Persistent Macular Thickening Following Intravitreous Aflibercept, Bevacizumab, or Ranibizumab for Central-Involved Diabetic Macular Edema With Vision Impairment: A Secondary Analysis of a Randomized Clinical Trial.

Bressler NM, Beaulieu WT, Glassman AR, Blinder KJ, Bressler SB, Jampol LM, Melia M, Wells JA 3rd; Diabetic Retinopathy Clinical Research Network.

IMPORTANCE: Prevalence of persistent central-involved diabetic macular edema (DME) through 24 weeks of anti-vascular endothelial growth factor therapy and its longer-term outcomes may be relevant to treatment.

OBJECTIVE: To assess outcomes of DME persisting at least 24 weeks after randomization to treatment with 2.0-mg aflibercept, 1.25-mg bevacizumab, or 0.3-mg ranibizumab.

DESIGN, SETTING, AND PARTICIPANTS: Post hoc analyses of a clinical trial, DRCR.net Protocol T among 546 of 660 participants (82.7%) meeting inclusion criteria for this investigation.

INTERVENTIONS: Six monthly intravitreous anti-vascular endothelial growth factor injections (unless success after 3 to 5 injections); subsequent injections or focal/grid laser as needed per protocol to achieve stability.

MAIN OUTCOMES AND MEASURES: Persistent DME through 24 weeks, probability of chronic persistent DME through 2 years, and at least 10-letter (≥ 2-line) gain or loss of visual acuity.

RESULTS: The mean age of participants was 60 years, 363 (66.5%) were white, and 251 (46.0%) were women. Persistent DME through 24 weeks was more frequent with bevacizumab (118 of 180 [65.6%]) than aflibercept (60 of 190 [31.6%]) or ranibizumab (73 of 176 [41.5%]) (aflibercept vs bevacizumab, P < .001; ranibizumab vs bevacizumab, P < .001; and aflibercept vs ranibizumab, P = .05). Among eyes with persistent DME through 24 weeks (n = 251), rates of chronic persistent DME through 2 years were 44.2% with aflibercept, 68.2% with bevacizumab (aflibercept vs bevacizumab, P = .03), and 54.5% with ranibizumab (aflibercept vs ranibizumab, P = .41; bevacizumab vs ranibizumab, P = .16). Among eyes with persistent DME through 24 weeks, proportions with vs without chronic persistent DME through 2 years gaining at least 10 letters from baseline were 62% of 29 eyes vs 63% of 30 eyes (P = .88) with aflibercept, 51% of 70 vs 54% of 31 (P = .96) with bevacizumab, and 44% of 38 vs 65% of 29 (P = .10) with ranibizumab. Only 3 eyes with chronic persistent DME lost at least 10 letters.

CONCLUSIONS AND RELEVANCE: Persistent DME was more likely with bevacizumab than with aflibercept or ranibizumab. Among eyes with persistent DME, eyes assigned to bevacizumab were more likely to have chronic persistent DME than eyes assigned to aflibercept. These results suggest meaningful.
gains in vision with little risk of vision loss, regardless of anti-vascular endothelial growth factor agent given or persistence of DME through 2 years. Caution is warranted when considering switching therapies for persistent DME following 3 or more injections; improvements could be owing to continued treatment rather than switching therapies.

PMID: 29392288

**Medicine (Baltimore). 2017 Dec;96(50):e9345.**

**Influence of vitreomacular interface on anti-vascular endothelial growth factor treatment outcomes in neovascular age-related macular degeneration: A MOOSE-compliant meta-analysis.**


Abstract: The aim of the study was to evaluate the influence of vitreomacular interface configuration on treatment outcomes after intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (AMD). The PubMed, Embase, and Cochrane Central Register of Controlled Trials databases were searched to identify relevant prospective or retrospective studies that evaluate the influence of vitreomacular adhesion (VMA) or vitreomacular traction (VMT) on functional and anatomical outcomes in neovascular AMD patients treated with anti-VEGF agents. The outcome measures were the mean change in best corrected visual acuity (BCVA) from baseline, the mean change in central macular thickness (CMT) from baseline, and the mean injection numbers of anti-VEGF treatment from baseline. In total, 9 studies were selected for this meta-analysis, including 2156 eyes (404 eyes in the VMA/VMT group and 1752 eyes in the non-VMA/VMT group). In neovascular AMD patients treated with anti-VEGF agents, the VMA/VMT group was associated with poorer visual acuity gains and CMT reductions at 1 year (WMD [95% CI], -6.17 [-11.91, -0.43] early treatment diabetic retinopathy study (ETDRS) letters, P = .04; WMD [95% CI], 22.19 [2.01, 42.38] μm, P = .03, respectively). There was no significant difference between 2 groups in the mean BCVA change and the CMT change over 2 years (WMD [95% CI], -5.59 [-21.19, 10.01] ETDRS letters, P = .48; WMD [95% CI], 6.56 [-24.78, 37.90] μm, P = .68, respectively). There was no significant difference in the mean injection numbers between 2 groups at 1 year (WMD [95% CI], 0.36 [-0.19, 0.90], P = .21), whereas the VMA/VMT group had a significantly higher mean injection numbers over 2 years (WMD [95% CI], 1.14 [0.11, 2.16], P = .03). The limited evidence suggests that vitreomacular interface configuration have a significant influence on the visual acuity gain and CMT reduction at 1 year, injection numbers at 2 years in neovascular AMD patients treated with anti-VEGF agents. However, the results of this meta-analysis should be interpreted with caution because of the heterogeneity among study designs. Eyes with VMA/VMT on optical coherence tomography at baseline may require more intensive treatment with decreased response to anti-VEGF agents.

PMID: 29390407

**Sci Rep. 2018 Feb 1;8(1):2101.**

**Pharmaceutical compounding of aflibercept in prefilled syringes does not affect structural integrity, stability or VEGF and Fc binding properties.**

Sivertsen MS, Jørstad ØK, Grevys A, Foss S, Moe MC, Andersen JT.

Abstract: Macular edema due to neovascular age-related macular degeneration, diabetes or retinal vein occlusion can cause central vision loss. Intravitreal treatment with antibody-based biopharmaceutical compounds designed to neutralize vascular endothelial growth factor (VEGF) has proven to be an efficient strategy to ameliorate macular edema and restore visual acuity. At the same time, the use of anti-VEGF drugs places an economic burden on the health care system; the drugs are expensive, and repeated injections are usually required to maintain the therapeutic effect. Thus, there is an unmet need for more
cost-effective procedures. We here describe how the most recently approved anti-VEGF drug, aflibercept, can be compounded into prefilled sterile syringes and stored for up to 4 weeks without compromising its quality, stability or functional properties, including VEGF and neonatal Fc receptor (FcRn) binding. The novel compounding method for repackaging of aflibercept in sterile plastic syringes can greatly reduce both cost and time spent per patient in the injection room.

PMID: 29391560

**Clin Ophthalmol. 2018 Jan 8;12:99-104. eCollection 2018.**

**Aflibercept for clinically significant diabetic macular edema: 12-month results in daily clinical practice.**

Campos Polo R, Rubio Sánchez C, García Guisado DM, Díaz Luque MJ.

**PURPOSE:** To assess the effectiveness and safety of intravitreal aflibercept in clinically significant diabetic macular edema (DME) in daily clinical practice.

**METHODS:** Prospective, open-label, single-center study. Anti-vascular endothelial growth factor naïve patients with clinically significant DME received intravitreal injections of aflibercept 2 mg, five monthly doses followed by a fixed schedule every 2 months for 12 months. The mean change in best-corrected visual acuity (BCVA) (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) was the primary outcome.

**RESULTS:** The mean BCVA improved significantly as compared with baseline at 12 months of treatment (47.3 [14.2] vs 62.2 [13.9] ETDRS letters, P<0.001). Significant improvement in BCVA was already observed at visit 2 after the loading doses of aflibercept. At 12 months, gains in ETDRS letters were documented in all eyes (100%), with gains ≥10 letters in 89.6%, ≥15 letters in 65.5%, and ≥20 letters in 6.9% (n=2). A significant reduction in central macular thickness from a mean of 460.5 (11.8) µm at baseline to 229.0 (43.8) µm at 12 months (P<0.001) was observed. Significant reductions of central macular thickness were already observed after the loading doses and continued lowering throughout the study period. No adverse events occurred.

**CONCLUSION:** Aflibercept as a first-line therapy was effective and well tolerated for treating clinically significant DME in naïve patients in daily practice. Successful results in terms of improvement of visual and reduction in central macular thickness contribute to provide evidence for the positioning of aflibercept as a first-line indication of newly diagnosed clinically significant DME.

PMID: 29386883 PMCID: PMC5764298

**BMC Ophthalmol. 2018 Feb 1;18(1):22.**

**Influence of new societal factors on neovascular age-related macular degeneration outcomes.**

Giocanti-Aurégan A, Chbat E, Darugar A, Morel C, Morin B, Conrath J, Devin F.

**BACKGROUND:** To assess the impact of unstudied societal factors for neovascular age-related macular degeneration (nAMD) on functional outcomes after anti-VEGFs.

**METHODS:** Charts of 94 nAMD patients treated in the Monticelli-Paradis Centre, Marseille, France, were reviewed. Phone interviews were conducted to assess societal factors, including transportation, living status, daily reading and social security scheme (SSS). Primary outcome was the impact of family support and disease burden on functional improvement in nAMD.

**RESULTS:** Between baseline and month 24 (M24), 42.4% of the variability in best-corrected visual acuity (BCVA) was explained by the cumulative effect of the following societal factors: intermittent out-patient
follow-up, marital status, daily reading, transportation type, commuting time. No isolated societal factor significantly correlated with ETDRS BCVA severity at M24. A trend to correlation was observed between the ETDRS score at M24 and the SSS (P = 0.076), economic burden (P = 0.075), time between diagnosis and treatment initiation (P = 0.070). A significant correlation was found for the disease burdensome on the patient (P = 0.034) and low vision rehabilitation (P = 0.014).

CONCLUSIONS: Societal factors could influence functional outcomes in nAMD patients treated with anti-VEGFs. They could contribute to the healing process or sustain disease progression.

PMID: 29385989

Cornea. 2018 Jan 30. [Epub ahead of print]

Effects of Repeated Intravitreal Aflibercept Injection on the Corneal Endothelium in Patients With Age-Related Macular Degeneration: Outcomes From the RE-VIEW Study.


PURPOSE: The effects of repeated intravitreal aflibercept injection (IAI) on the corneal endothelium were studied in patients with unilateral neovascular age-related macular degeneration.

METHODS: RE-VIEW was a phase 4, open-label, single-arm, multicenter study. Patients received IAI every 8 weeks after 3 monthly doses. Slit-lamp biomicroscopy was performed at all study visits. The central corneal endothelial health was evaluated by specular microscopy in the treated versus untreated fellow eyes at baseline and weeks 24 and 52.

RESULTS: No slit-lamp abnormalities were noted in 154 enrolled patients (eyes). Baseline versus 52-week mean (±SD) endothelial morphometric values (n = 118) for the treated versus untreated fellow eyes were respectively as follows: endothelial cell density was 2410 ± 364 versus 2388 ± 384 cells/mm at baseline and remained unchanged at 2401 ± 353 versus 2376 ± 364 cells/mm at 52 weeks (P = 0.87); the coefficient of variation was 33.5 ± 4.4% versus 34.0 ± 5.0% at baseline and remained unchanged at 34.2 ± 4.7% versus 34.1 ± 4.9% at 52 weeks (P = 0.18); the percentage of hexagonal cells was 59.5 ± 6.4% versus 59.6 ± 6.4% at baseline and remained unchanged at 59.5 ± 5.8% versus 59.5 ± 5.8% at 52 weeks (P = 0.96).

CONCLUSIONS: Repeated IAI for 52 weeks had no apparent corneal endothelial toxicity noted on specular microscopy in patients treated for neovascular age-related macular degeneration.

PMID: 29384810

J Manag Care Spec Pharm. 2018 Feb;24(2-a Suppl):S3-S15.

Optimizing Anti-VEGF Treatment Outcomes for Patients with Neovascular Age-Related Macular Degeneration.

Wykoff CC, Clark WL, Nielsen JS, Brill JV, Greene LS, Heggen CL.

BACKGROUND: The introduction of anti-vascular endothelial growth factor (anti-VEGF) drugs to ophthalmology has revolutionized the treatment of neovascular age-related macular degeneration (nAMD). Despite this significant progress, gaps and challenges persist in the diagnosis of nAMD, initiation of treatment, and management of frequent intravitreal injections. Thus, nAMD remains a leading cause of blindness in the United States.

OBJECTIVE: To present current knowledge, evidence, and expert perspectives on anti-VEGF therapies in nAMD to support managed care professionals and providers in decision making and collaborative
strategies to overcome barriers to optimize anti-VEGF treatment outcomes among nAMD patients.

SUMMARY: Three anti-VEGF therapies currently form the mainstay of treatment for nAMD, including 2 therapies approved by the FDA for treatment of nAMD (aflibercept and ranibizumab) and 1 therapy approved by the FDA for oncology indications and used off-label for treatment of nAMD (bevacizumab). In clinical trials, each of the 3 agents maintained visual acuity (VA) in approximately 90% or more of nAMD patients over 2 years. However, in long-term and real-world settings, significant gaps and challenges in diagnosis, treatment, and management pose barriers to achieving optimal outcomes for patients with nAMD. Many considerations, including individual patient characteristics, on-label versus off-label treatment, repackaging, and financial considerations, add to the complexity of nAMD decision making and management. Many factors may contribute to additional challenges leading to suboptimal long-term outcomes among nAMD patients, such as delays in diagnosis and/or treatment approval and initiation, individual patient response to different anti-VEGF therapies, lapses in physician regimentation of anti-VEGF injection and monitoring, and inadequate patient adherence to treatment and monitoring. These latter factors highlight the considerable logistical, emotional, and financial burdens of long-term, frequent intravitreal injections and the vital importance of personalized approaches to anti-VEGF treatment decision making and management for patients with nAMD. To address these challenges and reduce the number of yearly injections, studies have examined alternative dosing regimens, including extended fixed intervals, as needed, and treat-and-extend strategies in specific nAMD patient populations. New clinical evidence and insights into expert clinical practice discussed in this article can support managed care professionals in the key role they play in addressing challenges in nAMD treatment and management and optimizing patient outcomes through appropriate management of anti-VEGF treatment.

PMID: 29383980


Clinical outcomes of switching to aflibercept using a pro re nata treatment regimen in patients with neovascular age-related macular degeneration who incompletely responded to ranibizumab.

Elwes F, Borooah S, Aspinall P, Sim PY, Loo CY, Armbrecht AM, Dhillon B, Cackett P.

BACKGROUND: To assess the effect of switching patients previously incompletely treated with ranibizumab (RBZ) to aflibercept (AFL) using a pro re nata (PRN) treatment strategy in neovascular age-related macular degeneration (nvAMD).

METHODS: A retrospective case series was conducted on patients who had persistent or recurrent intra-and/or sub-retinal fluid treated initially with RBZ and subsequently switched to AFL. The main outcome measures were best corrected visual acuity (BCVA) and central retinal thickness (CRT) measured at different stages of the study. Friedman analysis of variance and Wilcoxon test were used to examine differences in BCVA and CRT.

RESULTS: Two hundred and seven eyes from 182 patients were included. BCVA and CRT improved significantly initially following 3 RBZ injections with a mean gain of 3.7 letters (p < 0.001) and a mean loss of 69 μm (p < 0.001) respectively. Following PRN RBZ therapy and immediately prior to switching to AFL (mean 129 weeks), there was a mean loss of 6.7 letters (p < 0.001) BCVA and a mean gain of 24 μm (p < 0.001) CRT. AFL loading resulted in a mean improvement of 0.7 letters (p = 0.28) BCVA and 55 μm (p < 0.001) CRT. At final follow-up following AFL PRN therapy (mean 85 weeks), there was a mean loss of 8.9 letters (p < 0.001) BCVA and a mean gain of 12 μm (p < 0.05) CRT.

CONCLUSION: AFL loading resulted in a significant anatomical improvement but no significant change in visual acuity. However, the benefits of switching were gradually lost over time with AFL PRN dosing despite an increased injection rate when compared with RBZ PRN treatment.

PMID: 29378528

Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers.


PURPOSE: To evaluate the expression of 19 angiogenic biomarkers in the aqueous humor before and after intravitreal bevacizumab injection (IVB) in eyes with neovascular age-related macular degeneration (AMD).

DESIGN: Prospective, noncomparative, interventional case series.

PARTICIPANTS: Twenty-three eyes of 23 treatment-naïve patients with choroidal neovascularization (CNV) secondary to neovascular AMD.

METHODS: Eyes were diagnosed with CNV secondary to neovascular AMD and were treated with 3 monthly IVBs. Aqueous humor samples were obtained by anterior chamber paracentesis at baseline and immediately before each intravitreal bevacizumab injection.

MAIN OUTCOME MEASURES: Aqueous humor levels of 19 angiogenic biomarkers (angiopoietin 2, bone morphogenetic protein 9 [BMP-9], epidermal growth factor [EGF], endoglin, endothelin 1, fibroblast growth factor [FGF]-1 and FGF-2, follistatin, granulocyte colony-stimulating factor [GCSF], heparin-binding EGF-like growth factor [HB-EGF], hepatocyte growth factor [HGF], interleukin 8, leptin, placental growth factor [PLGF], vascular endothelial growth factor [VEGF]-A, VEGF-C, VEGF-D, and tissue inhibitor of metalloproteinases [TIMP]-1 and TIMP-2) were measured. Best-corrected visual acuity (BCVA), spectral-domain OCT parameters, and intraocular pressure also were evaluated.

RESULTS: Baseline aqueous VEGF-A expression was elevated in all study eyes before treatment initiation. A statistically significant decrease of VEGF-A was observed at the 1- and 2-month follow-ups. A statistically significant increased concentration was observed in 7 biomarkers: VEGF-C, angiopoietin 2, endothelin 1, follistatin, HB-EGF, HGF, and interleukin 8. The other 11 study biomarker levels (VEGF-D, BMP-9, EGF, endoglin, FGF-1, FGF-2, GCSF, leptin, PLGF, TIMP-1, and TIMP-2) did not show any significant difference during follow-up. The BCVA statistically improved significantly at 2 months. Spectral-domain OCT parameters improved significantly at all follow-ups. Mean intraocular pressure values were not statistically different during the study period.

CONCLUSIONS: Despite a decrease in VEGF-A, the aqueous levels of VEGF-C, angiopoietin 2, endothelin 1, follistatin, HB-EGF, HGF, and interleukin 8 increased significantly after intravitreal injection of bevacizumab. These upregulated angiogenic biomarkers may represent new therapeutic targets in exudative AMD.

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Subfoveal choroidal thickness predicts macular atrophy in age-related macular degeneration: results from the TREX-AMD trial.


BACKGROUND: Our purpose was to evaluate the relationship between subfoveal choroidal thickness (SCT) and development of macular atrophy (MA) in eyes with age-related macular degeneration (AMD).

METHODS: This was a prospective, multicenter study. Sixty participants (120 eyes) in the TREX-AMD trial (NCT01648292) with treatment-naïve neovascular AMD (NVAMD) in at least one eye were included. SCT was measured by certified reading center graders at baseline using spectral domain optical coherence
tomography (SDOCT). The baseline SCT was correlated with the presence of MA at baseline and development of incident MA by month 18. Generalized estimating equations were used to account for information from both eyes.

RESULTS: Baseline SCT in eyes with MA was statistically significantly less than in those without MA in both the dry AMD (DAMD) (P = 0.04) and NVAMD (P = 0.01) groups. Comparison of baseline SCT between MA developers and non-MA developers revealed a statistically significant difference (P = 0.03). Receiver operating characteristic curve (ROC) analysis showed the cut-off threshold of SCT for predicting the development of MA in cases without MA at baseline was 124 μm (AUC = 0.772; Sensitivity = 0.923; Specificity = 0.5). Among eyes without MA at baseline, those with baseline SCT ≤124 μm were 4.3 times more likely to develop MA (Odds ratio: 4.3, 95% confidence interval: 1.6-12, P = 0.005) than those with baseline SCT >124 μm.

CONCLUSIONS: Eyes with AMD and MA had less SCT than those without MA. Eyes with less baseline SCT also appear to be at higher risk to develop MA within 18 months.

Pharmaceutics. 2018 Jan 27;10(1).


Stewart MW.

Abstract: Vascular endothelial growth factor (VEGF) plays a pivotal role in the development of neovascularization and edema from several common choriororetinal vascular conditions. The intravitreally injected drugs (aflibercept, bevacizumab, conbercept, pegaptanib, and ranibizumab) used to treat these conditions improve the visual acuity and macular morphology in most patients. Monthly or bimonthly injections were administered in the phase III pivotal trials but physicians usually individualize therapy with pro re nata (PRN) or treat and extend regimens. Despite these lower frequency treatment regimens, frequent injections and clinic visits are still needed to produce satisfactory outcomes. Newly developed drugs and refillable reservoirs with favorable pharmacokinetic profiles may extend durations of action and require fewer office visits. However, we have learned from previous experiences that the longer durations of action seen in strategically designed phase III trials often do not translate to less frequent injections in real-life clinical practice. Unfortunately, long-acting therapies that produce soluble VEGF receptors (encapsulated cell technology and adenovirus injected DNA) have failed in phase II trials. The development of longer duration therapies remains a difficult and frustrating process, and frequent drug injections are likely to remain the standard-of-care for years to come.

PMID: 29382038


Anterior scleritis following intravitreal injections in a patient with rheumatoid arthritis: A case report.


RATIONALE: Surgically induced scleritis is a rare complication following ophthalmologic surgery such as cataract surgery, pterygium excision, strabismus surgery, and retinal detachment repair. Rheumatoid arthritis (RA) is the connective tissue disease most commonly associated with scleritis.

PATIENT CONCERNS: A 70-year-old woman visited our clinic with complaint of visual disturbance, ocular
pain, and conjunctival injection in her right eye of 1 month's duration. She had a stable state of rheumatoid factor positive RA and had a history of multiple intravitreal injections placed in the symptomatic right eye due to age-related macular degeneration.

DIAGNOSES: Anterior scleritis induced by multiple intravitreal injections.

INTERVENTIONS: Topical and systemic steroids were administered.

OUTCOMES: Her symptoms and signs were relieved and no significant recurrence has been occurred with the maintenance of low dose oral steroid.

LESSONS: Surgically induced scleritis can also be induced by not only major surgical trauma but also by relatively minor trauma such as intravitreal injection (especially in patients who have connective tissue disease such as RA).

PMID: 29382031 PMCID: PMC5709030


Concurrent injection of dexamethasone intravitreal implant and anti-angiogenic agent in patients with macular edema: A retrospective cohort study.

Lin HY, Lee CY, Huang JY, Yang SF, Chao SC.

Abstract: To evaluate the safety and efficiency in macular edema patients who concurrently received a single injection of a dexamethasone intravitreal implant (DEX, 0.7mg) and ranibizumab (2.3mg). A retrospective cohort study was conducted, and medical records from 2012 to 2016 were reviewed. Patients who received concurrent DEX and ranibizumab injections with a follow-up period of at least 3 months were enrolled in the study group. An age and gender-matched group received ranibizumab injections and was designated the control group. The best-corrected visual acuity (BCVA), central macular thickness (CMT) and intraocular pressure (IOP) were included in the analysis. Steroid-induced ocular hypertension (SIOH) is defined as either an elevation of more than 10 mmHg from baseline or a single IOP measurement of more than 30 mmHg. A total of 26 patients were enrolled in the current study with 13 patients in each group. Both the BCVA (P = .04) and CMT (P < .01) achieved significant improvement after the follow-up period in the study group. The IOP increased after the injection but no significant elevation was observed throughout the follow-up period in the study group (P = .15). For SIOH, 1 patient in the study group had an elevated IOP of 10 mmHg (7.7%) at 2 postoperative months, and no single IOP measurement of more than 30 mmHg was obtained. Five patients (38.5%) in the study group received medical treatment that successfully retarded their IOP elevation, and no individuals required surgical management. In the control group, there were no significant fluctuations concerning BCVA, CMT, and IOP, and no ocular hypertension was observed. According to the inter-group analysis, the CMT and BCVA recovered more significantly in the study group than in the control group. Concurrent injection of DEX and ranibizumab is a preliminary method that shows effectiveness in treating ME. Furthermore, safety is also guaranteed, with moderate levels of severity and transient IOP elevation being observed. A future large-scale study is necessary to evaluate the long-term effects and safety of this combined treatment.

PMID: 29382007 PMCID: PMC5709006


Coats' Disease-Related Macular Edema Treated with Combined Aflibercept and Laser Photocoagulation.

Shieh WS, Shah GK, Blinder KJ.
PURPOSE: To describe the clinical response of refractory macular edema associated with Coats' disease following treatment with aflibercept and laser photoagulation.

METHODS: Case report.

RESULTS: A 17-year-old female presented with decreased vision of the left eye. Ophthalmic exam demonstrated intraretinal hemorrhages and exudation with associated edema centrally. Angiographic evaluation revealed central leaking microaneurysms and peripheral capillary dropout. These findings and a systemic work-up that yielded an incidental Factor V Leiden mutation lead to a diagnosis of Coats' disease. Initial treatment consisted of laser photoagulation and intravitreal bevacizumab but with poor response. Switching to intravitreal aflibercept resulted in resolution of the refractory macular edema and improvement of visual acuity to 20/25 in the left eye.

CONCLUSION: We describe a case of refractory macular edema which responded more favorably to intravitreal aflibercept compared with bevacizumab when combined with laser photoagulation in a patient with Coats' disease.

PMID: 29379657 PMCID: PMC5742908

Other treatment & diagnosis


Nanosecond Laser Treatment for Age-Related Macular Degeneration Does Not Induce Focal Vision Loss or New Vessel Growth in the Retina.

Vessey KA, Ho T, Jobling AI, Mills SA, Tran MX, Brandli A, Lam J, Guymer RH, Fletcher EL.

PURPOSE: Subthreshold, nanosecond pulsed laser treatment shows promise as a treatment for age-related macular degeneration (AMD); however, the safety profile needs to be robustly examined. The aim of this study was to investigate the effects of laser treatment in humans and mice.

METHODS: Patients with AMD were treated with nanosecond pulsed laser at subthreshold (no visible retinal effect) energy doses (0.15-0.45 mJ) and retinal sensitivity was assessed with microperimetry. Adult C57BL6J mice were treated at subthreshold (0.065 mJ) and suprathreshold (photoreceptor loss, 0.5 mJ) energy settings. The retinal and vascular responses were analyzed by fundus imaging, histologic assessment, and quantitative PCR.

RESULTS: Microperimetry analysis showed laser treatment had no effect on retinal sensitivity under treated areas in patients 6 months to 7 years after treatment. In mice, subthreshold laser treatment induced RPE loss at 5 hours, and by 7 days the RPE had retiled. Fundus imaging showed reduced RPE pigmentation but no change in retinal thickness up to 3 months. Electron microscopy revealed changes in melanosomes in the RPE, but Bruch's membrane was intact across the laser regions. Histologic analysis showed normal vasculature and no neovascularization. Suprathreshold laser treatment did not induce changes in angiogenic genes associated with neovascularization. Instead pigment epithelium-derived factor, an antiangiogenic factor, was upregulated.

CONCLUSIONS: In humans, low-energy, nanosecond pulsed laser treatment is not damaging to local retinal sensitivity. In mice, treatment does not damage Bruch's membrane or induce neovascularization, highlighting a reduced side effect profile of this nanosecond laser when used in a subthreshold manner.

PMID: 29392319
Bedside optical coherence tomography for Terson’s syndrome screening in acute subarachnoid hemorrhage: a pilot study.


OBJECTIVE: Approximately 10% of patients with subarachnoid hemorrhage (SAH) become permanently, legally blind. The average cost of lifetime support and unpaid taxes for each blind person amounts to approximately $900,000. This study evaluates the feasibility and potential role of bedside optical coherence tomography (OCT) in Terson's syndrome (TS) in patients with acute SAH (aSAH) and its potential role in blindness prevention.

METHODS: The authors conducted an open-label pilot study, in which 31 patients with an angiographic diagnosis of aSAH were first screened for TS with dilated funduscopy and then with OCT in the acute phase and at 6-week follow-up visits. Outpatient mood assessments (Patient Health Questionnaire-depression module, Hamilton Depression Scale), and quality of life general (NIH Patient-Reported Outcomes Measurement Information System) and visual scales (25-item National Eye Institute Visual Functioning Questionnaire) were measured at 1 and 6 weeks after discharge. Exclusion criteria included current or previous history of severe cataracts, severe diabetic retinopathy, severe macular degeneration, or glaucoma.

RESULTS: OCT identified 7 patients with TS, i.e., a 22.6% incidence in our aSAH sample: 7 in the acute phase, including a large retinal detachment that was initially missed by funduscopy and diagnosed by OCT in follow-up clinic. Dilated retinal funduscopy significantly failed to detect TS in 4 (57.1%) of these 7 cases. Intraventricular hemorrhage was significantly more common in TS cases (85.7% vs 25%). None of the participants experienced any complications from OCT examinations. Neither decreased quality of life visual scale scores nor a depressed mood correlated with objective OCT pathological findings at the 6-week follow-up after discharge. There were no significant mood differences between TS cases and controls.

CONCLUSIONS: OCT is the gold standard in retinal disease diagnosis. This pilot study shows that bedside OCT examination is feasible in aSAH. In this series, OCT was a safe procedure that enhanced TS detection by decreasing false-negative/inconclusive funduscopic examinations. It allows early diagnosis of macular holes and severe retinal detachments, which require acute surgical therapy to prevent legal blindness. In addition, OCT aids in ruling out potential false-positive visual deficits in individuals with a depressed mood at follow-up.

PMID: 29393753

Diagnostic Electron Microscopy of Retina.

Gupta RK, Kaur I, Nag TC, Chhablani J.

Abstract: The electron microscopy techniques were used in various fields as an analytical technique under in vitro conditions, which provides the sufficient resolution for better visualization and interpretation. This review gives a brief overview of the analytical application of transmission electron microscopy (TEM) and scanning electron microscopy (SEM) techniques and critical findings in different retinal pathologies. This review article aims to improvise understanding of retinal microstructures for clinicians which will help to improve the interpretation of the current advanced imaging techniques.

PMID: 29388866

Macular pigment optical density in a Brazilian sample.

Jorge LPC, Pereira CEG, Jorge E, de Ávila MP.

BACKGROUND: To evaluate macular pigment optical density (MPOD) and to identify its determinants in a sample of Brazilian individuals.

METHODS: This was a cross-sectional study. One hundred three healthy individuals had both eyes photographed using a Visucam 500 digital fundus camera (Carl Zeiss Meditec, Jena, Germany) in combination with the MPOD module. Four variables were obtained: maximum MPOD, mean MPOD, MPOD volume, and MPOD area. Demographic data and information on lifestyle habits were also collected.

RESULTS: Mean MPOD was 0.14 density unit ± 0.05. MPOD was not influenced by gender, smoking history, or refractive error. MPOD was significantly higher among black individuals than among white and biracial individuals. There was a positive but low correlation between MPOD and age.

CONCLUSION: This study found MPOD values to be similar to those found in European samples but lower than other studies performed on Asian and Australian samples. This is the first data regarding MPOD in a South American Population.

PMID: 29387455 PMCID: PMC5776767

Ophthalmol Ther. 2018 Jan 30. [Epub ahead of print]

Choriocapillaris Vascular Density Changes in Patients with Drusen: Cross-Sectional Study Based on Optical Coherence Tomography Angiography Findings.

Chatziralli I, Theodossiadis G, Panagiotidis D, Pousoulidi P, Theodossiadis P.

INTRODUCTION: The purpose of this study was to investigate the extent and morphology of the choriocapillaris’ density defect in patients with drusen in non-neovascular age-related macular degeneration (AMD).

METHODS: Participants in this study were 36 patients with non-neovascular AMD and drusen. All patients underwent best-corrected visual acuity, slit-lamp examination, spectral domain-optical coherence tomography (SD-OCT), and optical coherence tomography angiography (OCTA).

RESULTS: In all studied cases, the presence of drusen was associated with choriocapillaris’ reduced blood flow signal of different extent and severity. Three types of choriocapillaris' non-perfusion were observed, along with an association between the size of drusen and the morphology of choriocapillaris' density defect. Moreover, the extent of choriocapillaris' density change has been related to ellipsoid zone disruption and therefore to visual impairment.

CONCLUSIONS: Our study showed that in patients with drusen due to non-neovascular AMD, there is choriocapillaris' impairment of different morphology in OCTA, which is mainly related to the size and location of the drusen.

PMID: 29383674


Sensitivity, Specificity, and Limitations of Optical Coherence Tomography Angiography in Diagnosis of Polypoidal Choroidal Vasculopathy.
Huang YM, Hsieh MH, Li AF, Chen SJ.

PURPOSE: To evaluate the sensitivity and specificity of optical coherence tomography angiography (OCTA) in differentiating polypoidal choroidal vasculopathy (PCV) from age-related macular degeneration (AMD).

METHODS: Fundus color photographs, spectral-domain optical coherence tomography, and fluorescein angiography (step 1) and OCTA (step 2) of 50 eyes that had PCV or AMD were presented to two ophthalmologists. The final diagnoses of PCV were masked. Sensitivity and specificity were calculated and compared to the 2-step approach (before and after OCTA) in detecting PCV. The limitations were also evaluated.

RESULTS: Of the 50 eyes, 31 were PCV and 19 were non-PCV. The sensitivity increased from 69.5% to 90% after OCTA; however, there was no significant improvement in specificity after OCTA. 70.9% of the eyes with PCV had clear or obvious branching vascular nets (BVNs) in OCTA with high sensitivity (97.5%) after OCTA. Contrarily, 29.1% had insignificant BVNs with a low sensitivity (72.5%) after OCTA. 27% of the occult choroidal neovascularization (CNV) cases were overdiagnosed as PCV when OCTA was applied.

CONCLUSIONS: OCTA based on clear BVNs at the choroidal level increased sensitivity of diagnosis of PCV by 20%. However, the false-positive rate also increased in occult CNV. Several limitations for a correct diagnosis of PCV were noted.

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Pathogenesis


Effect of Anti-C5a Therapy in a Murine Model of Early/Intermediate Dry Age-Related Macular Degeneration.


PURPOSE: A large body of evidence supports a central role for complement activation in the pathobiology of age-related macular degeneration (AMD), including plasma complement component 5a (C5a). Interestingly, C5a is a chemotactic agent for monocytes, a cell type also shown to contribute to AMD. However, the role monocytes play in the pathogenesis of "dry" AMD and the pharmacologic potential of targeting C5a to regulate these cells are unclear. We addressed these questions via C5a blockade in a unique model of early/intermediate dry AMD and large panel flow cytometry to immunophenotype monocytic involvement.

METHODS: Heterozygous complement factor H (Cfh+/−) mice aged to 90 weeks were fed a high-fat, cholesterol-enriched diet (Cfh+/− HFC) for 8 weeks and were given weekly intraperitoneal injections of 30 mg/kg anti-C5a (4C9, Pfizer). Flow cytometry, retinal pigmented epithelium (RPE) flat mounts, and electroretinograms were used to characterize anti-C5a treatment.

RESULTS: Aged Cfh+/− mice developed RPE damage, sub-RPE basal laminar deposits, and attenuation of visual function and immune cell recruitment to the choroid that was accompanied by expression of inflammatory and extracellular matrix remodeling genes following 8 weeks of HFC diet. Concomitant systemic administration of an anti-C5a antibody successfully inhibited local recruitment of mononuclear phagocytes to the choroid-RPE interface but did not ameliorate these AMD-like pathologies in this mouse model.

CONCLUSIONS: These results show that immunotherapy targeting C5a is not sufficient to block the development of the AMD-like pathologies observed in Cfh+/− HFC mice and suggest that other
complement components or molecules/mechanisms may be driving "early" and "intermediate" AMD pathologies.

PMID: 29392311


A Novel Choroidal Endothelial Cell Line Has a Decreased Affinity for the Age-Related Macular Degeneration-Associated Complement Factor H Variant 402H.


PURPOSE: Choroidal endothelial cells play a central role in the pathogenesis of age-related macular degeneration (AMD). Protocols for isolating primary choroidal endothelial cells have been described but require access to human donor eyes, which is a limiting factor. Therefore, a conditionally immortalized choroidal endothelial cell (ciChEnC) line has been established.

METHODS: Choroidal endothelial cells were selected by magnetic-activated cell sorting and conditionally immortalized using temperature-sensitive simian virus 40 large T antigen and human telomerase. The cell line obtained was characterized based on expression of endothelial marker proteins and endothelial cell-specific responses to various stimuli. Binding of AMD-associated and non-AMD variants of complement factor H in the context of a recombinant CCP6-8 (complement control protein domains 6-8) construct was determined using ELISA.

RESULTS: ciChEnCs maintained morphology and von Willebrand factor and vascular endothelial cadherin expression for up to 27 passages. The cells internalized acetylated low-density lipoprotein, formed tubes on Matrigel, and increased intercellular adhesion molecule-1 expression in response to tumor necrosis factor-α. Cells grew into dense monolayers with barrier function and showed characteristics of choriocapillary cells, such as expression of plasmalemma vesicle-associated protein, human leukocyte antigen ABC, carbonic anhydrase IV, and membrane indentations reflecting fenestration. ciChEnCs synthesized glycosaminoglycans chondroitin sulfate and the complement factor H ligand heparan sulfate. Interestingly, binding of the AMD-associated 402H variant of factor H to ciChEnC was significantly decreased compared to the 402Y variant.

CONCLUSIONS: A novel ciChEnC cell line with choriocapillary characteristics has been established and should greatly facilitate investigation of the pathogenesis of AMD in the context of the choriocapillary microenvironment.

PMID: 29392318


Erythropoietin Signaling Increases Choroidal Macrophages and Cytokine Expression, and Exacerbates Choroidal Neovascularization.

Bretz CA, Divoky V, Prchal J, Kunz E, Simmons AB, Wang H, Hartnett ME.

Abstract: Erythropoietin (EPO) is recognized for neuroprotective and angiogenic effects and has been associated with aging and neovascular age-related macular degeneration (AMD). We hypothesized that systemic EPO facilitates the development of choroidal neovascularization (CNV). Wild type mice expressed murine EPOR (mWtEPOR) in RPE/choroids at baseline and had significantly increased serum EPO after laser treatment. To test the role of EPO signaling, we used human EPOR knock-in mice with the mWtEPOR gene replaced by either the human EPOR gene (hWtEPOR) or a mutated human EPOR gene
(hMtEPOR) in a laser-induced choroidal neovascularization (LCNV) model. Loss-of-function hWtEPOR mice have reduced downstream activation, whereas gain-of-function hMtEPOR mice have increased EPOR signaling. Compared to littermate controls (mWtEPOR), hMtEPOR with increased EPOR signaling developed larger CNV lesions. At baseline, hMtEPOR mice had increased numbers of macrophages, greater expression of macrophage markers F4/80 and CD206, and following laser injury, had greater expression of cytokines CCL2, CXCL10, CCL22, IL-6, and IL-10 than mWtEPOR controls. These data support a hypothesis that injury from age- and AMD-related changes in the RPE/choroid leads to choroidal neovascularization through EPOR-mediated cytokine production.

PMID: 29391474


Involvement of the ubiquitin-proteasome system in the expression of extracellular matrix genes in retinal pigment epithelial cells.

Ramos de Carvalho JE, Verwoert MT, Vogels IMC, Reits EA, Van Noorden CJF, Klaassen I, Schlingemann RO.

Abstract: Emerging evidence suggests that dysfunction of the ubiquitin-proteasome system is involved in the pathogenesis of numerous senile degenerative diseases including retinal disorders. The aim of this study was to assess whether there is a link between proteasome regulation and retinal pigment epithelium (RPE)-mediated expression of extracellular matrix genes. For this purpose, human retinal pigment epithelial cells (ARPE-19) were treated with different concentrations of transforming growth factor-β (TGFβ), connective tissue growth factor (CTGF), interferon-γ (IFNγ) and the irreversible proteasome inhibitor epoxomicin. First, cytotoxicity and proliferation assays were carried out. The expression of proteasome-related genes and proteins was assessed and proteasome activity was determined. Then, expression of fibrosis-associated factors fibronectin (FN), fibronectin EDA domain (FN EDA), metalloproteinase-2 (MMP-2), tissue inhibitor of metalloproteinases-1 (TIMP-1) and peroxisome proliferator-associated receptor-γ (PPARγ) was assessed. The proteasome inhibitor epoxomicin strongly arrested cell cycle progression and down-regulated TGFβ gene expression, which in turn was shown to induce expression of pro-fibrogenic genes in ARPE-19 cells. Furthermore, epoxomicin induced a directional shift in the balance between MMP-2 and TIMP-1 and was associated with down-regulation of transcription of extracellular matrix genes FN and FN-EDA and up-regulation of the anti-fibrogenic factor PPARγ. In addition, both CTGF and TGFβ were shown to affect expression of proteasome-associated mRNA and protein levels. Our results suggest a link between proteasome activity and pro-fibrogenic mechanisms in the RPE, which could imply a role for proteasome-modulating agents in the treatment of retinal disorders characterized by RPE-mediated fibrogenic responses.

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Models of retinal diseases and their applicability in drug discovery.

Malek G, Busik J, Grant MB, Choudhary M.

Abstract: The impact of vision debilitating diseases is a global public health concern, which will continue until effective preventative and management protocols are developed. Two retinal diseases responsible for the majority of vision loss in the working age adults and elderly populations are diabetic retinopathy (DR) and age-related macular degeneration (AMD), respectively. Model systems, which recapitulate aspects of human pathology, are valid experimental modalities that have contributed to the identification of signaling pathways involved in disease development and consequently potential therapies. Areas covered: The
pathology of DR and AMD, which serve as the basis for designing appropriate models of disease, is discussed. The authors also review in vitro and in vivo models of DR and AMD and evaluate the utility of these models in exploratory and pre-clinical studies. Expert opinion: The complex nature of non-Mendelian diseases such as DR and AMD has made identification of effective therapeutic treatments challenging. However, the authors believe that while in vivo models are often criticized for not being a ‘perfect’ recapitulation of disease, they have been valuable experimentally when used with consideration of the strengths and limitations of the experimental model selected and have a place in the drug discovery process.

PMID: 29382242

**Curr Mol Pharmacol. 2018 Jan 25. [Epub ahead of print]**

L-Sulforaphane confers protection against oxidative stress in an in vitro model of age-related macular degeneration.

Dulull NK, Dias DA, Thrimawithana TR, Kwa FAA.

**BACKGROUND:** In age-related macular degeneration, oxidative damage and abnormal neovascularization in the retina are caused by the upregulation of vascular endothelium growth factor and reduced expression of Glutathione-S-transferase genes. Current treatments are only palliative. Compounds from cruciferous vegetables (e.g. L-Sulforaphane) have been found to restore normal gene expression levels in diseases including cancer via the activity of histone deacetylases and DNA methyltransferases, thus retarding disease progression.

**OBJECTIVE:** To examine L-Sulforaphane as a potential treatment to ameliorate aberrant levels of gene expression and metabolites observed in age-related macular degeneration.

**METHOD:** The in vitro oxidative stress model of AMD was based on the exposure of Adult Retinal Pigment Epithelium-19 cell line to 200µM hydrogen peroxide. The effects of L-Sulforaphane on cell proliferation were determined by MTS assay. The role of GSTM1, VEGFA, DNMT1 and HDAC6 genes in modulating these effects were investigated using quantitative real-time polymerase chain reaction. The metabolic profiling of L-Sulforaphane-treated cells via gas-chromatography mass-spectrometry was established. Significant differences between control and treatment groups were validated using one-way ANOVA, student t test and post-hoc Bonferroni statistical tests (p<0.05).

**RESULTS:** L-Sulforaphane induced a dose-dependent increase in cell cell proliferation in the presence of hydrogen peroxide by upregulating Glutathione-S-Transferase µ1 gene expression. Metabolic profiling revealed that L-Sulforaphane increased levels of 2-monopalmitiglycerol, 9, 12, 15-((Z-Z-Z)-Octodecatrienoic acid, 2-[Bis(trimethylsilyl)amino]ethyl bis(trimethylsilyl)-phosphate and nonanoic acid but decreased β-alanine levels in the absence or presence of hydrogen peroxide, respectively.

**CONCLUSION:** This study supports the use of L-Sulforaphane to promote regeneration of retinal cells under oxidative stress conditions.

PMID: 29376497

**Epidemiology**

**Retina. 2018 Jan 31. [Epub ahead of print]**

SYSTEMIC BETA-BLOCKERS AND RISK OF PROGRESSION TO NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.
Kolomeyer AM, Maguire MG, Pan W, VanderBeek BL.

PURPOSE: To determine whether oral beta-blockers (BBs) are associated with the development of neovascular age-related macular degeneration (nAMD).

METHODS: Retrospective cohort study of patients from 2000 to 2014 using data from a large national U.S. insurer's administrative medical claims database. Patients with nonexudative AMD who initiated (index date) BB, a calcium channel blocker (CCB), an angiotensin-converting enzyme/angiotensin receptor blocker, or a diuretic. Patients were excluded for <2 years in the plan before the index date, any history of nAMD or diagnosis, or treatment for an ocular disease that could be confused with nAMD. Hazard of developing of nAMD was the main outcome measure. Primary analysis compared BB with CCB patients with BB versus the other classes as secondary analyses. In addition, a sensitivity analysis was performed between BB and CCB cohorts using 1:1 propensity score matching. Cox proportional hazard regression was performed to estimate the hazard ratio (HR) of developing nAMD at 90, 180, and 365 days for BB. Covariates of interest included demographic information, year of index date, number of antihypertensive medications, and other comorbid systemic conditions.

RESULTS: Eighteen thousand seven hundred and fifty-four BB patients and 12,784 CCB patients met criteria for inclusion. After controlling for covariates, patients on BB had a lower hazard for nAMD at both 90 and 180 days than patients on CCB (HRs: 0.67-0.71; P < 0.01 for both) and diuretics (HRs: 0.55-0.62; P < 0.01). Patients on BB versus angiotensin-converting enzyme/angiotensin receptor blocker at all time points and BB versus CCB and diuretics at 365 days did not have a significantly lower association with nAMD (HR: 0.73-0.85; P > 0.06 for all comparisons). A sensitivity analysis using propensity score matching yielded similar results with patients on BB significantly less likely to develop nAMD at 90 and 180 days (HR: 0.70-0.76; P < 0.049 for both) but not at 365 days (HR: 0.88; P = 0.30) compared with patients on CCB.

CONCLUSION: No evidence was found that BB usage increased the hazard for nAMD relative to other antihypertensive medications.

PMID: 29394237

**Genetics & gene therapy**

Ophthalmologica. 2018 Jan 26. [Epub ahead of print]

**Genetic Risk Factors Are Not Associated with Wet Age-Related Macular Degeneration Treatment Response to Ranibizumab.**

Chaudhary V, Brent M, Lam WC, Devenyi R, Teichman J, Mak MY, Kaur H, Barbosa J, Carter R, Farrokhyar F.

PMID: 29393246

Int Ophthalmol. 2018 Feb 1. [Epub ahead of print]

**Association of polymorphisms of complement factor I rs141853578 (G119R) with age-related macular degeneration in Iranian population.**

Bonyadi M, Norouzi N, Babaei E, Jabbarpoor Bonyadi MH, Javadzadeh A, Yaseri M, Soheilian M.

BACKGROUND: Age-related macular degeneration (AMD) is a complex disease, and recent studies have shown role of complement system genes in its development. Complement factor I regulates the complement pathways, and relationship between CFI polymorphisms and AMD is controversial. We evaluated the possible association of complement factor I rs141853578 (G119R) variation with advanced
AMD in Iranian patients.

MATERIALS AND METHODS: We included 371 case-control samples consisting of 220 advanced AMD patients and 151 genetically unrelated healthy controls. Extracted DNA samples amplified to obtain fragment including the polymorphic complement factor I rs141853578 (G119R) region.

RESULTS: The distribution of the genotypes was significantly different in the AMD patients compared to that of controls (p = 0.035). The TT genotype frequencies for CFI were significantly higher in AMD group (7.7 vs. 2%, OR 4.67, CI 1.33-16.45, p = 0.016). This significant difference was maintained after adjustment for the effects of age and gender (OR 5.09, CI 1.42-18.20, p = 0.012). The minor allele frequency (T allele) was also significantly higher in AMD patients compared to that of controls (29.3 vs. 21.5% OR 1.51, CI 1.07-2.13, p = 0.018).

CONCLUSION: Current study showed that CFI rs141853578 (G119R) is a risk factor for developing advanced type AMD. This study also suggests that the frequency of G119R polymorphism in our population is not as rare as reported from other populations.

PMID: 29392637


Myopia in Chinese families shows linkage to 10q26.13.

Musolf AM, Simpson CL, Long KA, Moiz BA, Lewis DD, Middlebrooks CD, Portas L, Murgia F, Ciner EB, Bailey-Wilson JE, Stambolian D.

PURPOSE: To determine genetic linkage between myopia and Han Chinese patients with a family history of the disease.

METHODS: One hundred seventy-six Han Chinese patients from 34 extended families were given eye examinations, and mean spherical equivalent (MSE) in diopters (D) was calculated by adding the spherical component of the refraction to one-half the cylindrical component and taking the average of both eyes. The MSE was converted to a binary phenotype, where all patients with an MSE of -1.00 D or less were coded as affected. Unaffected individuals had an MSE greater than 0.00 D (ages 21 years and up), +1.50 (ages 11-20), or +2.00 D (ages 6-10 years). Individuals between the given upper threshold and -1.00 were coded as unknown. Patients were genotyped on an exome chip. Three types of linkage analyses were performed: single-variant two-point, multipoint, and collapsed haplotype pattern (CHP) variant two-point.

RESULTS: The CHP variant two-point results identified a significant peak (heterogeneity logarithm of the odds [HLOD] = 3.73) at 10q26.13 in TACC2. The single-variant two-point and multipoint analyses showed highly suggestive linkage to the same region. The single-variant two-point results identified 25 suggestive variants at HTRA1, also at 10q26.13.

CONCLUSIONS: We report a significant genetic linkage between myopia and Han Chinese patients at 10q26.13. 10q26.13 contains several good candidate genes, such as TACC2 and the known age-related macular degeneration gene HTRA1. Targeted sequencing of the region is planned to identify the causal variant(s).

PMID: 29383007 PMCID: PMC5767476


Risk of macular degeneration affected by polymorphisms in Matrix metalloproteinase-2: A case-control study in Chinese Han population.
Cheng J, Hao X, Zhang Z.

Abstract: The purpose of this study was to investigate the correlation of single nucleotide polymorphisms (SNPs) in Matrix metalloproteinase -2 (MMP-2) gene and the risk of age-related macular degeneration (AMD) in Chinese Han population. A total of 126 AMD patients and 141 healthy controls participated in this study. Genotypes of MMP-2 gene polymorphisms were identified by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). χ² test was used to detect the differences of genotypes and alleles frequencies between case and control groups. Relative risk of AMD was evaluated by odds ratios (ORs) with 95% confidence intervals (CIs). Distribution of variant allele carriers (computed tomography+TT genotypes) of MMP-2 gene rs243865 SNP was significantly different between case and control groups, and might act as protective factors for the onset of AMD (P = .044, OR = 0.583, 95% CI = 0.344-0.987). Nevertheless, the T allele might reduce the AMD risk (P = .030, OR = 0.611, 95% CI = 0.390-0.956). However, no significant association existed between rs243865 and AMD risk in the subgroup analysis based on age. GA+AA genotypes of rs243866 SNP may associate with a decreased risk of AMD in the ages<65 years subgroup (P = .028, OR = 0.399, 95% CI = 0.174-0.915). MMP-2 gene rs243865 and rs243866 SNPs associated with the risk of AMD. Further studies should be performed to confirm the results.

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**Stem cells**

Stem Cells. 2018 Jan 27. [Epub ahead of print]

An Induced Pluripotent Stem Cell Patient Specific Model of Complement Factor H (Y402H) Polymorphism Displays Characteristic Features of Age-Related Macular Degeneration and Indicates a Beneficial Role for UV Light Exposure.

Anderson G, Bagnaninch P, McLeod A, Dhillon B.

PMID: 29377444

**Diet, lifestyle & low vision**

J Agric Food Chem. 2018 Feb 2. [Epub ahead of print]

Protective Effects of Blueberry Anthocyanins against H2O2-Induced Oxidative Injury in Human Retinal Pigment Epithelial Cells.


Abstract: Blueberry anthocyanins are considered to be protective for eye health due to their recognized antioxidant properties. In this study, blueberry anthocyanin extract (BAE), malvidin (Mv), malvidin-3-glucoside (Mv-3-glc), and malvidin-3-galactoside (Mv-3-gal) reduced H2O2-induced oxidative stress by decreasing the levels of reactive oxygen species and malondialdehyde and increasing the levels of superoxide dismutase, catalase, and glutathione peroxidase in human retinal pigment epithelial cells. BAE and anthocyanin standards enhanced cell viability from 63.69 ± 3.36% to 86.57 ± 6.92% (BAE), 115.72 ± 23.41% (Mv), 98.15 ± 9.39% (Mv-3-glc), and 127.97 ± 20.09% (Mv-3-gal) and significantly inhibited cell apoptosis (all P < 0.01). Mitogen-activated protein kinase pathways, including ERK1/2 and p38, were involved in the bioactivities. In addition, the anthocyanins decreased the vascular endothelial cell growth factor levels and activated Akt signal pathways. These combined results supported the hypothesis that blueberry anthocyanins could inhibit the induction and progression of age-related macular degeneration (AMD) through antioxidant mechanisms.

PMID: 29393642
Vision Screening in Adults Across the Life Span.

Cohen HS, Stitz J, Sangi-Haghpeykar H, Williams SP.

OBJECTIVES: The goal of this study was to determine whether adults across the life span differ in responses to quick vision screening and how those responses relate to adults’ use of specialized eye care.

METHODS: Subjects were 363 community-dwelling ambulatory adults, 21 to 95 years old, who were tested while they wore their corrective lenses during routine visits to a tertiary care facility. No subjects had known neurological impairments, age-related macular degeneration, or other significant eye disease. A wall-mounted Early Treatment in Diabetic Retinopathy Study chart was used.

RESULTS: Older adults 58 years old or older had significantly worse scores than younger adults. Scores did not differ between subjects who had been tested within or prior to the last 10 months. Older subjects had their vision tested significantly more recently than younger subjects.

CONCLUSIONS: Vision screening is quick, inexpensive, and easily performed by ancillary staff, and it may provide the physician with useful additional information for treatment planning.

PMID: 29394428

The economic impact of sight loss and blindness in the UK adult population.

Pezzullo L, Streatfeild J, Simkiss P, Shickle D.

BACKGROUND: To quantify the economic impact of sight loss and blindness in the United Kingdom (UK) population, including direct and indirect costs, and its burden on health.

METHODS: Prevalence data on sight loss and blindness by condition, Census demographic data, data on indirect costs, and healthcare cost databases were used. Blindness was defined as best corrected visual acuity (BCVA) of < 6/60, and sight loss as BCVA < 6/12 to 6/60, in the better-seeing eye.

RESULTS: Sight loss and blindness from age-related macular degeneration (AMD), cataract, diabetic retinopathy, glaucoma and under-corrected refractive error are estimated to affect 1.93 (1.58 to 2.31) million people in the UK. Direct health care system costs were £3.0 billion, with inpatient and day care costs comprising £735 million (24.6%) and outpatient costs comprising £771 million (25.8%). Indirect costs amounted to £5.65 (5.12 to 6.22) billion. The value of the loss of healthy life associated with sight loss and blindness was estimated to be £19.5 (15.9 to 23.3) billion or £7.2 (5.9 to 8.6) billion, depending on the set of disability weights used. For comparison with other published results using 2004 disability weights and the 2008 estimates, the total economic cost of sight loss and blindness was estimated to be £28.1 (24.0 to 32.5) billion in 2013. Using 2010 disability weights, the estimated economic cost of sight loss and blindness was estimated to be £15.8 (13.5 to 18.3) billion in 2013.

CONCLUSIONS: The large prevalence of sight loss and blindness in the UK population imposes significant costs on public funds, private expenditure, and health. Prevalence estimates relied on dated epidemiological studies and may not capture recent advances in treatment, highlighting the need for population-based studies that track the prevalence of sight-impairing eye conditions and treatment effects over time.

PMID: 29382329