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MD Research News

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Drug Treatment

Cochrane Database Syst Rev. 2016 Aug 4;8:CD006927. [Epub ahead of print]

Statins for age-related macular degeneration.

Gehlbach P1, Li T, Hatef E.

BACKGROUND: Age-related macular degeneration (AMD) is a progressive, late-onset disorder of the macula affecting central vision. It is the leading cause of blindness in people over 65 years in industrialized countries. Recent epidemiologic, genetic, and pathological evidence has shown that AMD shares a number of risk factors with atherosclerosis, leading to the hypothesis that statins may exert protective effects in AMD.

OBJECTIVES: The objective of this review was to examine the effectiveness of statins compared with other treatments, no treatment, or placebo in delaying the onset and progression of AMD.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to March 2016), EMBASE (January 1980 to March 2016), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to March 2016), PubMed (January 1946 to March 2016), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com) (last searched 5 June 2014), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 31 March 2016.

SELECTION CRITERIA: We included randomized controlled trials (RCTs) and quasi-randomized trials that compared statins with other treatments, no treatment, or placebo in people who were diagnosed as having the early stages of AMD.

DATA COLLECTION AND ANALYSIS: We used standard methodological procedures expected by Cochrane. Two review authors independently evaluated the search results against the selection criteria, abstracted data, and assessed risk of bias. We did not perform meta-analysis due to heterogeneity in the interventions and outcomes between the included studies.

RESULTS: Two RCTs with a total of 144 participants met the selection criteria. Both trials compared simvastatin versus placebo in older people (older than 50 or 60 years) with high risk of developing AMD (drusen present on examination). Overall, we judged the quality of the evidence to be low, as we downgraded all outcomes due to limitations in the designs of the trials and insufficient outcome reporting. The larger trial, with 114 participants, was conducted in Australia and used a higher dose (40 mg daily) of simvastatin for three years. Participants and

study personnel in this trial were adequately masked, however data were missing for 30% of participants at three years' follow-up. The smaller trial, with 30 participants, was conducted in Italy and used a lower dose (20 mg) of simvastatin for three months. This trial reported insufficient details to assess the risk of bias. Neither trial reported data for change in visual acuity. Low-quality evidence from the smaller trial, with 30 participants, did not show a statistically significant difference between the simvastatin and placebo groups in visual acuity values at three months of treatment (decimal visual acuity 0.21 ± 0.56 in simvastatin group and 0.19 ± 0.40 in placebo group) or 45 days after the completion of treatment (decimal visual acuity 0.20 ± 0.50 in simvastatin group and 0.19 ± 0.48 in placebo group). The lack of a difference in visual acuity was not explained by lens or retina status, which remained unchanged during and after the treatment period for both groups. Preliminary analyses of 42 participants who had completed 12 months' follow-up in the larger trial did not show a statistically significant difference between simvastatin and the placebo groups for visual acuity, drusen score, or visual function (effect estimates and confidence intervals were not available). Complete data for these outcomes at three years' follow-up were not reported. At three years, low-quality evidence showed an effect of simvastatin in slowing progression of AMD compared with placebo to be uncertain (odds ratio 0.51, 95% confidence interval 0.23 to 1.09).One trial did not report adverse outcomes. The second trial reported no difference between groups in terms of adverse events such as death, muscle aches, and acute hepatitis.

CONCLUSIONS: Evidence from currently available RCTs is insufficient to conclude that statins have a role in preventing or delaying the onset or progression of AMD.

PMID: 27490232

Indian J Ophthalmol. 2016 Jun;64(6):427-33.

Change of retinal pigment epithelial atrophy after anti-vascular endothelial growth factor treatment in exudative age-related macular degeneration.

Kim M, Kim ES, Seo KH, Yu SY, Kwak HW.

PURPOSE: The study aimed to investigate the quantitative changes of retinal pigment epithelial (RPE) atrophy during a 24-month follow-up period of anti-vascular endothelial growth factor (VEGF) for exudative age-related macular degeneration (AMD).

MATERIALS AND METHODS: This is a retrospective study. Sixty-five eyes of 62 consecutive patients with naove exudative AMD who had received treatment with anti-VEGF therapy and followed for more 24 months were enrolled. All patients received three initial monthly injections of anti-VEGF (ranibizumab or bevacizumab), followed by pro re nata or treat-and-extend protocol. Color fundus image, optical coherence tomography, and fundus autofluorescence were evaluated for RPE atrophy. Multiple regression analysis was performed to investigate the predictive factors found during univariate analysis to identify an association with increased RPE atrophic areas.

RESULTS: The mean number of anti-VEGF treatments was 9.18. RPE atrophic area was 1.293 ± 1.298 mm 2 at baseline and enlarged to 2.394 ± 1.940 mm 2 after 24 months, which differed significantly (P = 0.001). Multiple regression analysis revealed that larger areas of RPE atrophy at month 4 and larger numbers of anti-VEGF treatments were associated with increased RPE atrophic areas.

CONCLUSIONS: RPE atrophy progresses in eyes with exudative AMD during anti-VEGF treatment. Larger areas of RPE atrophy at month 4 and larger numbers of anti-VEGF injections were associated with an increased risk of progression of RPE atrophy the following treatment. These findings may be useful to clinicians using intravitreal anti-VEGF for the treatment of exudative AMD, both for selecting an appropriate treatment plan and for predicting the progression of RPE atrophy.

PMID: 27488150

Acta Ophthalmol. 2016 Aug 2. [Epub ahead of print]

Cost-effectiveness of treating wet age-related macular degeneration at the Kuopio University Hospital in Finland based on a two-eye Markov transition model.

Vottonen P, Kankaanpää E.

PURPOSE: Wet age-related macular degeneration (AMD) is the leading cause of blindness worldwide, which can be treated with regular intraocular anti-vascular endothelial growth factor (VEGF) injections. In this study, we wanted to evaluate whether less frequent injections of aflibercept would make it more cost-effective when compared with ranibizumab and low priced bevacizumab.

METHODS: We used a two-eye model to simulate the progression and the treatment of the disease. We selected an 8-year period, 3-month cycles and five health states based on the visual acuity of the better-seeing eye. The transition probabilities and utilities attached to the health states were gathered from previous studies. We conducted the analysis from the hospital perspective and we used the health care costs obtained from Kuopio University Hospital. The costs of intraocular adverse events were taken into account.

RESULTS: The incremental cost-effectiveness ratio (ICER) with 3% discount rate (€/QALY) for aflibercept compared with monthly bevacizumab was 1 801 228 and when compared with ranibizumab given as needed, the ICER was minus 3 716 943. The sensitivity analysis showed that a change of 20% of the estimated model parameters or a longer follow-up period did not influence these conclusions.

CONCLUSION: A two-eye Markov transition model was developed to analyse the cost-effectiveness of wet AMD treatment, as quality of life years (QALYs) are largely based on the visual acuity of the better-seeing eye. Monthly injected bevacizumab was the most cost-effective treatment and monthly ranibizumab the least effective.

PMID: 27481048

Clin Ophthalmol. 2016 Jul 18;10:1305-13.

Optical coherence tomography parameters predictive of visual outcome after anti-VEGF therapy for retinal vein occlusion.

Fujihara-Mino A, Mitamura Y, Inomoto N, Sano H, Akaiwa K, Semba K.

PURPOSE: To determine the optical coherence tomography (OCT) parameters that are predictive of visual outcome after anti-VEGF therapy for a retinal vein occlusion (RVO).

METHODS: Fifty-seven eyes with macular edema (ME) secondary to a central or branch RVO treated with bevacizumab or ranibizumab were studied. Spectral-domain OCT and microperimetry were performed before, 1, 3, and 6 months after the treatment and at the final visit. Central retinal thickness (CRT), macular volume (MV), integrity of the external limiting membrane (ELM), ellipsoid zone (EZ), and foveal bulge (FB), and photoreceptor outer segment (PROS) length were determined.

RESULTS: The mean follow-up period was 17.8±11.5 months. In 46 of the 57 eyes, a resolution of the ME was achieved. The pretreatment CRT and MV, presence of intact ELM, EZ, and FB, and PROS length at the time of ME resolution were significantly correlated with the best-corrected visual acuity and retinal sensitivity at the final visit ($P<0.050$). Multiple regression analyses showed that the pretreatment MV had the highest correlation with the posttreatment best-corrected visual acuity and retinal sensitivity ($P<0.050$).

CONCLUSION: The CRT, MV, ELM, EZ, FB, and PROS length are predictive factors for the visual outcome after anti-VEGF therapy for RVO.

PMID: 27486302 PMCID: PMC4957686

Semin Ophthalmol. 2016 Aug 3:1-5. [Epub ahead of print]

Efficacy of Topical Ofloxacin 0.3 % Administration on Conjunctival Bacterial Flora in Diabetic Patients Undergoing Intravitreal Injections.

Plotas P, Makri OE, Georgalas I, Pharmakakis N, Vantarakis A, Georgakopoulos CD.

PURPOSE: This prospective, randomized case series study aims to evaluate the efficacy of ofloxacin 0.3% eye drops in eradication of conjunctival bacterial flora in diabetic patients undergoing intravitreal injections (IVI).

METHODS: Ninety-two diabetic patients (92 eyes) scheduled to undergo intravitreal injection of ranibizumab due to diabetic macular edema were enrolled in the study. Patients were randomly assigned to three different groups. Group 1 (n=32) received ofloxacin eye drops the day before before IVI (four times); patients in Group 2 (n=29) were administered ofloxacin one hour before IVI (every 15 minutes), while Group 3 (n=31) comprised patients that received combined administration of ofloxacin both one day and one hour before IVI (eight doses). Samples were collected from the injection site before and after antibiotic administration. Culture results from BACTEC broth and positive cultures in blood agar and Sabouraud's dextrose agar plates were measured.

RESULTS: In Group 1, BACTEC broth positive cultures decreased from 84.4% at baseline to 50% after ofloxacin administration (p=0.007), and blood agar positive cultures reduced from 65.63% to 34.38% (p=0.02). In Group 2, positive cultures significantly decreased in BACTEC broth (from 79.3% at baseline to 48.28%; p=0.027) and in blood agar (from 68.97% to 37.13%; p=0.034). In Group 3, positive cultures decreased from 77.42% at baseline to 32.26% (p=0.0008) and from 58.06% at baseline to 22.58% (p=0.009) in BACTEC broth and blood agar, respectively. No microorganisms were isolated from Sabouraud's dextrose agar plates.

CONCLUSIONS: The combined one day/one hour (eight doses) ofloxacin administration in diabetic patients is extremely effective in reducing conjunctival bacterial flora. The application of topical ofloxacin for one day or one hour before IVI is also significantly effective.

PMID: 27487463

Korean J Ophthalmol. 2016 Aug;30(4):272-9. Epub 2016 Jul 21.

Intravitreal Anti-vascular Endothelial Growth Factor for Treating Polypoidal Choroidal Vasculopathy with Grape-like Polyp Clusters.

Chang YS, Kim JH, Kim JW, Lee TG, Kim CG.

PURPOSE: To evaluate 12-month outcomes of anti-vascular endothelial growth factor (VEGF) therapy for polypoidal choroidal vasculopathy (PCV) with grape-like polyp clusters.

METHODS: This retrospective observational study included 23 eyes of 23 patients who were newly diagnosed with PCV with grape-like polyp clusters, and who were subsequently treated with anti-VEGF monotherapy. The study compares the best-corrected visual acuity (BCVA) of the patients at diagnosis, at 3 months, and at 12 months after diagnosis. In addition, 12-month changes in BCVA values were compared between cases with subfoveal or juxtafoveal polyps and cases with extrafoveal polyps.

RESULTS: The baseline, 3-month, and 12-month logarithm of the minimal angle of resolution BCVA was 0.62 ± 0.35, 0.50 ± 0.43, and 0.58 ± 0.48, respectively. Compared to the baseline, patient BCVA was not significantly different at 12 months after diagnosis (p = 0.764). Six eyes (26.1%) gained ≥0.2 logarithm of the minimal angle of resolution BCVA. In cases with subfoveal or juxtafoveal polyps, BCVA values at baseline and at 12 months after diagnosis were 0.66 ± 0.37 and 0.69 ± 0.53, respectively. In cases with extrafoveal polyps, the values were 0.54 ± 0.33 and 0.37 ± 0.31, respectively. Changes in BCVA values were significantly different between the two groups (p = 0.023).

CONCLUSIONS: Although anti-VEGF therapy has favorable short-term efficacy for treating PCV with grape-like polyp clusters, long-term visual improvements are generally limited in the majority of afflicted eyes. The presence of subfoveal or juxtafoveal polyps may suggest unfavorable treatment outcomes.

PMID: 27478354 PMCID: PMC4965602

Korean J Ophthalmol. 2016 Aug;30(4):265-71. Epub 2016 Jul 21.

High Dose Intravitreal Bevacizuab for Refractory Pigment Epithelial Detachment in Age-related Macular Degeneration.

Lee DK, Kim SH, You YS, Kwon OW1.

PURPOSE: Intravitreal anti-vascular endothelial growth factor (anti-VEGF) is the first choice of treatment for age-related macular degeneration. However, quite a few eyes treated using conventional dose anti-VEGF (CDAV) have persistent pigment epithelial detachment (PED) on optical coherence tomography. This study investigated the efficacy and safety of high dose anti-VEGF (HDAV) for refractory PED.

METHODS: In this retrospective study, 31 eyes of neovascular age-related macular degeneration patients with persistent PED findings despite six or more intravitreal injections of CDAV (bevacizumab 1.25 mg or ranibizumab 2.5 mg) were analyzed. Changes in visual outcome, central foveal thickness, and PED height were compared before and after HDAV (bevacizumab 5.0 mg) for these refractory PED cases.

RESULTS: The mean age of patients was 67.7 years. The number of CDAV injections was 12.1. The number of HDAV injections was 3.39. Best-corrected visual acuity in logarithm of the minimum angle of resolution before and after HDAV was 0.49 and 0.41 ($p < 0.001$), respectively. Central foveal thickness before and after HDAV was 330.06 and 311.10 μm ($p = 0.125$), respectively. PED height before and after HDAV was 230.28 and 204.07 μm ($p = 0.014$), respectively. There were no serious adverse reactions in all the eyes.

CONCLUSIONS: Increasing the dose of bevacizumab in refractory PED may be a possible treatment option.

PMID: 27478353 PMCID: PMC4965601

Other Treatment and Diagnosis

Clin Ophthalmol. 2016 Jul 18;10:1305-13.

Optical coherence tomography parameters predictive of visual outcome after anti-VEGF therapy for retinal vein occlusion.

Fujihara-Mino A, Mitamura Y, Inomoto N, Sano H, Akaiwa K, Semba K.

PURPOSE: To determine the optical coherence tomography (OCT) parameters that are predictive of visual outcome after anti-VEGF therapy for a retinal vein occlusion (RVO).

METHODS: Fifty-seven eyes with macular edema (ME) secondary to a central or branch RVO treated with bevacizumab or ranibizumab were studied. Spectral-domain OCT and microperimetry were performed before, 1, 3, and 6 months after the treatment and at the final visit. Central retinal thickness (CRT), macular volume (MV), integrity of the external limiting membrane (ELM), ellipsoid zone (EZ), and foveal bulge (FB), and photoreceptor outer segment (PROS) length were determined.

RESULTS: The mean follow-up period was 17.8±11.5 months. In 46 of the 57 eyes, a resolution of the ME was achieved. The pretreatment CRT and MV, presence of intact ELM, EZ, and FB, and PROS length at the time of ME resolution were significantly correlated with the best-corrected visual acuity and retinal sensitivity at the final visit ($P<0.050$). Multiple regression analyses showed that the pretreatment MV had the highest correlation with the posttreatment best-corrected visual acuity and retinal sensitivity ($P<0.050$).

CONCLUSION: The CRT, MV, ELM, EZ, FB, and PROS length are predictive factors for the visual outcome after anti-VEGF therapy for RVO.

PMID: 27486302 PMCID: PMC4957686

Asia Pac J Ophthalmol (Phila). 2016 Jul-Aug;5(4):300-3.

Gene Therapy for Age-Related Macular Degeneration.

Constable IJ, Blumenkranz MS, Schwartz SD, Barone S, Lai CM, Rakoczy EP.

ABSTRACT: The purpose of this article was to evaluate safety and signals of efficacy of gene therapy with subretinal rAAV.sFlt-1 for wet age-related macular degeneration (wet AMD). A phase 1 dose-escalating single-center controlled unmasked human clinical trial was followed up by extension of the protocol to a phase 2A single-center trial. rAAV.sFlt-1 vector was used to deliver a naturally occurring anti-vascular endothelial growth factor agent, sFlt-1, into the subretinal space. In phase 1, step 1 randomized 3 subjects to low-dose rAAV.sFlt-1 (1 × 10 vector genomes) and 1 subject to the control arm; step 2 randomized an additional 3 subjects to treatment with high-dose rAAV.sFlt-1 (1 × 10 vector genomes) and 1 subject to the control arm. Follow-up studies demonstrated that rAAV.sFlt-1 was well tolerated with a favorable safety profile in these elderly subjects with wet AMD. Subretinal injection was highly reproducible, and no drug-related adverse events were reported. Procedure-related adverse events were mild and self-resolving. Two phakic patients developed cataract and underwent cataract surgery. Four of the 6 patients responded better than the small control group in this study and historical controls in terms of maintaining vision and a relatively dry retina with zero ranibizumab retreatments per annum. Two patients required 1 ranibizumab injection over the 52-week follow-up period. rAAV.sFlt-1 gene therapy may prove to be a potential adjunct or alternative to conventional intravitreal injection for patients with wet AMD by providing extended delivery of a naturally occurring antiangiogenic protein.

PMID: 27488071

Genetics

Asia Pac J Ophthalmol (Phila). 2016 Jul-Aug;5(4):282-92.

Strategies for Gene Mapping in Inherited Ophthalmic Diseases.

Srilekha S, Rao B, Rao DM, Sudha D, Chandrasekar SP, Pandian AJ, Soumittra N, Sripriya S.

ABSTRACT: Gene mapping of inherited ophthalmic diseases such as congenital cataracts, retinal degeneration, glaucoma, age-related macular degeneration, myopia, optic atrophy, and eye malformations has shed more light on the disease pathology, identified targets for research on therapeutics, earlier detection, and treatment options for disease management and patient care. This article details the different approaches to gene identification for both Mendelian and complex eye disorders.

PMID: 27488070

Asia Pac J Ophthalmol (Phila). 2016 Jul-Aug;5(4):229-35.

Age-Related Macular Degeneration: Genetics and Biology.

Kumaramanickavel G.

ABSTRACT: Age-related macular degeneration (AMD), widely prevalent across the globe, is a major stakeholder among adult visual morbidity and blindness, not only in the Western world but also in Asia. Several risk factors have been identified, including critical genetic factors, which were never imagined 2 decades ago. The etiopathogenesis is emerging to demonstrate that immune and complement-related inflammation pathway members chronically exposed to environmental insults could justifiably influence disease morbidity and treatment outcomes. Approximately half a dozen physiological and biochemical cascades are disrupted in the AMD disease genesis, eventually leading to the distortion and disruption of the subretinal space, subretinal pigment epithelium, and Bruch membrane, thus setting off chaos and disorder for signs and symptoms to manifest. Approximately 3 dozen genetic factors have so far been identified, including the recent ones, through powerful genomic technologies and large robust sample sizes. The noteworthy genetic variants (common and rare) are complement factor H, complement factor H-related genes 1 to 5, C3, C9, ARMS2/HTRA1, vascular endothelial growth factor A, vascular endothelial growth factor receptor 2/KDR, and rare variants (show causal link) such as TIMP3, fibrillin, COL4A3, MMP19, and MMP9. Despite the enormous amount of scientific information generated over the years, diagnostic genetic or biomarker tests are still not available for clinicians to understand the natural course of the disease and its management in a patient. However, further

research in the field should reduce this gap not only by aiding the clinician but also through the possibilities of clinical intervention with complement pathway-related inhibitors entering preclinical and clinical trials in the near future.

PMID: 27488064

Ophthalmic Genet. 2016 Aug 2:1-7. [Epub ahead of print]

Association between SKIV2L polymorphism rs429608 and age-related macular degeneration: A meta-analysis.

Shuai P, Ye Z, Liu Y, Qu C, Liu X, Luo H, Feng X, Li X, Shi Y, Gong B.

PURPOSE: This study was conducted to comprehensively evaluate the potential association of SKIV2L polymorphism rs429608 with age-related macular degeneration (AMD) through a meta-analysis.

METHODS: We performed a literature search in EMBASE, PubMed, Web of Science, and the Chinese Biomedical Database for AMD genetic studies published before August 30, 2015. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for single-nucleotide polymorphisms (SNPs) using fixed-effect models or random effect models according to between-study heterogeneity. Publication bias analyses were conducted using Egger's test.

RESULTS: A total of five studies from published articles were included, and a total number of 2789 AMD cases and 3451 healthy controls were tested in this meta-analysis. The results demonstrated that SKIV2L rs429608 is associated with AMD under allelic model (A vs. G; OR = 0.52, 95% CI 0.44-0.62, p < 0.001), heterozygous model (AG vs. GG; OR = 0.51; 95%CI, 0.38-0.68; p < 0.001; PQ = 0.48; I2 = 0) and dominant model (AA+AG vs. GG; OR = 0.49; 95%CI 0.37-0.65; p < 0.001; PQ = 0.44; I2 = 0), but not under other genetic models.

CONCLUSIONS: This meta-analysis showed that SKIV2L rs429608 was statistically associated with AMD and it might exert a protective effect on AMD. Further investigations are needed to validate the association and confirm the role of SKIV2L in AMD.

PMID: 27484132

Pathogenesis

Bioorg Med Chem Lett. 2016 Jul 21. [Epub ahead of print]

Design, synthesis and biological evaluation of photoaffinity probes of antiangiogenic homoisoflavonoids.

Lee B, Sun W, Lee H, Basavarajappa H, Sulaiman RS, Sishtla K, Fei X, Corson TW, Seo SY.

ABSTRACT: A naturally occurring homoisoflavonoid, cremastranone (1) inhibited angiogenesis in vitro and in vivo. We developed an analogue SH-11037 (2) which is more potent than cremastranone in human retinal microvascular endothelial cells (HRECs) and blocks neovascularization in animal models. Despite their efficacy, the mechanism of these compounds is not yet fully known. In the course of building on a strong foundation of SAR and creating a novel chemical tool for target identification of homoisoflavonoid-binding proteins, various types of photoaffinity probes were designed and synthesized in which benzophenone and biotin were attached to homoisoflavanonoids using PEG linkers on either the C-3' or C-7 position. Notably, the photoaffinity probes linking on the phenol group of the C-3' position retain excellent activity of inhibiting retinal endothelial cell proliferation with up to 72nM of GI50.

PMID: 27481561

Biochim Biophys Acta. 2016 Jul 30. [Epub ahead of print]

Lipids, oxidized lipids, oxidation-specific epitopes, and Age-related Macular Degeneration.

Handa JT, Cano M, Wang L, Datta S, Liu T.

ABSTRACT: Age-related Macular Degeneration (AMD) is the leading cause of blindness among the elderly in western societies. While antioxidant micronutrient treatment is available for intermediate non-neovascular disease, and effective anti-vascular endothelial growth factor treatment is available for neovascular disease, treatment for early AMD is lacking due to an incomplete understanding of the early molecular events. The role of lipids, which accumulate in the macula, and their oxidation, has emerged as an important factor in disease development. These oxidized lipids can either directly contribute to tissue injury or react with amine on proteins to form oxidation-specific epitopes, which can induce an innate immune response. If inadequately neutralized, the inflammatory response from these epitopes can incite tissue injury during disease development. This review explores how the accumulation of lipids, their oxidation, and the ensuing inflammatory response might contribute to the pathogenesis of AMD.

PMID: 27480216

Mitochondrion. 2016 Jul 28. [Epub ahead of print]

Targeting mitochondrial function to treat optic neuropathy.

Gueven N, Nadikudi M, Daniel A, Chhetri J.

ABSTRACT: Many reports have illustrated a tight connection between vision and mitochondrial function. Not only are most mitochondrial diseases associated with some form of vision impairment, many ophthalmological disorders such as glaucoma, age-related macular degeneration and diabetic retinopathy also show signs of mitochondrial dysfunction. Despite a vast amount of evidence, vision loss is still only treated symptomatically, which is only partially a consequence of resistance to acknowledge that mitochondria could be the common denominator and hence a promising therapeutic target. More importantly, clinical support of this concept is only emerging. Moreover, only a few drug candidates and treatment strategies are in development or approved that selectively aim to restore mitochondrial function. This review rationalizes the currently developed therapeutic approaches that target mitochondrial function by discussing their proposed mode(s) of action and provides an overview on their development status with regards to optic neuropathies.

PMID: 27476756

Invest Ophthalmol Vis Sci. 2016 Aug 1;57(10):3961-73

Connexin43 Mimetic Peptide Improves Retinal Function and Reduces Inflammation in a Light-Damaged Albino Rat Model.

Guo CX, Mat Nor MN, Danesh-Meyer HV, Vessey KA, Fletcher EL, O'Carroll SJ, Acosta ML, Green CR.

PURPOSE: Drugs that regulate connexin43 (Cx43) gap junction channels can reduce the spread of injury and improve functional outcomes after nervous system trauma. In the eye, Cx43 expression increases in the choroid following light damage. The aim of this study was to investigate whether Cx43 hemichannel block could preserve retinal function postinjury.

METHODS: Light damage was induced by exposure of adult albino Sprague-Dawley rats to 2700 Lux light for 24 hours. Intravitreal injections of a Cx43 mimetic peptide hemichannel blocker, Peptide5, or sham were administered 2 hours after the onset and at the end of the light damage period. Retinal function was assessed by electroretinogram and inflammatory responses in the choroid and retina were assessed using immunohistochemistry (ionized calcium binding adaptor molecule 1 [Iba-1], leukocyte common antigen [CD45], glial fibrillary acidic protein [GFAP]).

RESULTS: Light-damaged rat eyes had (1) reduced neuronal responses in both the rod and cone pathways and (2) marked inflammatory responses in the choroid and retina. Peptide5 significantly preserved function of photoreceptoral and postphotoreceptoral neurons in these animals. This was evident 24 hours after injury and 2 weeks later, as shown by improved mixed a-wave and mixed b-wave amplitudes, isolated rod PII and PIII amplitudes, and cone PII responses when compared with sham-treated controls. Retinal thinning and inflammation were also significantly reduced in Peptide5-treated eyes when compared with sham-treated controls.

CONCLUSIONS: Blocking Cx43 hemichannels after light damage can significantly improve functional outcomes of neurons in both

the rod and cone photo-transduction pathways in the light-damaged animal model, likely by reducing choroid inflammation and suppressing the glial-mediated inflammatory response. These data may have relevance for the treatment of conditions such as diabetic retinopathy and age-related macular degeneration.

PMID: 27490318

Sci Rep. 2016 Aug 2;6:30843.

Small Molecular-Sized Artesunate Attenuates Ocular Neovascularization via VEGFR2, PKCα, and PDGFR Targets.

Zong Y, Yuan Y, Qian X, Huang Z, Yang W, Lin L, Zheng Q, Li Y, He H, Gao Q.

ABSTRACT: Ocular neovascularization (NV) is the primary cause of blindness in many ocular diseases. Large molecular weight anti- vascular endothelial growth factor (VEGF) protein drugs, such as Avastin and Lucentis, have saved the vision of millions. However, approximately 20-30% of patients respond poorly to anti-VEGF treatment. We found that artesunate (ART), a small molecular derivative of artemisinin, had a significant inhibitory effect on ocular NV by downregulating the expression of VEGFR2, PKCα, and PDGFR. ART significantly inhibited retinal NV in rabbits and macular edema in monkeys with greater anterior chamber penetrability and more durable efficacy than Avastin. Our pilot study showed that intravitreal injection of 80 μg ART significantly inhibited iris and corneal NV in a severe retinal detachment case. Our results suggest that ART might be a potential persistent small-molecule drug to manage ocular NV via multi-targets.

PMID: 27480521

Retina. 2016 Aug 2. [Epub ahead of print]

RETINAL PIGMENT EPITHELIUM APERTURE: A Previously Unreported Finding in the Evolution of Avascular Pigment Epithelium Detachment.

Querques G, Capuano V, Costanzo E, Corvi F, Querques L, Introini U, Souied EH, Bandello F.

PURPOSE: To describe retinal pigment epithelium (RPE) aperture and to generate hypotheses about pathogenesis of this previously unreported finding in the evolution of avascular pigment epithelium detachment (PED) secondary to age-related macular degeneration.

METHODS: Medical records and multimodal imaging results from 10 patients with RPE apertures were reviewed between January 2009 and December 2014 by 2 institutions. Main outcome measures were analysis of RPE aperture imaging characteristics, including aperture areas and PED diameters, and their temporal course. Lesions preceding RPE aperture development were also evaluated.

RESULTS: Eleven RPE apertures were identified in 10 eyes of 10 patients (1 male, 9 females; mean age 73.1 ± 6.7 years) and included for analysis. The RPE apertures appeared as round discontinuities either at the apex or at the base of avascular PED. No rippling or retraction of the RPE was found at the sites of aperture. The RPE apertures enlarged homogeneously (mean round area of hypoautofluorescence significantly increased from 0.18 ± 0.13 to 0.93 ± 1.2; P = 0.005), and PED flattened (PED maximal height on spectral domain optical coherence significantly decreased from 445.2 ± 259 to 206.4 ± 218; P = 0.04) after a mean of 38.6 ± 16.3 months. Analysis of lesions preceding RPE apertures revealed areas of focal hyperautofluorescence at the site of development, in some cases appearing as drusenoid material connected with the base of avascular PED.

CONCLUSION: The RPE aperture represents a previously unreported possible evolution of avascular PED, which should be distinguished by typical RPE tears. Analysis of lesions preceding RPE apertures suggests focal atrophic progression of drusenoid material in its pathogenesis.

PMID: 27491047

Sci Rep. 2016 Aug 4;6:30933.

Macrophage polarization in experimental and clinical choroidal neovascularization.

Yang Y, Liu F, Tang M, Yuan M, Hu A, Zhan Z, Li Z, Li J, Ding X, Lu L.

ABSTRACT: Macrophages play an important role in the development of age-related macular degeneration (AMD). In this study, the spatial and temporal changes and the polarization of macrophages in murine laser-induced choroidal neovascularization (CNV) were investigated, and the polarized M1 and M2 biomarkers in the aqueous humors of neovascular AMD (nAMD) patients were studied. Macrophages, the main infiltrating inflammatory cells in CNV lesions, were evidenced by a significant increase in F4/80 mRNA expression and by the infiltration of F4/80+ cells in the lesions and the vicinity of laser-induced CNV. The mRNA expressions of M1-related markers were dramatically upregulated in the early stage, while the M2-related markers were slightly upregulated in the middle stage and sustained until the late stage. The results of immunostaining showed a similar early-but-transient M1 pattern and a delayed-but-sustained M2 pattern in laser-induced CNV. In addition, a higher M2/M1 ratio was found in both the murine models (Arg-1/iNOS and CCL22/CXCL10) and the aqueous humors of nAMD patients (CCL22/CXCL10) than in the controls. Our results suggested that the dynamic patterns of M1 and M2 were different in both the experimental and clinical CNV. The M2 macrophages were predominant and may play a more important role in the development of CNV.

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Differential Expression of Complement Markers in Normal and AMD Transmitochondrial Cybrids.

Nashine S, Chwa M, Kazemian M, Thaker K, Lu S, Nesburn A, Kuppermann BD, Kenney MC.

PURPOSE: Variations in mitochondrial DNA (mtDNA) and abnormalities in the complement pathways have been implicated in the pathogenesis of age-related macular degeneration (AMD). This study was designed to determine the effects of mtDNA from AMD subjects on the complement pathway.

METHODS: Transmitochondrial cybrids were prepared by fusing platelets from AMD and age-matched Normal subjects with Rho0 (lacking mtDNA) human ARPE-19 cells. Quantitative PCR and Western blotting were performed to examine gene and protein expression profiles, respectively, of complement markers in these cybrids. Bioenergetic profiles of Normal and AMD cybrids were examined using the Seahorse XF24 flux analyzer.

RESULTS: Significant decreases in the gene and protein expression of complement inhibitors, along with significantly higher levels of complement activators, were found in AMD cybrids compared to Older-Normal cybrids. Seahorse flux data demonstrated that the bioenergetic profiles for Older-Normal and Older-AMD cybrid samples were similar to each other but were lower compared to Young-Normal cybrid samples.

CONCLUSION: In summary, since all cybrids had identical nuclei and differed only in mtDNA content, the observed changes in components of complement pathways can be attributed to mtDNA variations in the AMD subjects, suggesting that mitochondrial genome and retrograde signaling play critical roles in this disease. Furthermore, the similar bioenergetic profiles of AMD and Older-Normal cybrids indicate that the signaling between mitochondria and nuclei are probably not via a respiratory pathway.

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Subretinal mononuclear phagocytes induce cone segment loss via IL-1β.

Eandi CM, Charles Messance H, Augustin S, Dominguez E, Lavalette S, Forster V, Hu SJ, Siquieros L, Craft CM, Sahel JA, Tadayoni R, Paques M, Guillonneau X, Sennlaub F.

ABSTRACT: Photo-transduction in cone segments (CS) is crucial for high acuity daytime vision. For ill-defined reasons, CS degenerate in retinitis pigmentosa (RP) and in the transitional zone (TZ) of atrophic zones (AZ), which characterize geographic atrophy (GA). Our experiments confirm the loss of cone segments (CS) in the TZ of patients with GA and show their association with subretinal CD14(+) mononuclear phagocyte (MP) infiltration that is also reported in RP. Using human and mouse MPs in vitro and inflammation-prone Cx3cr1(GFP/GFP) mice in vivo, we demonstrate that MP-derived IL-1β leads to severe CS degeneration. Our results strongly suggest that subretinal MP accumulation participates in the observed pathological photoreceptor changes in these diseases. Inhibiting subretinal MP accumulation or Il -1β might protect the CS and help preserve high acuity daytime vision in conditions characterized by subretinal inflammation, such as AMD and RP.

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Epidemiology

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The Prevalence of Visual Impairment in People with Dementia (the PrOVIDe study): a cross-sectional study of people aged 60–89 years with dementia and qualitative exploration of individual, carer and professional perspectives.

Bowen M, Edgar DF, Hancock B, Haque S, Shah R, Buchanan S, Iliffe S, Maskell S, Pickett J, Taylor JP, O'Leary N.

BACKGROUND: The prevalence of visual impairment (VI) and dementia increases with age and these conditions may coexist, but few UK data exist on VI among people with dementia.

OBJECTIVES: To measure the prevalence of eye conditions causing VI in people with dementia and to identify/describe reasons for underdetection or inappropriate management.

DESIGN: Stage 1 – cross-sectional prevalence study. Stage 2 – qualitative research exploring participant, carer and professional perspectives of eye care.

SETTING: Stage 1 – 20 NHS sites in six English regions. Stage 2 – six English regions.

PARTICIPANTS: Stage 1 – 708 participants with dementia (aged 60–89 years): 389 lived in the community (group 1) and 319 lived in care homes (group 2). Stage 2 – 119 participants.

INTERVENTIONS: Stage 1 gathered eye examination data following domiciliary sight tests complying with General Ophthalmic Services requirements and professional guidelines. Cognitive impairment was assessed using the Standardised Mini-Mental State Examination (sMMSE) test, and functional ability and behaviour were assessed using the Bristol Activities of Daily Living Scale and Cambridge Behavioural Inventory – Revised. Stage 2 involved individual interviews (36 people with dementia and 11 care workers); and separate focus groups (34 optometrists; 38 family and professional carers).

MAIN OUTCOME MEASURES: VI defined by visual acuity (VA) worse than 6/12 or worse than 6/18 measured before and after refraction.

RESULTS: Stage 1 – when participants wore their current spectacles, VI prevalence was 32.5% [95% confidence interval (CI) 28.7% to 36.5%] and 16.3% (95% CI 13.5% to 19.6%) for commonly used criteria for VI of VA worse than 6/12 and 6/18, respectively. Of those with VI, 44% (VA < 6/12) and 47% (VA < 6/18) were correctable with new spectacles. Almost 50% of remaining uncorrectable VI (VA < 6/12) was associated with cataract, and was, therefore, potentially remediable, and one-third was associated with macular degeneration. Uncorrected/undercorrected VI prevalence (VA < 6/12) was significantly higher in participants in care homes (odds ratio 2.19, 95% CI 1.30 to 3.73; p < 0.01) when adjusted for age, sex and sMMSE score. VA could not be measured in 2.6% of group 1 and 34.2% of group 2 participants (p < 0.01). The main eye examination elements (excluding visual fields) could be performed in > 80% of participants.

There was no evidence that the management of VI in people with dementia differed from that in older people in general. Exploratory analysis suggested significant deficits in some vision-related aspects of function and behaviour in participants with VI. Stage 2 key messages – carers and care workers underestimated how much can be achieved in an eye examination. People with dementia and carers were unaware of domiciliary sight test availability. Improved communication is needed between optometrists and carers; optometrists should be informed of the person's dementia. Tailoring eye examinations to individual needs includes allowing extra time. Optometrists wanted training and guidance about dementia. Correcting VI may improve the quality of life of people with dementia but should be weighed against the risks and burdens of undergoing examinations and cataract surgery on an individual basis.

LIMITATIONS: Sampling bias is possible owing to quota-sampling and response bias.

CONCLUSIONS: The prevalence of VI is disproportionately higher in people with dementia living in care homes. Almost 50% of presenting VI is correctable with spectacles, and more with cataract surgery. Areas for future research are the development of an eye-care pathway for people with dementia; assessment of the benefits of early cataract surgery; and research into the feasibility of specialist optometrists for older people.

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Diet, Lifestyle, and Low Vision

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Vision Loss in Older Adults.

Pelletier AL, Rojas-Roldan L, Coffin J.

ABSTRACT: Vision loss affects 37 million Americans older than 50 years and one in four who are older than 80 years. The U.S. Preventive Services Task Force concludes that current evidence is insufficient to assess the balance of benefits and harms of screening for impaired visual acuity in adults older than 65 years. However, family physicians play a critical role in identifying persons who are at risk of vision loss, counseling patients, and referring patients for disease-specific treatment. The conditions that cause most cases of vision loss in older patients are age-related macular degeneration, glaucoma, ocular complications of diabetes mellitus, and age-related cataracts. Vitamin supplements can delay the progression of age-related macular degeneration. Intravitreal injection of a vascular endothelial growth factor inhibitor can preserve vision in the neovascular form of macular degeneration. Medicated eye drops reduce intraocular pressure and can delay the progression of vision loss in patients with glaucoma, but adherence to treatment is poor. Laser trabeculoplasty also lowers intraocular pressure and preserves vision in patients with primary open-angle glaucoma, but long-term studies are needed to identify who is most likely to benefit from surgery. Tight glycemic control in adults with diabetes slows the progression of diabetic retinopathy, but must be balanced against the risks of hypoglycemia and death in older adults. Fenofibrate also slows progression of diabetic retinopathy. Panretinal photocoagulation is the mainstay of treatment for diabetic retinopathy, whereas vascular endothelial growth factor inhibitors slow vision loss resulting from diabetic macular edema. Preoperative testing before cataract surgery does not improve outcomes and is not recommended.

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Public Attitudes About Eye and Vision Health.

Scott AW, Bressler NM, Ffolkes S, Wittenborn JS, Jorkasky J.

IMPORTANCE: Understanding the importance of eye health to the US population across ethnic and racial groups helps guide strategies to preserve vision in Americans and inform policy makers regarding priority of eye research to Americans.

OBJECTIVE: To understand the importance and awareness of eye health in the US population across ethnic and racial groups.

DESIGN, SETTING, AND PARTICIPANTS: Online nationwide poll created by experienced policy makers in August 2014 designed to understand the importance of eye health in the US population, although the poll was not subjected previously to formal construct-validity testing. The population survey comprised 2044 US adults including non-Hispanic white individuals and minority groups with minority oversampling to provide predicted margins of error no greater than 5%.

MAIN OUTCOMES AND MEASURES: Respondent attitudes on the importance of eye health, concerns about losing vision, support for eye health research, and awareness of eye diseases and risk factors.

RESULTS: Of the 2044 survey respondents, the weighten mean age was 46.2 years, 48% were male, and 11% were uninsured. Sixty three percent reported wearing glasses. Most individuals surveyed (87.5%; 95% CI, 84.5%-90%) believed that good vision is vital to overall health while 47.4% (95% CI, 43.7%-51.1%) rated losing vision as the worst possible health outcome. Respondents ranked losing vision as equal to or worse than losing hearing, memory, speech, or a limb. When asked about various possible consequences of vision loss, quality of life ranked as the top concern followed by loss of independence. Nearly two-thirds of respondents were aware of cataracts (65.8%) or glaucoma (63.4%); only half were aware of macular degeneration; 37.3% were aware of diabetic retinopathy; and 25% were not aware of any eye conditions. Approximately 75.8% and 58.3%, respectively, identified sunlight and family heritage as risk factors for losing vision; only half were aware of smoking risks on vision loss.

CONCLUSIONS AND RELEVANCE: In this well-characterized survey across all US ethnic and racial groups, vision health was a priority with high support for ongoing research for vision and eye health. Many Americans were unaware of important eye diseases and their behavioral or familial risk factors. The consistency of these findings among the varying ethnic/racial groups underscores the importance of educating the public on eye health and mobilizing public support for vision research.

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The impact of typical neovascular age-related macular degeneration and polypoidal choroidal vasculopathy on vision-related quality of life in Asian patients.

Fenwick EK, Cheung CM, Ong PG, Tan G, Lee SY, Yeo I, Cheng CY, Wong TY, Lamoureux EL.

AIMS: To determine the impact of neovascular age-related macular degeneration (nAMD) on vision-related quality of life (VRQoL) in an Asian population.

METHODS: In this cross-sectional study, 162 subjects with nAMD from the Asian AMD Phenotyping Study and 105 randomly sampled age-matched and gender-matched controls from the population-based Singapore Chinese Eye Study were recruited. nAMD was categorised as either polypoidal choroidal vasculopathy (PCV) or 'typical' AMD (tAMD). The reading, mobility and emotional well-being subscales of the impact of vision impairment (IVI) scale were validated using Rasch analysis and used as the main outcome measures and collectively referred to as VRQoL. Multivariate linear regression analyses were performed to assess the impact of nAMD overall, and PCV and tAMD subtypes, on the three IVI domains.

RESULTS: Of the 162 with nAMD, 103 (63.6%) had PCV and 59 (36.4%) had tAMD. In multivariate models, nAMD overall was independently associated with a 21% reduction in reading (β=-1.08; CI -1.58 to 0.57); 16% reduction in mobility (β=-0.74; -1.14 to -0.33) and 44% reduction in emotional well-being (β=-2.15; -2.83 to -1.47) compared with controls. There were significant VRQoL deficits (p<0.05) associated -

with both PCV and tAMD; these deficits were similar and not statistically different between the two nAMD subtypes (p>0.05).

CONCLUSIONS: Neovascular AMD, including both PCV and tAMD subtypes, has a detrimental impact on VRQoL in Asian subjects independent of level of vision impairment. Interventions to increase reading capacity, enhance mobility and independence and improve mental health outcomes for subjects with neovascular AMD further address the impact of the condition on VRQoL in addition to pharmacological therapies.

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