock-in (Elovl4+/mut), and knock-out (Elovl4+/-) approaches. Here we analyzed quantitatively the ELOVL4 protein and its enzymatic products (VLC-FA and VLC-PUFA) in the retinas of 8-10-weeks-old TG- (TG1+, TG2+) and Elovl4+/mut that harbor the mutant ELOVL4 and compared them to their wild type littermates and Elovl4+/- that do not express the mutant protein. We also analyzed skin from these mice to gain insight into the pathogenesis resulting from the ELOVL4 mutation.

Methods: ELOVL4 protein localization in the retina was determined by immunohistochemistry. Levels of wild type ELOVL4 protein in skin and retinas were determined by western blotting. Total lipids from skin and retinas were measured by GC-MS. Retinal glycerophosphatidylcholines (PC) were analyzed by tandem mass spectrometry.

Results: Immunohistochemical and western analysis indicated that wild type ELOVL4 protein was reduced in both heterozygous Elovl4+/mut and Elovl4+/- retinas, but not in TG2+ retinas. We found that VLC-FA were reduced by 50% in the skin of Elovl4+/- and by 60-65% in Elovl4+/mut. We found VLC-PUFA levels at ~50% in both the retinas, and wild type levels of VLC-PUFA in TG2+ retinas.

Conclusions: We conclude that the presence of the mutant ELOVL4 does not affect the function of wild type ELOVL4 in the fully developed 8-10-week-old retinas.

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Eur J Hum Genet. 2014 Mar 19. doi: 10.1038/ejhg.2014.37. [Epub ahead of print]

Common variant rs10033900 near the complement factor I gene is associated with age-related macular degeneration risk in Han Chinese population.

Qian D, Kan M, Weng X, Huang Y, Zhou C, Yu G, Wang T, Zhou D, Zhang Z, Zhang D, Tang W, Liu Y.

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Hum Mol Genet. 2014 Mar 14. [Epub ahead of print]

Comprehensive Analysis of Gene Expression in Human Retina and Supporting Tissues.

Li M, Jia C, Kazmierkiewicz KL, Bowman AS, Tian L, Liu Y, Gupta NA, Gudsieva HV, Yee SS, Kim M, Dentchev T, Kimble JA, Parker JS, Messinger JD, Hakonarson H, Curcio CA, Stambolian D.

Abstract: Understanding the influence of gene expression on the molecular mechanisms underpinning human phenotypic diversity is fundamental to being able to predict health outcomes and treat disease. We have carried out whole transcriptome expression analysis on a series of eight normal human post-mortem eyes by RNA sequencing. Here we present data showing that ~80% of the transcriptome is expressed in the posterior layers of the eye and that there is significant differential expression not only between the layers of the posterior part of the eye but also between locations of a tissue layer. These differences in expression also extend to alternative splicing and splicing factors. Differentially expressed genes are enriched for genes associated with psychiatric, immune and cardiovascular disorders. Enrichment categories for Gene Ontology included ion transport, synaptic transmission, and visual and sensory perception. Lastly, allele specific expression was found to be significant for CFH, C3 and CFB, which are known risk genes for age-related macular degeneration. These expression differences should be useful in determining the underlying biology of associations with common diseases of the human retina, retinal pigment epithelium and choroid and in guiding the analysis of the genomic regions involved in the control of normal gene expression.

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Dis Markers. 2014;2014:507356. doi: 10.1155/2014/507356. Epub 2014 Feb 6.

Variability of the Transferrin Receptor 2 Gene in AMD.

Wysokinski D, Blasiak J, Dorecka M, Kowalska M, Robaszkiewicz J, Pawlowska E, Szaflik J, Szaflik JP.

Abstract: Oxidative stress is a major factor in the pathogenesis of age-related macular degeneration (AMD). Iron may catalyze the Fenton reaction resulting in overproduction of reactive oxygen species. Transferrin receptor 2 plays a critical role in iron homeostasis and variability in its gene may influence oxidative stress and AMD occurrence. To verify this hypothesis we assessed the association between polymorphisms of the TFR2 gene and AMD. A total of 493 AMD patients and 171 matched controls were genotyped for the two polymorphisms of the TFR2 gene: c.1892C>T (rs2075674) and c.-258+123T>C (rs4434553). We also assessed the modulation of some AMD risk factors by these polymorphisms. The CC and TT genotypes of the c.1892C>T were associated with AMD occurrence but the latter only in obese patients. The other polymorphism was not associated with AMD occurrence, but the CC genotype was correlated with an increasing AMD frequency in subjects with BMI < 26. The TT genotype and the T allele of this polymorphism decreased AMD occurrence in subjects above 72 years, whereas the TC genotype and the C allele increased occurrence of AMD in this group. The c.1892C>T and c.-258+123T>C polymorphisms of the TRF2 gene may be associated with AMD occurrence, either directly or by modulation of risk factors.

PMID: 24648608 [PubMed - in process]

Diet & lifestyle

JAMA Intern Med. 2014 Mar 17. doi: 10.1001/jamainternmed.2014.328. [Epub ahead of print]

Effect of Long-Chain ω-3 Fatty Acids and Lutein + Zeaxanthin Supplements on Cardiovascular Outcomes: Results of the Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial.

Writing Group for the AREDS2 Research Group, Bonds DE, Harrington M, Worrall BB, Bertoni AG, Eaton

CB, Hsia J, Robinson J, Clemons TE, Fine LJ, Chew EY.

IMPORTANCE: Dietary supplements have been proposed as a mechanism to improve health and prevent disease.

OBJECTIVE: To determine if supplementing diet with long-chain ω-3 polyunsaturated fatty acids or with macular xanthophylls results in a reduced rate of cardiovascular disease (CVD).

DESIGN, SETTING, AND PARTICIPANTS: The Cardiovascular Outcome Study (COS) was an ancillary study of the Age-Related Eye Disease Study 2 (AREDS2), a factorial-designed randomized clinical trial of 4203 participants recruited from 82 US academic and community ophthalmology clinics, who were followed up for a median of 4.8 years. Individuals were eligible to participate if they were between the ages of 50 and 85 years, had intermediate or advanced age-related macular degeneration in 1 eye, and were willing to be randomized. Participants with stable, existing CVD (>12 months since initial event) were eligible to participate. Participants, staff, and outcome assessors were masked to intervention.

INTERVENTIONS: Daily supplementation with long-chain ω-3 polyunsaturated fatty acids (350-mg docosahexaenoic acid [DHA] + 650-mg eicosapentaenoic acid [EPA]), macular xanthophylls (10-mg lutein + 2-mg zeaxanthin), combination of the two, or matching placebos. These treatments were added to background therapy of the AREDS vitamin and mineral formulation for macular degeneration.

MAIN OUTCOMES AND MEASURES: A composite outcome of myocardial infarction, stroke, and cardiovascular death with 4 prespecified secondary combinations of the primary outcome with hospitalized heart failure, revascularization, or unstable angina.

RESULTS: Study participants were primarily white, married, and highly educated, with a median age at baseline of 74 years. A total of 602 cardiovascular events were adjudicated, and 459 were found to meet 1 of the study definitions for a CVD outcome. In intention-to-treat analysis, no reduction in the risk of CVD or secondary CVD outcomes was seen for the DHA + EPA (primary outcome: hazard ratio [HR], 0.95; 95% CI, 0.78-1.17) or lutein + zeaxanthin (primary outcome: HR, 0.94; 95% CI, 0.77-1.15) groups. No differences in adverse events or serious adverse event were seen by treatment group. The sample size was sufficient to detect a 25% reduction in CVD events with 80% power.

CONCLUSIONS AND RELEVANCE: Dietary supplementation of long-chain ω-3 polyunsaturated fatty acids or macular xanthophylls in addition to daily intake of minerals and vitamins did not reduce the risk of CVD in elderly participants with age-related macular degeneration.

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Graefes Arch Clin Exp Ophthalmol. 2014 Mar 21. [Epub ahead of print]

Resveratrol and the eye: activity and molecular mechanisms.

Bola C, Bartlett H, Eperjesi F.

PURPOSE: Alcohol consumption is inversely correlated with the incidence of cardiovascular disease. It is thought that red wine is specifically responsible for these cardiovascular benefits, due to its ability to reduce vascular inflammation, facilitate vasorelaxation, and inhibit angiogenesis. This is because of its high polyphenolic content. Resveratrol is the main biologically active polyphenol within red wine. Owing to its vascular-enhancing properties, resveratrol may be effective in the microcirculation of the eye, thereby helping prevent ocular diseases such as age-related macular degeneration, diabetic retinopathy, and glaucoma. Such conditions are accountable for worldwide prevalence of visual loss.

METHOD: A review of the relevant literature was conducted on the ScienceDirect, Web of Science, and PubMed databases. Key words used to carry out the searches included 'red wine', 'polyphenols', 'resveratrol', 'eye' and 'ocular'. Articles relating to the effects of resveratrol on the eye were reviewed.

RESULTS: The protective effects of resveratrol within the eye are extensive. It has been demonstrated to have anti-oxidant, anti-apoptotic, anti-tumourogenic, anti-inflammatory, anti-angiogenic and vasorelaxant properties. There are potential benefits of resveratrol supplementation across a wide range of ocular diseases. The molecular mechanisms underlying these protective actions are diverse.

CONCLUSION: Evidence suggests that resveratrol may have potential in the treatment of several ocular diseases. However, while there are many studies indicating plausible biological mechanisms using animal models and in-vitro retinal cells there is a paucity of human research. The evidence base for the use of resveratrol in the management of ocular diseases needs to be increased before recommendations can be made for the use of resveratrol as an ocular supplement.

PMID: 24652235 [PubMed - as supplied by publisher]