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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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## Drug treatment

**J Ocul Pharmacol Ther. 2014 Feb 19. [Epub ahead of print]**

### **Aflibercept in the Treatment of Neovascular Age-Related Macular Degeneration in Previously Treated Patients.**

Hall LB, Zebardast N, Huang JJ, Adelman RA.

**Abstract Purpose:** To study the visual outcomes and change in central macular thickness (CMT) in patients with neovascular age-related macular degeneration (AMD) who were previously treated with ranibizumab (Lucentis) and/or bevacizumab (Avastin) and were subsequently switched to aflibercept (VEGF Trap-Eye; Eylea).

**Methods:** Retrospective study of patients who received intravitreal aflibercept from December 2011 to December 2012 and had previous anti-vascular endothelial growth factor treatment for AMD. The main outcome measures were best-corrected visual acuity (BCVA) and CMT as measured by optical coherence tomography.

**Results:** The study population included 30 patients aged  $80.4 \pm 1.45$  (mean  $\pm$  SEM) who received  $6.27 \pm 0.37$  (range 4-11) aflibercept injections. Eighteen patients had previously received only bevacizumab ( $12.4 \pm 2.18$  injections), 2 had received only ranibizumab ( $19 \pm 6$  injections), and 10 had received both ranibizumab and bevacizumab (mean 19.3 injections). BCVA logMAR at the initial visit (aflibercept initiation) was  $0.506 \pm 0.054$  (mean VA 20/64), and then, follow ups at 1-month  $0.504 \pm 0.055$  (20/64)  $P=0.903$ , 3-months  $0.458 \pm 0.061$  (20/57)  $P=0.112$ , 6-months  $0.413 \pm 0.071$  (20/52)  $P=0.036$ , and 12-months  $0.521 \pm 0.076$  (20/66)  $P=0.836$ . CMT at the initial visit was  $261 \pm 10.9$ , and then, at 1-month  $238 \pm 12.4$   $P=0.021$ , 3-months  $245 \pm 10.6$   $P=0.102$ , 6-months  $245 \pm 10.4$   $P=0.099$ , and 12-months  $237 \pm 10.2$   $P=0.012$ . Results were similar in a subset of patients ( $n=15$ ) with central macular edema or submacular fluid at aflibercept initiation. While on aflibercept, 2 patients developed intraocular pressure increases that required treatment.

**Conclusions:** These findings demonstrate a significant decrease in CMT but no statistically significant improvement in BCVA through the 12-month follow up in patients previously treated who were switched to aflibercept for AMD. Patients may develop ocular hypertension after multiple aflibercept injections.

PMID: 24552305 [PubMed - as supplied by publisher]

**ISRN Ophthalmol. 2013 Aug 29;2013:151027. doi: 10.1155/2013/151027. eCollection 2013.**

### **Bevacizumab versus Ranibizumab on As-Needed Treatment Regimen for Neovascular Age-Related Macular Degeneration in Turkish Patients.**

Ozkaya A, Alkin Z, Karakucuk Y, Yasa D, Yazici AT, Demirok A.

**Purpose:** To compare the efficacy of intravitreal bevacizumab versus ranibizumab in the treatment of neovascular age-related macular degeneration (nAMD).

**Methods:** Retrospective, comparative study. The newly diagnosed nAMD patients who were treated with intravitreal bevacizumab or ranibizumab on an as-needed treatment regimen were included in the study. Main outcome measures were the change in best corrected visual acuity (BCVA), and central retinal thickness (CRT). Secondary outcome measures were the number of injections, and complications.

**Results:** A total of 154 patients were included in the study. Bevacizumab group consisted of 79 patients, and ranibizumab group consisted of 74 patients. Mean follow-up time was 18.9 months, and 18.3 months in the bevacizumab and ranibizumab groups, respectively. There was not a significant difference between the two groups regarding the change in BCVA and CRT at all time points ( $P > 0.05$  for all). The mean number of injections at month 12 was 4.8 and 4.7 in bevacizumab and ranibizumab groups, respectively ( $P > 0.05$ ). No serious complications were detected in any of the groups.

**Conclusion:** Both of the bevacizumab and ranibizumab found to be effective in the treatment of nAMD in regards of functional and anatomical outcomes with similar number of treatments and similar side effects.

PMID: 24558597 [PubMed]

**Expert Opin Emerg Drugs. 2014 Mar;19(1):157-64. doi: 10.1517/14728214.2014.884559.**

**Emerging treatments for wet age-related macular degeneration.**

Smith AG, Kaiser PK.

**Introduction:** Wet or exudative age-related macular degeneration (AMD) is the leading cause of blindness in the United States for individuals over the age of 65 years. Wet AMD is characterized by the formation of choroidal neovascularization, which can lead to edema, hemorrhage and scarring of the macula. This leads to metamorphopsia and vision loss. Without treatment, the loss of vision is permanent. The current gold standard treatment of wet AMD consists of intravitreal injections of anti-vascular endothelial growth factor (VEGF) medications.

**Areas covered:** Numerous new therapies in the drug pipeline aim at addressing limitations of current treatments. Future therapies involve novel compounds that attack different parts of the VEGF cascade, novel delivery systems aimed at reducing the frequency of intraocular injections, combination therapies and the use of radiation in conjunction with intravitreal therapies.

**Expert opinion:** Limitations of current treatments include the need for repeated injections, the high financial costs and treatment burdens of repeated injections, the risk of adverse ocular and systemic adverse events, and the inability to completely reverse the disease process of wet AMD. There are many new therapies and approaches in the pipeline which hold promise for improving the treatment of wet AMD.

PMID: 24555421 [PubMed - in process]

**Ophthalmology. 2014 Feb 14. pii: S0161-6420(13)01161-5. doi: 10.1016/j.ophtha.2013.11.035. [Epub ahead of print]**

**The IL-8, VEGF, and CFH Polymorphisms and Bevacizumab in Age-related Macular Degeneration. [Report]**

Hautamäki A, Kivioja J, Seitsonen S, Savolainen ER, Liinamaa MJ, Luoma A, Järvelä I, Immonen I.

PMID: 24534755 [PubMed - as supplied by publisher]

**J Fr Ophtalmol. 2014 Feb 14. pii: S0181-5512(14)00016-3. doi: 10.1016/j.jfo.2013.08.005. [Epub ahead of print]**

**[Relationship between intravitreal anti-VEGF therapy and subretinal hemorrhage in patients with exudative age-related macular degeneration.] [Article in French]**

Kauffmann Y, Isaico R, Lefebvre A, Bron AM, Creuzot-Garcher C.

**PURPOSE:** To assess and compare frequencies and incidence rates of subretinal hemorrhage (SRH) after intravitreal anti-VEGF injections and spontaneous SRH in patients with exudative age-related macular degeneration (AMD).

**PATIENTS AND METHODS:** This retrospective monocentric study included 1079 patients followed for exudative AMD in the ophthalmology department of the university hospital of Dijon from January 2007 to July 2012. For each SRH occurring during this period, the number of previous treatments with intravitreal anti-VEGF was determined, as well as the time between the last injection and the hemorrhage. The SRH was considered as an adverse effect of the anti-VEGF injection if it occurred within 2 months after the last IVT (post-IVT SRH). Frequencies and incidence rates of post-IVT SRH and spontaneous SRH were calculated.

**RESULTS:** Sixty-six SRH's occurred during the study period with a total frequency of 6.12% (CI95% [4.69-7.55]). Frequencies of spontaneous and post-IVT SRH were respectively 5.65% (CI95% [4.28-7.03]) and 0.46% (CI95% [0.06-0.87]), representing a 12.2 ratio. Post-IVT SRH incidence was 8.3/1000 patient-years (CI95% [1.0-15.5]) and the spontaneous SRH incidence rate was 11.6/1000 patient-years (CI95% [8.3-14.8]), (P=0.472). The incidence rate ratio was 0.72 (CI95% [0.29-1.78]).

**CONCLUSION:** This study did not show a statistically significant change in the incidence of SRH after intravitreal anti-VEGF therapy. The benefit/risk ratio of intravitreal anti-VEGF injections for exudative AMD remains high.

PMID: 24534623 [PubMed - as supplied by publisher]

**Am J Ophthalmol. 2014 Feb 13. pii: S0002-9394(14)00082-8. doi: 10.1016/j.ajo.2014.02.019. [Epub ahead of print]**

**A randomized trial to assess functional and structural effects of ranibizumab versus laser in diabetic macular edema (The LUCIDATE study).**

Comyn O, Sivaprasad S, Peto T, Neveu MM, Holder GE, Xing W, Bunce CV, Patel PJ, Egan CA, Bainbridge JW, Hykin PG.

**PURPOSE:** To compare the functional and structural effects of ranibizumab versus macular laser therapy in patients with center-involving diabetic macular edema **DESIGN:** Prospective, randomized, single-masked clinical trial

**METHODS:** Setting - single center

**STUDY POPULATION:** - 33 eyes of 33 patients with center-involving diabetic macular edema, with best corrected visual acuity 55-79 Early Treatment Diabetic Retinopathy Study letters at baseline, completing the 48 week study period

**INTERVENTION:** - subjects were randomized 2:1 to ranibizumab, three loading doses then retreatment four-weekly as required; or macular laser therapy at baseline, repeated as required every twelve weeks. Exploratory outcome measures - Structural imaging studies: greatest linear dimension and area of foveal avascular zone, perifoveal capillary dropout grade; presence of morphological features of diabetic macular edema on Spectralis™ optical coherence tomography. Functional measures: visual acuity; retinal sensitivity

in central 4° and 12° on microperimetry; color contrast sensitivity protan and tritan thresholds; pattern and full field electroretinogram amplitudes and implicit times; multifocal electroretinogram amplitude distribution. These are reported at 12, 24 and 48 weeks.

**RESULTS:** Ranibizumab treated subjects gained 6.0 letters vs. 0.9 letters lost for laser, demonstrated improved tritan and protan color contrast thresholds and improved retinal sensitivity. Electrophysiological function also improved after ranibizumab therapy. No safety issues were evident. Retinal thickness reduction and structural improvement in optical coherence tomography features of diabetic macular edema was better seen with ranibizumab therapy than in the laser group. There was no evidence of progressive ischemia with ranibizumab therapy.

**CONCLUSIONS:** Ranibizumab therapy in the treatment of diabetic macular edema appears to improve retinal function and structure as demonstrated by this evaluation of different assessment modalities.

PMID: 24531025 [PubMed - as supplied by publisher]

## Other treatment & diagnosis

**Contemp Clin Trials. 2014 Feb 13. pii: S1551-7144(14)00023-8. doi: 10.1016/j.cct.2014.02.003. [Epub ahead of print]**

**Randomized trial of the ForeseeHome monitoring device for early detection of neovascular age-related macular degeneration. The HOme Monitoring of the Eye (HOME) study design - HOME Study report number 1.**

Chew EY, Clemons TE, Bressler SB, Elman MJ, Danis RP, Domalpally A, Heier J, Kim JE, Garfinkel R; Appendix 1 for AREDS2-HOME Study Research Group.

### Abstract

**OBJECTIVE:** To evaluate the effects of a home-monitoring device with tele-monitoring compared with standard care in detection of progression to choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD), the leading cause of blindness in the US.

**PATIENTS AND METHODS:** Participants, aged 53 to 90years, at high risk of developing CNV associated with AMD were recruited to the HOme Monitoring of Eye (HOME) Study, an unmasked, multi-center, randomized trial of the ForeseeHome (FH) device plus standard care vs. standard care alone. The FH device utilizes preferential hyperacuity perimetry and tele-monitoring to detect changes in vision function associated with development of CNV, potentially prior to symptom and visual acuity loss. After establishing baseline measurements, subsequent changes on follow-up are detected by the device, causing the monitoring center to alert the clinical center to recall participants for an exam. Standard care consists of instructions for self-monitoring visual changes with subsequent self-report to the clinical center. The primary objective of this study is to determine whether home monitoring plus standard care in comparison with standard care alone, results in earlier detection of incident CNV with better present visual acuity. The primary outcome is the decline in visual acuity at CNV diagnosis from baseline. Detection of CNV prior to substantial vision loss is critical as vision outcome following anti-angiogenic therapy is dependent on the visual acuity at initiation of treatment.

**DISCUSSION:** HOME Study is the first large scale study to test the use of home tele-monitoring system in the management of AMD patients.

PMID: 24530651 [PubMed - as supplied by publisher]

**Invest Ophthalmol Vis Sci. 2014 Feb 18. pii: iovs.13-12375v1. doi: 10.1167/iov.13-12375. [Epub ahead of print]**

**Misclassification Can Explain Most Apparent Regression of Age-Related Macular Degeneration: Results from Multi-State Models with Misclassification.**

Gangnon R, Lee KE, Klein BE, Iyengar SK, Sivakumaran TA, Klein R.

**Purpose:** To investigate the impact of misclassification of age-related macular degeneration (AMD) on the baseline intensity and estimated effects of age, sex, and the Y402H variant in the complement factor H (CFH) gene on incidence, progression, and regression of AMD.

**Methods:** The Beaver Dam Eye Study, a longitudinal population-based study of age-related eye diseases conducted in the city and township of Beaver Dam, Wisconsin, performed examinations every 5 years over a 20-year period (1988-1990 through 2008-2010). Study participants (N=4379) aged 43 to 86 years at the baseline examination had retinal photographs taken at baseline and up to 4 subsequent examinations. Multistate models with misclassification in continuous time were used to model the effects of age, sex and CFH genotype on incidence, progression and regression of AMD and mortality.

**Results:** After accounting for AMD misclassification, the occurrence of any AMD regression was rare (1-4%), while it was relatively common (14-21%) in models that do not account for misclassification. Failure to account for misclassification attenuated estimated age effects on incidence and progression to moderately severe early AMD and estimated CFH effects on incidence and progressions to moderately severe and severe early AMD.

**Conclusions:** Apparent regression of AMD can largely, if not completely, be explained by misclassification. Estimated age effects on incidence and progression to moderately severe early AMD and estimated CFH effects on incidence and progressions to moderately severe and severe early AMD were attenuated in multistate models that did not account for misclassification.

PMID: 24550369 [PubMed - as supplied by publisher]

**Invest Ophthalmol Vis Sci. 2014 Feb 18. pii: iovs.13-13745v1. doi: 10.1167/iov.13-13745. [Epub ahead of print]**

**Diagnostic Sensitivity and Specificity of Dark Adaptometry for detection of Age-Related Macular Degeneration.**

Jackson GR, Scott IU, Kim IK, Quillen DA, Iannaccone A, Edwards JG.

**Purpose:** Difficulty with night vision is a common complaint of patients with age-related macular degeneration (AMD). Consistent with this complaint, dark adaptation (DA) is substantially impaired in these patients. Because of the severity of the deficit, measurement of DA has been suggested as a means for the diagnosis of AMD. Previous methods for measurement of DA were time intensive (> 30 min) which made them unsuitable for clinical use. This study evaluates a rapid DA test ( $\leq 6.5$  min) for the detection of AMD.

**Methods:** DA was measured using the AdaptDx dark adaptometer in two groups: subjects with normal retinal health and subjects with AMD. Subjects were assigned to their group based on clinical examination and grading of fundus photographs. Subjects were classified as having DA consistent with normal retinal health (rod intercept  $\leq 6.5$  min) or having dark adaptation consistent with AMD (rod intercept > 6.5 min).

**Results:** The eligible sample for analysis included 21 normal adults and 127 AMD patients. The rapid test was found to have a diagnostic sensitivity of 90.6% ( $p < 0.001$ ) and specificity of 90.5% ( $p < 0.027$ ). Thus abnormal DA was detected in 115 of 127 AMD patients, and normal DA was found in 19 of 21 normal adults.

Conclusions: The high diagnostic sensitivity and specificity compares favorably to long duration research methods for the measurement of DA, and slit lamp biomicroscopy performed by a retina specialist. These results suggest that a rapid DA test is useful for the detection of AMD.

PMID: 24550363 [PubMed - as supplied by publisher]

**Invest Ophthalmol Vis Sci. 2014 Feb 18. pii: iovs.13-12833v1. doi: 10.1167/iov.13-12833. [Epub ahead of print]**

**Porous Poly( $\epsilon$ -caprolactone) Scaffolds for Retinal Pigment Epithelium Transplantation.**

McHugh KJ, Tao SL, Saint-Geniez M.

**Purpose:** Retinal pigment epithelium (RPE) transplantation is a promising strategy for the treatment of dry age-related macular degeneration (AMD). However, previous attempts at sub-retinal RPE cell transplantation have experienced limited success due to poor adhesion, organization, and function on aged or diseased Bruch's membrane. Instead, cell-based strategies may benefit from a synthetic scaffold that mimics the functions of healthy Bruch's membrane to promote the formation of a functional RPE monolayer while maintaining metabolite exchange between the vasculature and outer retina.

**Methods:** This study evaluated the behavior of human RPE on nanopatterned porous poly( $\epsilon$ -caprolactone) (PCL) films as a potential scaffold for therapeutic transplantation. Fetal human RPE (fhRPE) were cultured on porous PCL, non-porous PCL, or Costar® porous polyester transwells for up to 8 weeks and assessed using light microscopy, fluorescent microscopy, transepithelial resistance, quantitative PCR, ELISAs, and phagocytosis assays.

**Results:** fhRPE on porous PCL displayed improved markers of maturity and function compared to both porous polyester transwells and non-porous PCL including pigmentation, increased cell density, superior barrier function, upregulation of RPE-specific genes, and polarized growth factor secretion.

**Conclusions:** This study indicates that porous PCL is an attractive scaffold for RPE transplantation. In addition to being biocompatible with the sub-retinal space, porous PCL also allows for trans-scaffold metabolite transport and significantly improves RPE cell behavior compared to non-porous PCL or porous polyester transwells.

PMID: 24550370 [PubMed - as supplied by publisher]

**Am J Ophthalmol. 2014 Feb 13. pii: S0002-9394(14)00070-1. doi: 10.1016/j.ajo.2014.02.007. [Epub ahead of print]**

**Management of thick submacular hemorrhage with subretinal tissue plasminogen activator and pneumatic displacement for age-related macular degeneration.**

Chang W, Garg SJ, Maturi R, Hsu J, Sivalingam A, Gupta SA, Regillo CD, Ho AC.

**PURPOSE:** To evaluate the outcome of pars plana vitrectomy, subretinal tissue plasminogen activator (t-PA) infusion and intraocular gas tamponade with and without post surgical anti-vascular endothelial growth factor (VEGF) injection for thick submacular hemorrhage due to exudative age-related macular degeneration (AMD) **DESIGN:** Retrospective, comparative, interventional case series.

**METHODS:** Setting: Two retina referral centers. Patient population: 101 eyes of 101 patients with neovascular AMD with thick submacular hemorrhage who underwent surgical displacement of the hemorrhage with or without post-operative anti-VEGF injections. Main outcome measures included degree of blood displacement, best and final postoperative visual acuity (VA), and adverse events. Snellen acuity was converted to logMAR for statistical analysis.

**RESULTS:** All patients were followed for a minimum of 3 months (mean 15.3 months, range 3 to 70 months). In 83 (82%) of 101 eyes, the procedure resulted in complete hemorrhage displacement from the fovea. Mean pre-operative VA was 20/2255 (2.05 logMAR). The acuity significantly improved to 20/893 (1.65 logMAR) at month 1 ( $p<0.001$ ) at month 1, 20/678 (1.53 logMAR) at month 3 ( $p<0.001$ ), and 20/1150 (1.76 logMAR) at month 12 ( $p=0.002$ ). Best post-operative visual acuity improved by at least one line in 83 (82%) of 101 eyes and 19.6% of eyes gained 3 lines or more at month 3. The visual acuity of the group of eyes that received post-operative anti-VEGF injection ( $n=39$ ) showed greater visual acuity improvement 6 months postoperatively compared to the group of eyes that did not receive post-operative anti-VEGF. Postoperative complications included vitreous hemorrhage in 2 eyes, rhegmatogenous retinal detachment in 4 eyes, and recurrent thick subretinal hemorrhage in 6 eyes.

**CONCLUSIONS:** Vitrectomy with subretinal t-PA injection and gas tamponade was found to be relatively effective for displacement of thick submacular hemorrhage with a significant improvement in visual acuity. There is a loss of acuity over time; the addition of post-operative anti-VEGF therapy may help maintain the visual acuity gains.

PMID: 24531021 [PubMed - as supplied by publisher]

**J Vis. 2014 Feb 17;14(2). pii: 12. doi: 10.1167/14.2.12.**

**A new theoretical approach to improving face recognition in disorders of central vision: Face caricaturing.**

Irons J, McKone E, Dumbleton R, Barnes N, He X, Provis J, Ivanovici C, Kwa A.

**Abstract:** Damage to central vision, of which age-related macular degeneration (AMD) is the most common cause, leaves patients with only blurred peripheral vision. Previous approaches to improving face recognition in AMD have employed image manipulations designed to enhance early-stage visual processing (e.g., magnification, increased HSF contrast). Here, we argue that further improvement may be possible by targeting known properties of mid- and/or high-level face processing. We enhance identity-related shape information in the face by caricaturing each individual away from an average face. We simulate early- through late-stage AMD-blur by filtering spatial frequencies to mimic the amount of blurring perceived at approximately 10° through 30° into the periphery (assuming a face seen premagnified on a tablet computer). We report caricature advantages for all blur levels, for face viewpoints from front view to semiprofile, and in tasks involving perceiving differences in facial identity between pairs of people, remembering previously learned faces, and rejecting new faces as unknown. Results provide a proof of concept that caricaturing may assist in improving face recognition in AMD and other disorders of central vision.

PMID: 24534882 [PubMed - in process]

**Exp Eye Res. 2014 Feb 12. pii: S0014-4835(14)00038-4. doi: 10.1016/j.exer.2014.02.001. [Epub ahead of print]**

**Cholesterol-poly(ethylene) glycol nanocarriers for the transscleral delivery of sirolimus.**

Elsaid N, Somavarapu S, Jackson TL.

**Abstract:** The aim of this study was to prepare and characterize cholesterol-poly(ethylene) glycol (chol-PEG) nanocarriers of two different molecular weights (1 and 5 kDa) and to determine their effect on the transscleral retention and permeation of a lipophilic multi-therapeutic agent, sirolimus (rapamycin), with potential application in angiogenic and immunogenic ocular diseases. Sirolimus-containing nanocarriers were prepared using the thin-film hydration method and characterized for their physicochemical properties including size, drug entrapment (EE) and loading (DL) efficiencies, stability, surface charge, morphology,

critical micelle concentration (CMC) and thermal properties. Ussing chambers were used to determine the retention and permeability of sirolimus-containing nanocarriers in porcine sclera followed by ultrastructural tissue examination. Sirolimus-containing nanocarriers had an average size of 11.7 nm (chol-PEG 1 kDa) and 13.8 nm (chol-PEG 5 kDa) and zeta potentials of 0.41 and -1.05, respectively. Both nanocarriers had similar transscleral permeabilities (chol-PEG 1 kDa  $6.44 \times 10^{-7}$  and 5 kDa  $6.16 \times 10^{-7}$  cm<sup>2</sup>s<sup>-1</sup>), and very high scleral retention compared with a free solution of sirolimus (chol-PEG 1 kDa 16.9 µg/g; chol-PEG 5 kDa 7.48 µg/g; free sirolimus 0.57 µg/g). The DL (EE) for chol-PEG 1 and 5 kDa were 2.93% (77.4%) and 3.10% (81.6%), respectively. The CMC values for the nanocarriers were similar to those previously reported in literature ( $3.85 \times 10^{-7}$  M for chol-PEG 1 kDa;  $4.26 \times 10^{-7}$  M for chol-PEG 5 kDa). In conclusion, chol-PEG nanocarriers successfully loaded sirolimus and resulted in scleral permeation and high retention, which shows potential utility for the topical delivery of lipophilic ocular drugs.

PMID: 24530465 [PubMed - as supplied by publisher]

**Surv Ophthalmol. 2014 Mar-Apr;59(2):260. doi: 10.1016/j.survophthal.2013.06.002.**

**Vitreomacular adhesion and neovascular age-related macular degeneration.**

Katz MS, Jonna G, Fingerhut DE.

PMID: 24529313 [PubMed - in process]

**Telemed J E Health. 2014 Feb 14. [Epub ahead of print]**

**A Novel Tele-Eye Protocol for Ocular Disease Detection and Access to Eye Care Services.**

Maa AY, Evans C, Delaune WR, Patel PS, Lynch MG.

**Abstract Background:** Telemedicine can improve access to care, especially for rural patients, and ophthalmology is a field that lends itself readily to telemedicine because interpretation of photographs is a routine part of diagnosing eye disease and patient care. We developed a novel tele-eye protocol based on diabetic teleretinal screening. We performed a feasibility study to see if our tele-eye program was comparable to the gold standard face-to-face eye exam.

**Materials and Methods:** Fifty-two subjects underwent the tele-eye protocol and then received a face-to-face exam. A masked reader reviewed the tele-eye data remotely and developed an impression and plan for the patient. The provider assessments from the face-to-face exams and the tele-eye exams were compared. Sensitivity, specificity, and percentage agreement were calculated for the tele-eye protocol, focusing on the most common age-related eye diseases: cataract, macular degeneration, and glaucoma. The difference between the autorefraction and manifest eyeglass prescription was calculated.

**Results:** The pilot study showed excellent percentage agreement between the screening protocol and the face-to-face exam. The percentage agreement for cataract was 100%, that for macular degeneration was 96%, and that for glaucoma suspect was 87%. The difference between the autorefraction's eyeglass prescription and the final manifest refraction was within American National Standards Institute for lens manufacturing guidelines.

**Conclusions:** The initial data suggest that the tele-eye program is feasible to execute and appears fairly accurate when compared with the gold standard face-to-face eye exam. However, the study is significantly limited by the small sample size. This pilot provides justification of a much larger study of a similar design.

PMID: 24527668 [PubMed - as supplied by publisher]

## Pathogenesis

PLoS One. 2014 Feb 18;9(2):e89150. doi: 10.1371/journal.pone.0089150. eCollection 2014.

### **Fucoidan reduces secretion and expression of vascular endothelial growth factor in the retinal pigment epithelium and reduces angiogenesis in vitro.**

Dithmer M, Fuchs S, Shi Y, Schmidt H, Richert E, Roeder J, Klettner A.

**Abstract:** Fucoidan is a polysaccharide isolated from brown algae which is of current interest for anti-tumor therapy. In this study, we investigated the effect of fucoidan on the retinal pigment epithelium (RPE), looking at physiology, vascular endothelial growth factor (VEGF) secretion, and angiogenesis, thus investigating a potential use of fucoidan for the treatment of exudative age-related macular degeneration. For this study, human RPE cell line ARPE-19 and primary porcine RPE cells were used, as well as RPE/choroid perfusion organ cultures. The effect of fucoidan on RPE cells was investigated with methyl thiazolyl tetrazolium - assay, trypan blue exclusion assay, phagocytosis assay and a wound healing assay. VEGF expression was evaluated in immunocytochemistry and Western blot, VEGF secretion was evaluated in ELISA. The effect of fucoidan on angiogenesis was tested in a Matrigel assay using calcein-AM vital staining, evaluated by confocal laser scanning microscopy and quantitative image analysis. Fucoidan displays no toxicity and does not diminish proliferation or phagocytosis, but reduces wound healing in RPE cells. Fucoidan decreases VEGF secretion in RPE/choroid explants and RPE cells. Furthermore, it diminishes VEGF expression in RPE cells even when co-applied with bevacizumab. Furthermore, fucoidan reduces RPE-supernatant- and VEGF-induced angiogenesis of peripheral endothelial cells. In conclusion, fucoidan is a non-toxic agent that reduces VEGF expression and angiogenesis in vitro and may be of interest for further studies as a potential therapy against exudative age-related macular degeneration.

PMID: 24558482 [PubMed - in process]

FASEB J. 2014 Feb 20. [Epub ahead of print]

### **Progressive dysfunction of the retinal pigment epithelium and retina due to increased VEGF-A levels.**

Ablonczy Z, Dahrouj M, Marneros AG.

**Abstract:** Patients with nonexudative ("dry") age-related macular degeneration (AMD) frequently also develop neovascular ("wet") AMD, suggesting a common pathomechanism. Increased vascular endothelial growth factor A (VEGF-A) has been implicated in the pathogenesis of choroidal neovascularization (CNV) in neovascular AMD, while its role in nonexudative AMD that manifests with progressive retinal pigment epithelium (RPE) and photoreceptor degeneration is not well defined. Mice with overall increased VEGF-A levels develop progressive morphological features of both forms of AMD, suggesting that an increase in VEGF-A has a direct age-dependent adverse effect on RPE and photoreceptor function independently of its CNV-promoting proangiogenic effect. Here we provide evidence for this hypothesis and show that morphological RPE abnormalities and retinal thinning in mice with increased VEGF-A levels correlate with progressive age-dependent attenuation of visual function with abnormal electroretinograms and reduced retinal rhodopsin levels. Retinoid profiling revealed a progressive reduction of 11-cis and all-trans retinal in the retinas of these mice, consistent with an impaired retinoid transport between the RPE and photoreceptors. These findings suggest that increased VEGF-A leads to an age-dependent RPE and retinal dysfunction that occurs also at sites where no CNV lesions form. The data support a central role of increased VEGF-A not only in the pathogenesis of neovascular but also of nonexudative AMD.-Ablonczy, Z., Dahrouj, M., Marneros, A. G. Progressive dysfunction of the retinal pigment epithelium and retina due to increased VEGF-A levels.

PMID: 24558195 [PubMed - as supplied by publisher]

**Br J Ophthalmol. 2014 Feb 19. doi: 10.1136/bjophthalmol-2013-304226. [Epub ahead of print]**

**Internal structure consistent with remodelling in very small drusen, revealed by filipin histochemistry for esterified cholesterol.**

Rudolf M, Seckerdieck K, Grisanti S, Curcio CA.

**BACKGROUND/AIMS:** Drusen, the pathognomonic lesion of age-related macular degeneration, are dynamic and undergo both growth and regression. Using histochemistry to localise esterified cholesterol (EC), we investigated small drusen to discover signs of dynamism.

**METHODS:** Flat mounts of Bruch's membrane were prepared from peripheral retinas of six donor eyes without chorioretinal pathology that were preserved within 6 h of death. Tissues were pretreated with ethanol to extract native unesterified cholesterol, incubated with cholesterol esterase and stained with filipin to bind unesterified cholesterol that was newly released by hydrolysis. Tissues were imaged with wide-field epifluorescence microscopy. Diameters were measured and internal substructures (shells, lakes) assessed using previous descriptors.

**RESULTS:** Of 676 drusen with mean diameter of 26.87  $\mu\text{m}$ , 41.6% were stained homogeneously and 45.7% had lakes of pooled EC. Clusters of 2-7 drusen with similar staining patterns accounted for 25.3% of drusen. Increased EC content near the druse rim (shells) occurred in 10.5%.

**CONCLUSIONS:** Over half of very small drusen at the edge of clinical detectability have evidence for internal remodelling, suggesting that both formative and removal events are present early in the druse lifecycle.

PMID: 24554738 [PubMed - as supplied by publisher]

**Proc Natl Acad Sci U S A. 2014 Feb 18. [Epub ahead of print]**

**Suppressing thyroid hormone signaling preserves cone photoreceptors in mouse models of retinal degeneration.**

Ma H, Thapa A, Morris L, Redmond TM, Baehr W, Ding XQ.

**Abstract:** Cone phototransduction and survival of cones in the human macula is essential for color vision and for visual acuity. Progressive cone degeneration in age-related macular degeneration, Stargardt disease, and recessive cone dystrophies is a major cause of blindness. Thyroid hormone (TH) signaling, which regulates cell proliferation, differentiation, and apoptosis, plays a central role in cone opsin expression and patterning in the retina. Here, we investigated whether TH signaling affects cone viability in inherited retinal degeneration mouse models. Retinol isomerase RPE65-deficient mice [a model of Leber congenital amaurosis (LCA) with rapid cone loss] and cone photoreceptor function loss type 1 mice (severe recessive achromatopsia) were used to determine whether suppressing TH signaling with antithyroid treatment reduces cone death. Further, cone cyclic nucleotide-gated channel B subunit-deficient mice (moderate achromatopsia) and guanylate cyclase 2e-deficient mice (LCA with slower cone loss) were used to determine whether triiodothyronine (T3) treatment (stimulating TH signaling) causes deterioration of cones. We found that cone density in retinol isomerase RPE65-deficient and cone photoreceptor function loss type 1 mice increased about sixfold following antithyroid treatment. Cone density in cone cyclic nucleotide-gated channel B subunit-deficient and guanylate cyclase 2e-deficient mice decreased about 40% following T3 treatment. The effect of TH signaling on cone viability appears to be independent of its regulation on cone opsin expression. This work demonstrates that suppressing TH signaling in retina dystrophy mouse models is protective of cones, providing insights into cone preservation and therapeutic interventions.

PMID: 24550448 [PubMed - as supplied by publisher]

Sci Rep. 2014 Feb 18;4:4114. doi: 10.1038/srep04114.

### **Does DcR1 (TNF-related apoptosis-inducing ligand Receptor 3) have any role in human AMD pathogenesis?**

Anand A, Sharma NK, Singh R, Gupta A, Prabhakar S, Jindal N, Bhatt AK, Sharma SK, Gupta PK.

**Abstract:** It has been postulated that there is a link between age related degenerative diseases and cancer. The TNF-related apoptosis-inducing ligand (TRAIL) has been shown to selectively kill tumor cells by binding to pro-apoptotic and anti-apoptotic receptors. Our aim was to study the levels of anti-apoptotic receptor (DcR1) in age related macular degeneration (AMD) and controls. AMD patients (115) were classified into two groups: Dry and Wet AMD. Wet AMDs were further classified into occult, predominant classic and minimal classic. 61 healthy individuals were recruited as normal controls. After normalization with total protein, DcR1 levels were analyzed by ELISA. Mann Whitney U-statistic was used for analysis of DcR1 ELISA results. We have observed DcR1 levels in serum sample which were significantly lower in AMD patients as compared to controls ( $p = 0.001$ ). On the other hand, we did not find difference in DcR1 levels between wet and dry AMD. The present study defines the plausible role of DcR1 in AMD pathology signifying a new therapeutic target for AMD.

PMID: 24534820 [PubMed - in process]

## **Epidemiology**

**Expert Opin Drug Saf. 2014 Feb 19. [Epub ahead of print]**

### **Does long-term aspirin use increase the risk of neovascular age-related macular degeneration?**

Christen WG, Chew EY.

**Introduction:** Aspirin is used regularly for rheumatoid pain management and cardioprotection. However, aspirin has also been associated with significant adverse events, such as cerebral and gastrointestinal bleeding. Recent findings from several observational epidemiologic studies indicate that regular aspirin use may also be associated with increased risks of some forms of age-related macular degeneration (AMD).

**Areas covered:** In this report, we review recent findings from observational epidemiologic studies suggesting a possible adverse effect of regular aspirin use in AMD, and in particular, neovascular AMD. These findings are considered in light of the relative strengths and limitations of observational studies and randomized trials.

**Expert opinion:** While the findings are important and warrant further investigation, the inherent limitations of observational studies, most notably uncontrolled confounding, preclude an interpretation of causality. Alternatively, the most reliable evidence with which to evaluate the effects of regular aspirin use in AMD will derive from well-designed randomized trials of sufficient size and duration. Such information is unlikely to alter current recommendations for persons at high risk of cardiovascular disease, but should help clarify the benefit-to-risk ratio of regular aspirin use in the large majority of individuals at low-to-moderate risk.

PMID: 24547895 [PubMed - as supplied by publisher]

**Ophthalmic Epidemiol. 2014 Feb 14. [Epub ahead of print]**

### **Female Reproductive Factors and Major Eye Diseases in Asian Women -The Singapore Malay Eye Study.**

Lam JS, Tay WT, Aung T, Saw SM, Wong TY.

**Abstract Purpose:** To examine the association of reproductive factors and major eye diseases, including glaucoma, age-related macular degeneration (AMD), diabetic retinopathy and cataract, in Asian women.

**Methods:** The Singapore Malay Eye Study is a population-based cross-sectional epidemiological study which examined 3280 persons (78.7% response) of Malay ethnicity aged 40-80 years; 1704 were female. Information on reproductive factors and use of hormone replacement therapy (HRT) was collected using an interviewer-administered questionnaire. Glaucoma was defined according to the International Society for Geographical and Epidemiological Ophthalmology criteria. Retinal photographs were graded for AMD following the Wisconsin grading system, and diabetic retinopathy according to the modified Airlie House classification system. Cataract was graded according to the Lens Opacity Classification System III.

**Results:** A total of 1176 women reported having experienced menopause by the time of the study with 1073 (91%) having a natural menopause, 88 (7.5%) a hysterectomy and 9 (0.8%) due to other reasons; HRT was used by 70 (6%) women. Women whose age at menopause was  $\leq 52$  years were 3.5 times more likely to have glaucoma (95% confidence interval, CI, 1.23-9.98,  $p$  value = 0.02) than those whose age at menopause was  $\geq 53$  years. Age of menopause was not associated with AMD (age-adjusted odds ratio, OR, 1.22, 95% CI 0.65-2.31), diabetic retinopathy (age-adjusted OR 1.01, 95% CI 0.66-1.54) or cataract (age-adjusted OR 1.38, 95% CI 0.95-2.00). Use of HRT was not associated with any of these eye diseases.

**Conclusion:** Women who had menopause at a younger age were more likely to have glaucoma. This association needs to be confirmed in other studies.

PMID: 24527687 [PubMed - as supplied by publisher]

## Genetics

**J Biol Chem. 2014 Feb 18. [Epub ahead of print]**

**Bis-retinoid-mediated complement activation on retinal pigment epithelial cells is dependent on complement factor H haplotype.**

Radu RA, Hu J, Jiang Z, Bok D.

**Abstract:** Age-related macular degeneration (AMD) is a common central-blinding disease of the elderly. Homozygosity for a sequence variant causing Y402H- and I62V-substitutions in the gene for complement factor H (CFH) is strongly associated with risk of AMD. CFH, secreted by many cell types including those of the retinal pigment epithelium (RPE), is a regulatory protein that inhibits complement activation. Recessive Stargardt maculopathy (STGD1) is another central-blinding disease caused by mutations in the gene for ABCA4, a transporter in photoreceptor outer-segments (OS) that clears retinaldehyde and prevents formation of toxic bis-retinoids. Photoreceptors shed their distal OS daily, which are phagocytosed by the RPE cells. Here, we investigated the relationship between the CFH haplotype of human RPE (hRPE) cells, exposure to OS containing bis-retinoids, and complement activation. We show that hRPE cells of the AMD-predisposing CFH haplotype (HH402/VV62) are attacked by complement following exposure to bis-retinoid-containing Abca4<sup>-/-</sup> OS. This activation was dependent on factor B, indicating involvement of the alternative pathway. In contrast, hRPE cells of the AMD-protective CFH haplotype (YY402/II62) showed no complement activation following exposure to either Abca4<sup>-/-</sup> or wild-type OS. The AMD-protective YY402/II62 hRPE cells were more resistant to the membrane attack complex (MAC), while HH402/VV62 hRPE cells showed significant MAC deposition following ingestion of Abca4<sup>-/-</sup> OS. These results suggest that bis-retinoid accumulation in hRPE cells stimulates activation and dysregulation of complement. Cells with an intact complement negative-regulatory system are protected from complement attack, while cells with reduced CFH synthesis due to the Y402H- and I62V-substitutions are vulnerable to disease.

PMID: 24550392 [PubMed - as supplied by publisher]

**JAMA Ophthalmol. 2014 Feb 20. doi: 10.1001/jamaophthalmol.2013.8175. [Epub ahead of print]**

**Growth of Geographic Atrophy on Fundus Autofluorescence and Polymorphisms of CFH, CFB, C3, FHR1-3, and ARMS2 in Age-Related Macular Degeneration.**

Caire J, Recalde S, Velazquez-Villoria A, Garcia-Garcia L, Reiter N, Anter J, Fernandez-Robredo P, García-Layana A; for the Spanish Multicenter Group on AMD.

**IMPORTANCE:** Identification of the genetic risk factors that contribute to geographic atrophy (GA) could lead to advancements in interventional trials and/or therapeutic approaches for combating vision loss.

**OBJECTIVE:** To investigate whether single-nucleotide polymorphisms (SNPs) are associated with the presence and progression of established GA in age-related macular degeneration (AMD).

**DESIGN, SETTING, AND PARTICIPANTS:** Prospective, controlled, multicenter study of 154 patients with GA/AMD and 141 age-matched control participants at 8 Spanish hospitals. **MAIN OUTCOMES AND MEASURES** Samples of DNA were collected to analyze SNPs within AMD-related genes (CFH, CFB, C3, FHR1-3, and ARMS2). Fundus autofluorescence imaging was used to evaluate GA progression during a 2-year period in 73 patients with GA/AMD. Finally, logistic regression was used to analyze the associations of SNPs, age, body mass index, and cigarette smoking with the rate of progression and relative growth of GA.

**RESULTS:** This case-control analysis revealed a significant ( $P < .05$ ) association between the presence of GA and SNPs within CFH, ARMS2, and FHR1-3. Moreover, logistic regression analysis identified significant associations of the rate of progression with genetic polymorphisms (CFH-402His [ $P = .04$ ] and CFH-62Ile [ $P = .04$ ]) and demographic factors (sex [ $P = .02$ ] and age [ $P = .02$ ]), whereas relative growth was associated with 1 polymorphism (CFB-32Gln [ $P = .04$ ]).

**CONCLUSIONS AND RELEVANCE:** Taken together, our findings confirm that genetic risk factors related to the presence of GA are not identical to those associated with GA progression. In fact, we demonstrate that gene variants of CFH and CFB, as well as demographic risk factors, confer significant risk for GA progression (both rate of progression and relative growth) within a Spanish population.

PMID: 24557084 [PubMed - as supplied by publisher]

**Genet Mol Res. 2014 Jan 17;13(1):302-9. doi: 10.4238/2014.January.17.15.**

**Toll-like receptor 3 polymorphism is not associated with neovascular age-related macular degeneration and polypoidal choroidal vasculopathy in the Chinese.**

Cheng Y, Li MW1, Li HP, Zeng WT, Zhou P, Huang LZ, Li XX, Sun YY.

**Abstract:** Toll-like receptor 3 (TLR3) variants in mainland northern Chinese patients with polypoidal choroidal vasculopathy (PCV) and neovascular age-related macular degeneration (nAMD) were investigated. The complete genes of TLR3, including all exons and the promoter region, were assessed using direct sequencing technology of 284 unrelated mainland northern Chinese individuals: 96 nAMD patients, 92 PCV patients, and 96 controls. Six single nucleotide polymorphisms were identified: rs5743303, rs5743305, rs5743312, rs3775291, rs3775290, and rs6830345. The distribution of TLR3 genotypes for nAMD and PCV was not significantly different compared with normal controls. This study indicates that the TLR3 gene polymorphism is not associated with nAMD and PCV in northern Chinese patients.

PMID: 24535857 [PubMed - in process]

**J Struct Biol. 2014 Feb 12. pii: S1047-8477(14)00025-2. doi: 10.1016/j.jsb.2014.02.001. [Epub ahead of print]**

**The macular degeneration-linked C1QTNF5 (S163) mutation causes higher-order structural rearrangements.**

Tu X, Palczewski K.

**Abstract:** The C1q-tumor necrosis factor 5 (C1QTNF5) protein plays a significant role in retinal pigmented epithelium (RPE) cellular adhesion. The C1QTNF5 gene is co-transcribed with the frizzled-related protein (MFRP) gene. A Ser-to-Arg mutation at site 163 (S163R) in C1QTNF5 is known to cause late-onset retinal macular degeneration (L-ORMD). Here we also found that C1QTNF5 monomers can multimerize into a bouquet-like octadecamer. We found that a novel intermolecular hydrogen-bond network of S163 that glues adjacent globular heads of C1QTNF5 together and was weakened or abolished by the R163 pathogenic mutation. These findings could underlie the structural basis of this protein's adhesive function and relate to the pathogenesis of its S163R mutation. Additionally, the fact that C1QTNF5 immobilized to a resin selectively enriched detergent extracted membrane-bound MFRP, further confirming their interaction and implying functions other than cellular adhesion for C1QTNF5.

PMID: 24531000 [PubMed - as supplied by publisher]

## Diet & lifestyle

**Invest Ophthalmol Vis Sci. 2014 Feb 20. pii: iovs.14-13916v1. doi: 10.1167/iov.14-13916. [Epub ahead of print]**

**Circulating omega-3 fatty acids and neovascular age-related macular degeneration.**

Merle BM, Benlian P, Puche N, Bassols A, Declourt C, Souied E.

**Purpose:** To assess the associations of serum, red-blood cell membranes (RBCM) and dietary long-chain n-3 polyunsaturated fatty acids (LC-PUFAs) with neovascular age-related macular degeneration (AMD).

**Methods:** We included 290 patients of the Nutritional AMD Treatment 2 Study (NAT2) with neovascular AMD in one eye and early AMD lesions in the other eye and 144 normal vision controls without AMD. Dietary intake of seafood was estimated by food frequency questionnaire. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) composition in serum and RBCM were determined by gas chromatography from 12h-fasting blood samples and was expressed as percentages of total fatty acids profile. Logistic regressions estimated associations of neovascular AMD with dietary intake of seafood and circulating n-3 LC-PUFAs.

**Results:** Dietary oily fish and seafood intake were significantly lower in AMD patients than in controls. After adjustment for all potential confounders (age, gender, CFH Y402H, ARMS2 A69S, and ApoE4 polymorphisms, plasma triglycerides, hypertension, hypercholesterolemia and family history of AMD), serum EPA was significantly associated with a lower risk for neovascular AMD (OR=0.41 (0.22-0.77); p=0.005). Analysis of RBCM revealed that EPA and EPA+DHA were significantly associated with a lower risk for neovascular AMD (OR=0.25 (0.13-0.47); p<0.0001 and OR=0.52 (0.29-0.94); p=0.03, respectively).

**Conclusions:** RBCM EPA and EPA+DHA, as long term biomarkers of n-3 dietary PUFA status, were strongly associated with neovascular AMD and may represent an objective marker identifying subjects at high risk for neovascular AMD, whom may most benefit from nutritional interventions.

PMID: 24557349 [PubMed - as supplied by publisher]

**J Lipids. 2014;2014:495761. Epub 2014 Jan 16.**

**Why Fish Oil Fails: A Comprehensive 21st Century Lipids-Based Physiologic Analysis.**

Peskin BS.

Abstract: The medical community suffered three significant fish oil failures/setbacks in 2013. Claims that fish oil's EPA/DHA would stop the progression of heart disease were crushed when The Risk and Prevention Study Collaborative Group (Italy) released a conclusive negative finding regarding fish oil for those patients with high risk factors but no previous myocardial infarction. Fish oil failed in all measures of CVD prevention-both primary and secondary. Another major 2013 setback occurred when fish oil's DHA was shown to significantly increase prostate cancer in men, in particular, high-grade prostate cancer, in the Selenium and Vitamin E Cancer Prevention Trial (SELECT) analysis by Brasky et al. Another monumental failure occurred in 2013 whereby fish oil's EPA/DHA failed to improve macular degeneration. In 2010, fish oil's EPA/DHA failed to help Alzheimer's victims, even those with low DHA levels. These are by no means isolated failures. The promise of fish oil and its so-called active ingredients EPA / DHA fails time and time again in clinical trials. This lipids-based physiologic review will explain precisely why there should have never been expectation for success. This review will focus on underpublicized lipid science with a focus on physiology.

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