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MD Research News

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Drug treatment

Ophthalmologica. 2013 Mar 14. [Epub ahead of print]

Treatment of Exudative Age-Related Macular Degeneration with Intravitreal Ranibizumab in Clinical Practice: A 3-Year Follow-Up.

Marques IP, Fonseca P, Luz Cachulo M, Pires I, Figueira J, Faria de Abreu JR, Silva R.

Department of Ophthalmology, University Hospital of Coimbra, Coimbra, Portugal.

Purpose: To evaluate the 36-month efficacy of intravitreal ranibizumab injections for choroidal neovascularization secondary to age-related macular degeneration (AMD) in real world clinical practice.

Methods: Retrospective study involving 84 eyes of 77 patients; 52 eyes completed 3 years of follow-up. Subjects were observed initially on a monthly basis and with extended follow-up intervals if signs of quiescence were detected, according to an established protocol. A comprehensive ophthalmologic examination was performed, including best-corrected visual acuity (BCVA) determined with Early Treatment Diabetic Retinopathy Study charts, stereoscopic macular biomicroscopy and optical coherence tomography (OCT) with fluorescein angiography and indocyanine green angiography if considered necessary. Treatment was given if signs of active lesions were present.

Results: The mean baseline BCVA was 49.33 and 49.52 letters at the 36-month visit. The average of treatments was 8.6 at 3 years. At this time point, 77% of treated eyes stabilized or improved their vision (VA loss ≤5 letters). A predictive value for better VA was found for younger age, better baseline VA, good response on OCT and more frequent treatments.

Conclusion: At 3 years, intravitreal ranibizumab is able to maintain baseline VA in exudative AMD patients, with a reduced number of injections, but not to show VA improvement, in clinical practice.

PMID: 23485818 [PubMed - as supplied by publisher]

Curr Opin Ophthalmol. 2013 Mar 13. [Epub ahead of print]

Long-term follow-up of vascular endothelial growth factor inhibitor therapy for neovascular age-related macular degeneration.

Scott AW, Bressler SB.

Retina Division, Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland,

USA.

PURPOSE OF REVIEW: To discuss the most recent literature regarding the long-term use (≥52 weeks of follow-up) of antivascular endothelial growth factor (VEGF) therapy for neovascular age-related macular degeneration (NVAMD).

RECENT FINDINGS: Intravitreal ranibizumab has been demonstrated to provide outstanding vision outcomes relative to the standard therapy in patients with NVAMD. The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD studies showed that patients managed with intravitreal aflibercept achieved visual acuity and anatomic improvements similar to individuals managed with monthly ranibizumab while receiving an average of five fewer injections during the first 12 months of treatment. In the Comparison of AMD Treatment Trials, intravitreal bevacizumab dosed monthly met noninferiority to ranibizumab monthly, as well as noninferiority to ranibizumab dosed as-needed with respect to change in visual acuity 1 year after the treatment initiation. Furthermore, patients switched to as-needed regimens in their second year of follow-up from monthly dosing during the first year demonstrated an incremental loss of visual acuity during the second year of follow-up irrespective of the drug used. To date, trials evaluating anti -VEGF therapy for NVAMD demonstrate a low incidence of serious ocular or systemic adverse events. However, the potential for deleterious effects of long-term (beyond 2 years) pan-VEGF blockade remains unknown.

SUMMARY: Patients with NVAMD enjoy heretofore unprecedented vision gains when managed with anti-VEGF therapy, and the limited body of evidence to date regarding long-term anti-VEGF treatment shows these vision gains can be maintained through 2 years. Further investigation is needed to explore the effects of long-term anti-VEGF therapy beyond 2 years.

PMID: 23492430 [PubMed - as supplied by publisher]

J Ophthalmic Vis Res. 2008 Apr;3(2):102-7.

Two Different Doses of Intravitreal Bevacizumab for Treatment of Choroidal Neovascularization Associated with Age-related Macular Degeneration.

Modarreszadeh M, Naseripour M, Ghasemi-Falavarjani K, Nikeghbali A, Hashemi M, Parvaresh MM.

Eye Research Center, Rasoul Akram Hospital, Iran Medical University, Tehran, Iran.

PURPOSE: To compare the efficacy and safety of 1.25 mg versus 2.5 mg intravitreal bevacizumab (IVB) for treatment of choroidal neovascularization (CNV) associated with agerelated macular degeneration (AMD).

METHODS: In this randomized clinical trial, consecutive patients with active CNV associated with AMD received 1.25 mg or 2.5 mg IVB. Best corrected visual acuity (BCVA), foveal thickness and side effects of therapy were evaluated one and three months after intervention.

RESULTS: Overall 86 subjects were enrolled and completed the scheduled follow-up. Forty seven and 39 patients received 1.25 and 2.5 mg IVB respectively. The study groups were balanced in terms of baseline characteristics such as age, BCVA and foveal thickness. Mean improvement in BCVA was 0.06±0.3 logMAR in the 1.25 mg group and 0.07±0.34 logMAR in the 2.5 mg group (P=0.9). Mean decrease in foveal thickness was 49±36 μm in the 1.25 mg group and 65±31μm in the 2.5 mg group (P=0.6). Three cases of vitreous reaction and one case of massive subretinal hemorrhage were observed in the 2.5 mg group.

CONCLUSION: Double dose (2.5 mg) IVB does not seem to be more effective than regular dose (1.25 mg) injections for treatment of CNV due to AMD and may lead to more complications.

PMID: 23479531 [PubMed]

Retina. 2013 Mar 13. [Epub ahead of print]

MYOCARDIAL INFARCTION AFTER INTRAVITREAL VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS: A Whole Population Study.

Kemp A, Preen DB, Morlet N, Clark A, McAllister IL, Briffa T, Sanfilippo FM, Ng JQ, McKnight C, Reynolds W, Gilles MC.

*Centre for Health Services Research, School of Population Health, The University of Western Australia, Australia †Illawarra Health and Medical Research Institute, University of Wollongong ‡Department of Ophthalmology, Royal Perth Hospital, Australia §Curtin Health Innovation Research Institute, Curtin University, Australia ¶Lions Eye Institute, Centre for Ophthalmology and Visual Science **Cardiovascular Research Group, School of Population Health, and ††Eye and Vision Epidemiology Research Group, School of Population Health, The University of Western Australia, Perth, Australia ‡‡Save Sight Institute, University of Sydney, Sydney, Australia.

PURPOSE: To determine the risk of thromboembolic and gastrointestinal bleeding events in the 12 months after injections of bevacizumab or ranibizumab compared with photodynamic therapy and a nontreated community sample.

METHODS: Hospital and death records were examined for 1,267 patients treated with vascular endothelial growth factor inhibitor and 399 patients treated with photodynamic therapy attending Western Australian eye clinics from 2002 to 2008, and 1,763 community controls, aged ≥50 years. Hospital records from 1995 to 2009 were analyzed for history of myocardial infarction (MI), stroke, and gastrointestinal bleeding before treatment. Records were searched for evidence of these events in the 12 months after treatment.

RESULTS: The 12-month MI rate was higher for vascular endothelial growth factor inhibitor patients than photodynamic therapy patientsand the community group (1.9/100 vs. 0.8 and 0.7, respectively). No differences were observed between patients treated with bevacizumab and ranibizumab. The adjusted MI rate was 2.3 times greater than the community group (95% confidence interval, 1.2-4.5) and photodynamic therapy rate (95% confidence interval, 0.7-7.7). The 12-month MI risk did not increase with the number of injections administered (hazard ratio, 0.9; 95% confidence interval, 0.5-1.5). Stroke and gastrointestinal bleeding did not differ between any exposure groups.

CONCLUSION: Although all the adverse events examined were rare, patients treated with vascular endothelial growth factor inhibitors were significantly more likely to experience fatal or nonfatal MI than the community group. This increased risk may be related to the underlying age-related macular degeneration or vascular endothelial growth factor inhibitor use itself.

PMID: 23492942 [PubMed - as supplied by publisher]

Expert Rev Clin Pharmacol. 2013 Mar;6(2):103-13. doi: 10.1586/ecp.12.81.

Aflibercept (VEGF Trap-Eye) for the treatment of exudative age-related macular degeneration.

Stewart MW.

Mayo College of Medicine, Jacksonville, FL, USA. stewart.michael@mayo.edu.

Abstract: Aflibercept, a soluble receptor molecule that binds VEGF, has been recently approved for the treatment of exudative age-related macular degeneration. This fusion protein with binding sequences from VEGF receptors 1 and 2 possesses high binding affinity for isomers of VEGF-A, VEGF-B and PlGF, and prevents VEGF from initiating proliferation and migration of vascular endothelial cells. Phase III trials showed that intravitreal aflibercept given monthly or every 2 months produces visual improvement and decrease in macular thickness comparable with monthly ranibizumab. The second year of the trials demonstrated that as-needed aflibercept maintained vision with few required injections. Aflibercept

promises to decrease the treatment burden faced by patients with exudative age-related macular degeneration.

PMID: 23473589 [PubMed - in process]

J Ocul Pharmacol Ther. 2013 Mar 12. [Epub ahead of print]

Incidence and Risk Factors for Macular Hemorrhage Following Intravitreal Ranibizumab Injection for Neovascular Age-Related Macular Degeneration.

Moon SW, Oh J, Yu HG, Cho HY, Song SJ.

Department of Ophthalmology, Kyung Hee University School of Medicine , Seoul, Korea.

Abstract Purpose: To analyze the incidence of and risk factors for newly developed or increased macular hemorrhage after intravitreal ranibizumab injection (IVR) for neovascular age-related macular degeneration (AMD).

Methods: We performed a retrospective chart review of 220 subjects (220 eyes) from 5 hospitals who received IVRs for neovascular AMD between 1 June 2009 and 30 June 2010. Systemic conditions (age, sex, presence of diabetes, hypertension, cardiovascular disease, smoking, and use of anticoagulation agent) and presence of hemorrhage at the initial exam were evaluated. The primary study outcome was the incidence of newly developed or increased macular hemorrhage during the 1-month postinjection period.

Results: The incidence of newly developed or increased macular hemorrhage including vitreous hemorrhage was 8% (18/220). Presence of diabetes was found to be a risk factor for macular hemorrhage [odds ratios (OR): 2.16, 95% confidence intervals (CI): 1.07-8.13]. When subjects had both diabetes and hypertension, the risk of macular hemorrhage after injection increased 4.8-fold (OR: 4.84, CI: 1.24-18.85).

Conclusion: The systemic condition of subjects was found to be an important risk factor for newly developed or increased macular hemorrhage after IVR for neovascular AMD. More consideration should be given to the statuses of diabetes and hypertension in subjects who receive ranibizumab for neovascular AMD.

PMID: 23480269 [PubMed - as supplied by publisher]

J Ophthalmic Vis Res. 2008 Apr;3(2):95-101.

Intravitreal Bevacizumab versus Combined Bevacizumab and Triamcinolone Acetonide for Neovascular Age-Related Macular Degeneration.

Riazi-Esfahani M, Ahmadieh H, Faghihi H, Piri N, Taei R, Karkhaneh R, Alami-Harandi Z, Lashay A, Mirshahi A, Nili-Ahmadabadi M, Soheilian M, Sanagou M.

Eye Research Center, Farabi Hospital, Tehran Medical University, Tehran, Iran.

PURPOSE: To compare the short-term outcomes of intravitreal bevacizumab (IVB) with the combination of IVB and intravitreal triamcinolone acetonide (IVB/IVT) for treatment of neovascular age-related macular degeneration (AMD).

METHODS: This randomized clinical trial was performed on 92 eyes of 90 patients with subfoveal and juxtafoveal choroidal neovascularization (CNV) secondary to AMD. The eyes were randomly assigned to receive IVB 1.25 mg alone (53 eyes) or in combination with IVT 2 mg (39 eyes). Best-corrected visual acuity (BCVA) and fundus autofluorescence were assessed, and fluorescein angiography (FA) and optical coherence tomography (OCT) were performed at baseline and repeated 6 weeks after treatment.

RESULTS: Mean age was 70.6±8.7 (range 50-89) years and 57.7% of the patients were male. BCVA improved from 1.03±0.40 to 0.93±0.38 logMAR (P=0.001) in the IVB group and from 1.08±0.33 to 0.91±0.38 logMAR (P=0.008) in the IVB/IVT group. There was a trend toward greater visual improvement with combined therapy (P=0.06). BCVA improvement was greater in eyes with +1 versus those with +2 (P=0.049) and +3 (P<0.001) fundus autofluorescence at baseline. Mean decrease in central macular thickness was 113±115 µm (P<0.001) in the IVB group versus 53.96±125 µm (P=0.008) in the IVB/IVT group with no intergroup difference (P=0.38). FA showed decreased leakage in 57.4%, increased leakage in 12.8% and no change in 29.8% of patients in the IVB group. Corresponding figures were 60.0%, 5.7% and 34.3% in the IVB/IVT group (P=0.556).

CONCLUSION: Addition of triamcinolone acetonide to bevacizumab for treatment of neovascular AMD does not seem to significantly increase its short-term efficacy. More severe fundus autofluorescence appears to be predictive of poorer response to treatment.

PMID: 23479530 [PubMed]

Retina. 2013 Mar 13. [Epub ahead of print]

PARS PLANA VITRECTOMY IN THE MANAGEMENT OF PATIENTS DIAGNOSED WITH ENDOPHTHALMITIS FOLLOWING INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTION.

Chaudhary KM, Romero JM, Ezon I, Fastenberg DM, Deramo VA.

*Hofstra North Shore - Long Island Jewish Department of Ophthalmology, Great Neck, New York †Long Island Vitreo-Retinal Consultants, Great Neck, New York.

PURPOSE: To evaluate the possible benefit of pars plana vitrectomy in the treatment of patients with endophthalmitis following antivascular endothelial growth factor (VEGF) injection.

METHOD: The authors retrospectively reviewed the medical records of all patients in their practice with a diagnosis of endophthalmitis from January 1, 2007, through December 31, 2011. Only those with a clinical presentation consistent with endophthalmitis after intravitreal anti-VEGF injection were included. Clinical data that were collected and recorded included visual acuities and the method of initial and subsequent treatment of endophthalmitis following anti-VEGF injection: tap and injection of intravitreal antibiotics (TAP) and tap and inject with subsequent pars plana vitrectomy (VIT).

RESULTS: The authors identified 23 patients meeting criteria. Nineteen patients had received bevacizumab and four patients had received ranibizumab. The median time from last injection to presentation was 4 days (range, 1-18 days) with a median follow-up of 15 months (range, 5-48 months) after being diagnosed of endophthalmitis. Nine patients had positive cultures. The median baseline visual acuity (preendophthalmitis) was 20/70 (range, 20/25 to counting fingers at 2 ft) with a median presenting visual acuity of counting fingers at 1 ft (range, 20/50 to light perception vision). Overall, 90% (9/10) of the patients in TAP only group regained visual acuity within 1 line or better of baseline versus 46% (6 of 13) in the TAP and VIT group. Only one of the patients treated with TAP alone suffered more than one line of visual acuity loss.

CONCLUSION: Patients diagnosed with endophthalmitis after anti-VEGF intravitreal injection who underwent TAP regained baseline visual acuity more often than those who underwent TAP and VIT. This study did not support a benefit for VIT in all patients, rather only in those cases who warranted it because of worsening clinical course. The study suggests that TAP is a viable primary intervention for endophthalmitis after anti-VEGF injection.

PMID: 23492945 [PubMed - as supplied by publisher]

J Ophthalmic Vis Res. 2008 Apr;3(2):81-2.

Pharmacotherapy for age-related macular degeneration.

Ahmadieh H.

Ophthalmic Research Center, Labbafinejad Medical Center, Tehran, Iran.

PMID: 23479526 [PubMed]

JAMA Ophthalmol. 2013 Mar 14:1-2. doi: 10.1001/jamaophthalmol.2013.692. [Epub ahead of print]

Effect of Intravitreous Anti-Vascular Endothelial Growth Factor Therapy on Choroidal Thickness in Neovascular Age-Related Macular Degeneration Using Spectral-Domain Optical Coherence Tomography.

Branchini L, Regatieri C, Adhi M, Flores-Moreno I, Manjunath V, Fujimoto JG, Duker JS.

PMID: 23494008 [PubMed - as supplied by publisher]

Eye (Lond). 2013 Mar;27(3):289-90. doi: 10.1038/eye.2013.1.

Bevacizumab vs ranibizumab-an appraisal of the evidence from CATT and IVAN.

Ahfat FG, Zaidi FH.

Eye, Ear and Mouth Unit, Maidstone and Tunbridge Wells NHS Trust, Maidstone, UK.

PMID: 23485959 [PubMed - in process]

Other treatment & diagnosis

Ophthalmology. 2013 Mar 12. pii: S0161-6420(13)00150-4. doi: 10.1016/j.ophtha.2013.02.016. [Epub ahead of print]

Stereotactic Radiotherapy for Neovascular Age-Related Macular Degeneration: 52-Week Safety and Efficacy Results of the INTREPID Study.

Jackson TL, Chakravarthy U, Kaiser PK, Slakter JS, Jan E, Bandello F, O'Shaughnessy D, Gertner ME, Danielson L, Moshfeghi DM; INTREPID Study Group(□).

King's College London, London, United Kingdom.

PURPOSE: To determine the safety and efficacy of low-voltage, external-beam, stereotactic radiotherapy (SRT) for patients with neovascular age-related macular degeneration (nvAMD).

DESIGN: Randomized, double-masked, sham-controlled, multicenter, clinical trial.

PARTICIPANTS: Two hundred thirty patients with onset of nvAMD within 3 years who received 3 or more injections of ranibizumab or bevacizumab within the preceding year and who needed continuing ranibizumab or bevacizumab treatment.

INTERVENTIONS: Participants were randomized 2:1:2:1 to 16 Gy plus pro re nata (PRN) ranibizumab, sham 16 Gy plus PRN ranibizumab, 24 Gy plus PRN ranibizumab, or sham 24 Gy plus PRN ranibizumab, respectively.

MAIN OUTCOME MEASURES: The primary efficacy end point was the mean number of ranibizumab injections at 52 weeks. Secondary end points were change in mean best-corrected visual acuity (VA), loss of fewer than 15 Early Treatment Diabetic Retinopathy Study letters, gain of 0 or more and 15 or more letters, and change in angiographic total lesion size and choroidal neovascularization (CNV) lesion size.

RESULTS: Both the 16-Gy and 24-Gy SRT arms received significantly fewer ranibizumab treatments compared with the sham arms: mean number of treatments, 2.64 (median, 2), 2.43 (median, 2), and 3.74 (median, 3.5), respectively (P = 0.013 and P = 0.004, respectively, vs. sham). Change in mean VA was -0.28, +0.40, and -1.57 letters for the 16-Gy, 24-Gy, and sham arms, respectively. The 16-Gy, 24-Gy, and sham arms lost fewer than 15 letters in 93%, 89%, and 91% of eyes, respectively, with 53%, 57%, and 56% gaining 0 or more letters, respectively, and 4% gaining 15 letters or more in all arms. Mean total angiographic lesion area changed by -1.15 mm2, +0.49 mm2, and +0.75 mm2, respectively; mean CNV lesion area decreased by 0.16 mm2, 0.18 mm2, and 0.10 mm2, respectively. Optical coherence tomography central subfield thickness decreased by 85.90 μm, 70.39 μm, and 33.51 μm, respectively. The number of adverse events (AEs) and number of serious AEs (SAEs) were similar across arms. No AEs were attributed to radiation. No SAEs occurred in the study eye.

CONCLUSIONS: A single dose of SRT significantly reduces ranibizumab retreatment for patients with nvAMD, with a favorable safety profile at 1 year. Whereas chronic nvAMD typically results in loss of VA over time, SRT is associated with relatively well-preserved VA over 1 year.

PMID: 23490327 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Mar 12. pii: S0161-6420(13)00134-6. doi: 10.1016/j.ophtha.2013.01.074. [Epub ahead of print]

Epimacular Brachytherapy for Neovascular Age-Related Macular Degeneration (CABERNET): Fluorescein Angiography and Optical Coherence Tomography.

Jackson TL, Dugel PU, Bebchuk JD, Smith KR, Petrarca R, Slakter JS, Jaffe GJ, Nau JA; CABERNET Study Group*.

King's College London, London, United Kingdom; NeoVista, Inc., Newark, California. Electronic address: t.jackson1@nhs.net.

PURPOSE: To report the fluorescein angiography (FA) and optical coherence tomography (OCT) results of a clinical trial of epimacular brachytherapy (EMBT) used for the treatment of neovascular age-related macular degeneration (AMD).

DESIGN: Pivotal multicenter, active-controlled, randomized clinical trial.

PARTICIPANTS: A total of 494 participants with treatment-naïve, neovascular AMD.

METHODS: Participants with classic, minimally classic, and occult lesions were randomized to receive (a) EMBT and 2 mandated monthly ranibizumab injections followed by pro re nata (PRN) ranibizumab or (b) 3 mandated monthly ranibizumab injections followed by mandated quarterly plus PRN ranibizumab. Participants underwent FA at screening and at months 1, 6, 12, 18, and 24. Optical coherence tomography scans were undertaken monthly for 24 months. The FA and OCT images were analyzed at respective independent reading centers.

MAIN OUTCOME MEASURES: Change at 24 months in mean FA total lesion size and choroidal neovascularization (CNV) size and change in mean OCT centerpoint thickness.

RESULTS: The mean (standard deviation) changes in FA total lesion size in the EMBT and control arms were +1.9 (8.7) and -3.0 (7.2) mm2, respectively, with a mean change in total CNV size of +0.4 (8.4) and -4.7 (6.5) mm2, respectively. Mean (standard deviation) changes in OCT centerpoint thickness were -144

(246) and -221 (185) µm, respectively. Retrospective subgroup analyses showed no significant difference between treatment arms in mean centerpoint thickness in some subgroups, including eyes with classic lesions. The control arm showed a significantly larger reduction in mean total lesion size and mean CNV size than the EMBT arm in all subgroups analyzed. Nine eyes in the EMBT arm showed features consistent with mild, nonproliferative radiation retinopathy, but with a mean gain of 5.0 Early Treatment Diabetic Retinopathy Study letters.

CONCLUSIONS: Both FA and OCT suggest that EMBT with PRN ranibizumab results in an inferior structural outcome than quarterly plus PRN ranibizumab. Some subgroup analyses suggest that classic lesions may be more responsive than occult lesions, although generally both subgroups are inferior to ranibizumab. A non-vision-threatening radiation retinopathy occurs in 2.9% of eyes over 24 months, but longer follow-up is needed.

PMID: 23490325 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2013 Mar 1;131(3):335-340.

Progression of Lesion Size in Untreated Eyes With Exudative Age-Related Macular Degeneration: A Meta-analysis Using Lineweaver-Burk Plots.

Liu TY, Shah AR, Del Priore LV.

OBJECTIVE: To test the hypothesis that the natural history of choroidal neovascularization lesion size is uniform across prior randomized controlled clinical trials of exudative age-related macular degeneration (AMD), with apparent differences arising from different entry times of eyes into clinical trials.

METHODS: We conducted a retrospective meta-analysis of control eye data from 5 age-related macular degeneration trials (Treatment of Age-Related Macular Degeneration with Photodynamic Therapy; Verteporfin in Photodynamic Therapy; VEGF Inhibition Study in Ocular Neovascularization; Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration; and Phase 3b, Multicenter, Randomized, Double-masked, Sham Injection-controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic Choroidal Neovascularization Secondary to AMD Study), which were plotted on a double reciprocal plot of 1 / lesion size (disc area) vs 1 / time (months after enrollment). To account for the different entry times, we introduced a horizontal translation factor to shift each data subset until r2 was maximized for the cumulative trend line.

RESULTS: Cumulative data for untreated control eyes fit a straight line on a double reciprocal plot (r2 = 0.98) after the introduction of horizontal translation factors. Our model predicts that a choroidal neovascular lesion will eventually enlarge to a size of 10.6 disc areas without treatment and that the lesion will reach half of its maximum size within 14.0 months after onset of exudation. The linear expansion rate of untreated lesions is approximately 26.0 µm per day for the smallest lesions and decreases gradually as the lesions enlarge.

CONCLUSIONS: The pattern of choroidal neovascularization lesion size enlargement in AMD eyes is uniform across a wide range of clinical trials, with apparent differences arising from different entry times of patients into various trials. The main determinant of choroidal neovascularization lesion size enlargement is the duration of exudative disease.

PMID: 23494038 [PubMed - as supplied by publisher]

Biomaterials. 2013 Mar 11. pii: S0142-9612(13)00196-8. doi: 10.1016/j.biomaterials.2013.02.027. [Epub ahead of print]

Tissue engineering the retinal ganglion cell nerve fiber layer.

Kador KE, Montero RB, Venugopalan P, Hertz J, Zindell AN, Valenzuela DA, Uddin MS, Lavik EB, Muller KJ, Andreopoulos FM, Goldberg JL.

Bascom Palmer Eye Institute and Interdisciplinary Stem Cell Institute, Miller School of Medicine, University of Miami, 1501 NW 10th Ave, BRB Building Room 832, Miami, FL 33136, USA.

Abstract: Retinal degenerative diseases, such as glaucoma and macular degeneration, affect millions of people worldwide and ultimately lead to retinal cell death and blindness. Cell transplantation therapies for photoreceptors demonstrate integration and restoration of function, but transplantation into the ganglion cell layer is more complex, requiring guidance of axons from transplanted cells to the optic nerve head in order to reach targets in the brain. Here we create a biodegradable electrospun (ES) scaffold designed to direct the growth of retinal ganglion cell (RGC) axons radially, mimicking axon orientation in the retina. Using this scaffold we observed an increase in RGC survival and no significant change in their electrophysiological properties. When analyzed for alignment, 81% of RGCs were observed to project axons radially along the scaffold fibers, with no difference in alignment compared to the nerve fiber layer of retinal explants. When transplanted onto retinal explants, RGCs on ES scaffolds followed the radial pattern of the host retinal nerve fibers, whereas RGCs transplanted directly grew axons in a random pattern. Thus, the use of this scaffold as a cell delivery device represents a significant step towards the use of cell transplant therapies for the treatment of glaucoma and other retinal degenerative diseases.

PMID: 23489919 [PubMed - as supplied by publisher]

Ophthalmic Physiol Opt. 2013 Mar 15. doi: 10.1111/opo.12048. [Epub ahead of print]

Relationship between fixation stability measured with MP-1 and reading performance.

Amore FM, Fasciani R, Silvestri V, Crossland MD, de Waure C, Cruciani F, Reibaldi A.

National Centre of Services and Research for the Prevention of Blindness and Rehabilitation of Low Vision Patients, Rome, Italy.

BACKGROUND: People with visual impairment have reduced reading performance, which is thought to be related to unstable or eccentric fixation. New microperimeters such as the MP-1 offer straightforward analysis of fixation stability. The aim of this study was to investigate the relationship between fixation stability and reading speed in a large cohort of people with diverse causes of visual impairment and to verify the correlation between reading speed and different methods for the quantification of fixation.

METHODS: The better eye of one hundred and twenty subjects was assessed. Fixation values were obtained from the MP-1 microperimeter. Reading speed was evaluated using newspaper text with magnifiers if required.

RESULTS: The poorest fixation stability and reading performance was found in people with age-related macular degeneration while the best fixation was in retinitis pigmentosa subjects. A linear relationship was found between reading speed and the proportion of fixations within 2° ($r^2 = 0.51$, $p < 0.001$) and 4° ($r^2 = 0.36$, $p < 0.001$). A negative correlation was found between reading speed and all three bivariate contour ellipse areas (BCEA; for log transformation of 1-S.D., 2-S.D. and 3-S.D.: $r^2 = 0.39$, $p < 0.001$). In a multiple regression model, proportion of points falling within 2° and 4° circle was significantly related to reading speed ($r^2 = 0.55$, $p < 0.01$; $r^2 = 0.43$ $p < 0.01$); also BCEAs values were strongly related to reading ability only in patients with central vision loss ($r^2 = 0.62$, $p < 0.01$ for LogBCEA 68.2%; $r^2 = 0.61$, $p < 0.01$ for LogBCEA 95.4% and 99.6%) and peripheral defect ($r^2 = 0.52$, $p < 0.01$ for LogBCEA 68.2%; $r^2 = 0.50$, $p < 0.01$ for LogBCEA 95.4%; $r^2 = 0.49$, $p < 0.01$ for LogBCEA 99.6%) but not in combined defect subjects.

CONCLUSIONS: The study confirms that in people with visual impairment the reduced reading performance is correlated with fixation instability. Moreover, there is a strong relationship between reading speed and both the proportion of fixations falling within 2° and 4° and bivariate contour ellipse area values.

PMID: 23489240 [PubMed - as supplied by publisher]

Stem Cells. 2013 Mar 14. doi: 10.1002/stem.1372. [Epub ahead of print]

Developing Rods Transplanted into the Degenerating Retina of Crx-knockout Mice Exhibit Neural Activity Similar to Native Photoreceptors.

Homma K, Okamoto S, Mandai M, Gotoh N, Rajasimha HK, Chang YS, Chen S, Li W, Cogliati T, Swaroop A, Takahashi M.

Laboratory for Retinal Regeneration, Center for Developmental Biology, Riken; 2-2-3 Minatojima-Minami, Chuo-ku, Kobe 650-0047, Japan; Neurobiology-Neurodegeneration & Repair Laboratory, National Eye Institute, National Institutes of Health; 6 Center Drive, Bethesda, Maryland 20892-0610. kohei.homma@nih.gov.

Abstract: Replacement of dysfunctional or dying photoreceptors offers a promising approach for retinal neurodegenerative diseases, including age-related macular degeneration and retinitis pigmentosa. Several studies have demonstrated the integration and differentiation of developing rod photoreceptors when transplanted in wild type or degenerating retina; however, the physiology and function of the donor cells are not adequately defined. Here, we describe the physiological properties of developing rod photoreceptors that are tagged with GFP driven by the promoter of rod differentiation factor, Nrl. GFP-tagged developing rods show Ca2+ responses and rectifier outward currents that are smaller than those observed in fully developed photoreceptors, suggesting their immature developmental state. These immature rods also exhibit hyperpolarization-activated current (Ih) induced by the activation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels. When transplanted into the subretinal space of wild type or retinal degeneration mice, GFP-tagged developing rods can integrate into the photoreceptor outer nuclear layer in wild-type mouse retina, and exhibit Ca2+ responses and membrane current comparable to native rod photoreceptors. A proportion of grafted rods develop rhodopsin-positive outer segment-like structures within two weeks after transplantation into the retina of Crx-knockout mice, and produce rectifier outward current and Ih upon membrane depolarization and hyperpolarization. GFP-positive rods derived from induced pluripotent stem (iPS) cells also display similar membrane current Ih as native developing rod photoreceptors, express rod-specific phototransduction genes, and HCN-1 channels. We conclude that Nrl-promoter driven GFP-tagged donor photoreceptors exhibit physiological characteristics of rods and that iPS cell-derived rods in vitro may provide a renewable source for cell replacement therapy.

PMID: 23495178 [PubMed - as supplied by publisher]

Eye (Lond). 2013 Mar 15. doi: 10.1038/eye.2013.14. [Epub ahead of print]

Digital reader vs print media: the role of digital technology in reading accuracy in age-related macular degeneration.

Gill K, Mao A, Powell AM, Sheidow T.

Department of Ophthalmology,University of Western Ontario, London, Ontario, Canada.

Purpose: To compare patient satisfaction, reading accuracy, and reading speed between digital e-readers (Sony eReader, Apple iPad) and standard paper/print media for patients with stable wet age-related macular degeneration (AMD).

Methods: Patients recruited for the study were patients with stable wet AMD, in one or both eyes, who would benefit from a low-vision aid. The selected text sizes by patients reflected the spectrum of low vision in regard to their macular disease. Stability of macular degeneration was assessed on a clinical examination with stable visual acuity. Patients recruited for the study were assessed for reading speeds on both digital readers and standard paper text. Standardized and validated texts for reading speeds were used. Font sizes in the study reflected a spectrum from newsprint to large print books. Patients started with the smallest print size they could read on the standardized paper text. They then used digital readers to read the same size standardized text. Reading speed was calculated as words per minute by the formula (correctly read words/reading time (s)·60). The visual analog scale was completed by patients after reading each passage. These included their assessment on 'ease of use' and 'clarity of print' for each device and the print paper.

Results: A total of 27 patients were used in the study. Patients consistently read faster (P<0.0003) on the Apple iPad with larger text sizes (size 24 or greater) when compared with paper, and also on the paper compared with the Sony eReader (P<0.03) in all text group sizes. Patients chose the iPad to have the best clarity and the print paper as the easiest to use.

Conclusions: This study has demonstrated that digital devices may have a use in visual rehabilitation for low-vision patients. Devices that have larger display screens and offer high contrast ratios will benefit AMD patients who require larger texts to read.Eye advance online publication, 15 March 2013; doi:10.1038/eye.2013.14.

PMID: 23492860 [PubMed - as supplied by publisher]

Rev Neurosci. 2013 Mar 15:1-22. doi: 10.1515/revneuro-2012-0086. [Epub ahead of print]

Red/near-infrared irradiation therapy for treatment of central nervous system injuries and disorders.

Fitzgerald M, Hodgetts S, Van Den Heuvel C, Natoli R, Hart NS, Valter K, Harvey AR, Vink R, Provis J, Dunlop SA.

Abstract: Abstract Irradiation in the red/near-infrared spectrum (R/NIR, 630-1000 nm) has been used to treat a wide range of clinical conditions, including disorders of the central nervous system (CNS), with several clinical trials currently underway for stroke and macular degeneration. However, R/NIR irradiation therapy (R/NIR-IT) has not been widely adopted in clinical practice for CNS injury or disease for a number of reasons, which include the following. The mechanism/s of action and implications of penetration have not been thoroughly addressed. The large range of treatment intensities, wavelengths and devices that have been assessed make comparisons difficult, and a consensus paradigm for treatment has not yet emerged. Furthermore, the lack of consistent positive outcomes in randomised controlled trials, perhaps due to sub-optimal treatment regimens, has contributed to scepticism. This review provides a balanced précis of outcomes described in the literature regarding treatment modalities and efficacy of R/NIR-IT for injury and disease in the CNS. We have addressed the important issues of specification of treatment parameters, penetration of R/NIR irradiation to CNS tissues and mechanism/s, and provided the necessary detail to demonstrate the potential of R/NIR-IT for the treatment of retinal degeneration, damage to white matter tracts of the CNS, stroke and Parkinson's disease.

PMID: 23492552 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Mar 12. [Epub ahead of print]

Characterization of Neovascular Age-Related Macular Degeneration Patients with Outer Retinal Tubulations.

Faria-Correia F, Barros-Pereira R, Queirós-Mendanha L, Fonseca S, Mendonça L, Falcão MS, Brandão E,

Falcão-Reis F, Carneiro AM.

Department of Ophthalmology, Hospital São João, Porto, Portugal.

Purpose: To characterize the neovascular lesions of patients with age-related macular degeneration (AMD) and outer retinal tubulations (ORTs).

Methods: A retrospective study of 377 eyes with exudative AMD, submitted to intravitreal anti-angiogenic treatment. Patients were divided into 2 groups according to the presence or absence of ORTs on spectral-domain optical coherence tomography (SD-OCT; group 1 - with ORTs; group 2 - without ORTs). Age, best corrected visual acuity (BCVA), fluorescein angiography characteristics, presence of subretinal fibrosis and subfoveal photoreceptor integrity on SD-OCT were analyzed.

Results: Although both groups had a BCVA gain during the follow-up period, initial and final BCVA were lower in group 1 ($p = 0.020$ and $p = 0.042$, respectively). There was no statistically significant difference in the BCVA variation between the 2 groups ($p = 0.907$). Regarding the initial angiographic lesion type, there was a statistically significant difference between the 2 groups ($p = 0.008$): group 1 had more lesions with a classic component and group 2 had more occult lesions with no classic component. There was a statistically significant difference concerning the loss of subfoveal photoreceptor integrity ($p = 0.0007$).

Conclusions: Even though AMD patients with ORTs were associated with poor visual outcomes, we reported BCVA improvement. AMD patients with a classical component in their lesions are prone to develop ORTs.

PMID: 23485655 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2013 Mar 6:0. doi: 10.5301/ejo.5000271. [Epub ahead of print]

Choroidal neovascularization in acquired partial lipodystrophy.

Broadhead GK, Chang A.

The University of Sydney, Sydney and Sydney Retina Clinic and amp; Day Surgery, Sydney - Australia.

Purpose: To report a case of choroidal neovascularization (CNV) associated with acquired partial lipodystrophy (PLD).

Methods: A 55-year-old woman with a known history of PLD presented with acute onset visual loss affecting her right eye and underwent investigations to diagnose the underlying pathology.

Results: Fluorescein angiography and time-domain optical coherence tomography demonstrated the presence of intraretinal edema consistent with CNV. The patient was treated with intravitreal ranibizumab with excellent results, and her vision remains unimpaired 4 years posttreatment.

Conclusions: Choroidal neovascularization is an angiogenic process that can occur following retinal pigment epithelium disruption of any cause. These vessels may then bleed into retinal tissue, with potentially devastating visual consequences. Although rare, PLD has been associated with retinal drusenoid lesions. This is the first case to report CNV in association with PLD, and highlights the importance of considering CNV in the differential diagnosis of acute visual loss in patients with drusenoid diseases such as PLD.

PMID: 23483505 [PubMed - as supplied by publisher]

Retina. 2013 Mar 7. [Epub ahead of print]

OPTICAL COHERENCE TOMOGRAPHY-BASED CORRELATION BETWEEN CHOROIDAL THICKNESS AND DRUSEN LOAD IN DRY AGE-RELATED MACULAR DEGENERATION.

Ko A, Cao S, Pakzad-Vaezi K, Brasher PM, Merkur AB, Albiani DA, Kirker AW, Cui J, Matsubara J, Forooghian F.

Departments of *Ophthalmology, and †Statistics, University of British Columbia, Vancouver, British Columbia, Canada ‡Department of Ophthalmology, University of British Columbia, Vancouver, British Columbia, Canada.

PURPOSE: Spectral domain optical coherence tomography can be used to measure both choroidal thickness and drusen load. The authors conducted an exploratory study using spectral domain optical coherence tomography to determine if a correlation between choroidal thickness and drusen load exists in patients with dry age-related macular degeneration.

METHODS: Forty-four patients with dry age-related macular degeneration were recruited. The drusen area and volume were determined using the automated software algorithm of the spectral domain optical coherence tomography device, and choroidal thickness was measured using enhanced depth imaging. Correlations were determined using multivariable and univariable analyses.

RESULTS: The authors found an inverse correlation between choroidal thickness and drusen load ($r = -0.35$, $P = 0.04$). Drusen load was also correlated with visual acuity ($r = 0.32$, $P = 0.04$). A correlation between choroidal thickness and visual acuity was suggested ($r = -0.22$, $P = 0.21$).

CONCLUSION: Spectral domain optical coherence tomography can be used to assess the correlation between drusen load and choroidal thickness, both of which show a relationship with visual acuity. The measurement of these outcomes may serve as important outcome parameters in routine clinical care and in clinical trials for patients with dry age-related macular degeneration.

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Clin Exp Optom. 2013 Mar 8. doi: 10.1111/cxo.12031. [Epub ahead of print]

Functional and perceived benefits of wearing coloured filters by patients with age-related macular degeneration.

Bailie M, Wolffsohn JS, Stevenson M, Jackson AJ.

Faculty of Life and Health Sciences, University of Ulster, Coleraine, Northern Ireland.

BACKGROUND: The aim was to investigate the visual effect of coloured filters compared to transmission-matched neutral density filters, in patients with dry age-related macular degeneration.

METHODS: Visual acuity (VA, logMAR), contrast sensitivity (Pelli-Robson) and colour vision (D15) were recorded for 39 patients (average age 79.1 ± 7.2 years) with age-related macular degeneration, both in the presence and absence of glare from a fluorescent source. Patients then chose their preferred coloured and matched neutral density transmission filters (NoIR). Visual function tests were repeated with the chosen filters, both in the presence and absence of glare from the fluorescent source. Patients trialled the two filters for two weeks each, in random order. Following the trial of each filter, a telephone questionnaire was completed.

RESULTS: VA and contrast sensitivity were unaffected by the coloured filters but reduced through the neutral density filters ($p < 0.01$). VA and contrast sensitivity were reduced by similar amounts, following the introduction of the glare source, both in the presence and absence of filters ($p < 0.001$). Colour vision error scores were increased following the introduction of a neutral density filter (from 177.6 ± 60.2 to 251.9 ±

115.2) and still further through coloured filters (275.1 ± 50.8; p < 0.001). In the absence of any filter, colour vision error scores increased by 29.1 ± 55.60 units in the presence of glare (F2,107 = 3.9, p = 0.02); however, there was little change in colour vision error scores, in the presence of glare, with either the neutral density or coloured filters. Questionnaires indicated that patients tended to gain more benefit from the coloured filters.

CONCLUSIONS: Coloured filters had minimal impact on VA and contrast sensitivity in patients with age-related macular degeneration; however, they caused a small reduction in objective colour vision, although this was not registered subjectively by patients. Patients indicated that they received more benefit from the coloured filters compared with neutral density filters.

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Maturitas. 2013 Mar 6. pii: S0378-5122(13)00027-3. doi: 10.1016/j.maturitas.2013.01.018. [Epub ahead of print]

Age-related eye disease.

Voleti VB, Hubschman JP.

100 Stein Plaza, Los Angeles, CA 90095, USA.

Abstract: As with many organs, compromised function of the eye is accompanied with age and has become increasingly prevalent with the aging population. When decreased visual loss becomes significant, patients' ability to perform activities of daily living becomes compromised. This decrease in function is met with morbidity and mortality, as well as a large socioeconomic burdon throughout the world. This review summarizes the most common age-related eye diseases, including cataract, glaucoma, diabetic retinopathy, retinal vein occlusion, and age-related macular degeneration. Although our understanding of the genetic and biochemical pathways of these diseases is sill at its primitive stages, we have become able to help our patients improve the quality of life as they age.

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Pathogenesis

Retina. 2013 Mar 13. [Epub ahead of print]

INTRAOCULAR GROWTH FACTORS AND CYTOKINES IN PATIENTS WITH DRY AND NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Muether PS, Neuhann I, Buhl C, Hermann MM, Kirchhof B, Fauser S.

*Department of Vitreoretinal Surgery, Center of Ophthalmology, University of Cologne, Cologne, Germany; and †Eye Department, Red Cross Hospital, Munich, Germany.

PURPOSE: To analyze intraocular growth factor and cytokine concentrations in eyes with different stages of age-related macular degeneration (AMD) compared with controls.

METHODS: The Clinical Age-Related Maculopathy Staging (CARMS) system was used for assignment of patients into the respective categories. Aqueous humor specimens were taken before cataract surgery in 21 controls (CARMS 1) and in 17 early (CARMS 2) and 16 intermediate (CARMS 3) AMD patients. In 18 neovascular (CARMS 5) AMD patients, specimens were taken immediately before anti-vascular endothelial growth factor intravitreal therapy. Luminex multiplex bead assays were conducted for endostatin, angiogenin, vascular endothelial growth factor, platelet-derived growth factor AA, placental growth factor, thrombospondin 2, and fibroblast growth factor a.

RESULTS: Vascular endothelial growth factor concentrations were elevated in CARMS 3 (P = 0.037) and tended to be elevated in CARMS 5 (P = 0.093), whereas levels in CARMS 2 (P = 0.425) were similar to CARMS 1. Platelet-derived growth factor levels were diminished in CARMS 2 (P = 0.020), with a trend to lower levels for CARMS 3 (P = 0.099) and CARMS 5 (P = 0.082) compared with CARMS 1. For CARMS 5, antiangiogenic endostatin was elevated (P < 0.002), while antiangiogenic thrombospondin 2 was reduced (P = 0.029).

CONCLUSION: Clinical Age-Related Maculopathy Staging 3 dry AMD was associated with higher vascular endothelial growth factor levels than CARMS 5 neovascular AMD. Therefore, intraocular vascular endothelial growth factor concentrations do not seem to reflect choroidal neovascularization activity in neovascular AMD directly. Platelet-derived growth factor was decreased in most forms of AMD. The antiangiogenic endostatin was exclusively elevated in neovascular AMD, while thrombospondin 2 was reduced. Age-related macular degeneration disease seems to be associated with a generally altered cytokine system.

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Proc Natl Acad Sci U S A. 2013 Mar 4. [Epub ahead of print]

Dimerization of complement factor H-related proteins modulates complement activation in vivo.

Goicoechea de Jorge E, Caesar JJ, Malik TH, Patel M, Colledge M, Johnson S, Hakobyan S, Morgan BP, Harris CL, Pickering MC, Lea SM.

Centre for Complement and Inflammation Research, Department of Medicine, Imperial College, London W12 0NN, United Kingdom.

Abstract: The complement system is a key component regulation influences susceptibility to age-related macular degeneration, meningitis, and kidney disease. Variation includes genomic rearrangements within the complement factor H-related (CFHR) locus. Elucidating the mechanism underlying these associations has been hindered by the lack of understanding of the biological role of CFHR proteins. Here we present unique structural data demonstrating that three of the CFHR proteins contain a shared dimerization motif and that this hitherto unrecognized structural property enables formation of both homodimers and heterodimers. Dimerization confers avidity for tissue-bound complement fragments and enables these proteins to efficiently compete with the physiological complement inhibitor, complement factor H (CFH), for ligand binding. Our data demonstrate that these CFHR proteins function as competitive antagonists of CFH to modulate complement activation in vivo and explain why variation in the CFHRs predisposes to disease.

PMID: 23487775 [PubMed - as supplied by publisher]

Front Cell Neurosci. 2013;7:22. Epub 2013 Mar 13.

Microglial aging in the healthy CNS: phenotypes, drivers, and rejuvenation.

Wong WT.

Unit on Neuron-Glia Interactions in Retinal Disease, National Eye Institute, National Institutes of Health Bethesda, MD, USA.

Abstract: Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and age-related macular degeneration (AMD), share two characteristics in common: (1) a disease prevalence that increases markedly with advancing age, and (2) neuroinflammatory changes in which microglia, the primary resident immune cell of the CNS, feature prominently. These characteristics have led to the hypothesis that pathogenic mechanisms underlying age-related neurodegenerative disease involve aging changes in

microglia. If correct, targeting features of microglial senescence may constitute a feasible therapeutic strategy. This review explores this hypothesis and its implications by considering the current knowledge on how microglia undergo change during aging and how the emergence of these aging phenotypes relate to significant alterations in microglial function. Evidence and theories on cellular mechanisms implicated in driving senescence in microglia are reviewed, as are "rejuvenative" measures and strategies that aim to reverse or ameliorate the aging microglial phenotype. Understanding and controlling microglial aging may represent an opportunity for elucidating disease mechanisms and for formulating novel therapies.

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J Lipid Res. 2013 Mar 11. [Epub ahead of print]

Post-translational Modification by an Isolevuglandin Diminishes Activity of the Mitochondrial Cytochrome P450 27A1.

Charvet CD, Laird J, Xu Y, Salomon RG, Pikuleva IA.

Case Western Reserve University, United States.

Abstract: Post-translational modification by isolevuglandins (isoLGs), arachidonate oxidation products, is an important yet understudied process associated with altered protein properties. This type of modification affects cytochrome P450 27A1 (CYP27A1), a multi-function enzyme expressed in almost every cell and involved in the metabolism of cholesterol and other sterols. Previously, the CYP27A1 Lys358-isoLG adduct was found in human retina afflicted with age-related macular degeneration. Yet, the effect of Lys358 modification on enzyme activity was not investigated. Herein, we characterized catalytic properties of Lys358 as well as Lys476 CYP27A1 mutants before and after isoLG treatment and quantified the extent of modification by multiple reaction monitoring. The K358R mutant was less susceptible to isoLG-induced loss of catalytic activity than the WT, whereas the K476R mutant was nearly as vulnerable as the WT. Both mutants showed less isoLG modification than WT. Thus, modification of Lys358, a residue involved in redox partner interactions, is the major contributor to isoLG-associated loss of CYP27A1 activity. Our data show the specificity of isoLG modification, provide direct evidence that isoLG adduction impairs enzyme activity, and support our hypothesis that isoLG modification in the retina is detrimental to CYP27A1 enzyme activity, potentially disrupting cholesterol homeostasis.

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J Biol Chem. 2013 Mar 14. [Epub ahead of print]

Oxidative Stress Sensitizes RPE Cells to Complement-Mediated Injury in a Natural Antibody-, Lectin Pathway- and Phospholipid Epitope-Dependent Manner.

Joseph K, Kulik L, Coughlin B, Kunchithapautham K, Bandyopadhyay M, Thiel S, Thielens NM, Holers VM, Rohrer B.

Medical University of South Carolina, United States;

Abstract: Uncontrolled activation of the alternative complement pathway (AP) is thought to be associated with age-related macular degeneration (AMD). Previously, we have shown that in retinal pigmented epithelial (RPE) monolayers, oxidative stress reduced complement inhibition on the cell surface, resulting in sublytic complement activation and loss of transepithelial resistance (TER); but the potential ligand and pathway involved are unknown. ARPE-19 cells were grown as monolayers on Transwell plates, and sublytic complement activation induced with H2O2 and normal human serum (NHS). TER deteriorated rapidly in H2O2-exposed monolayers upon adding NHS. While the effect required AP activation, AP was not sufficient, since elimination of MASP, but not C1q, prevented TER reduction. Reconstitution

experiments to unravel essential components of the lectin pathway (LP) showed that both ficolin and MBL can activate the LP through natural IgM anti-bodies (Ab, IgM-C2) which recognize phospholipid cell surface modifications on oxidatively-stressed RPE cells. The same epitopes were found on human primary embryonic RPE monolayers. Likewise, mouse laser-induced CNV, an injury which involves LP activation, could be increased in Ab-deficient rag1-/- mice using the phospholipid-specific IgM-C2. In summary, using a combination of depletion and reconstitution strategies, we have shown that the LP is required to initiate the complement cascade following natural antibody recognition of neoepitopes, which is then further amplified by the AP. LP-activation is triggered by IgM bound to phospholipids. Taken together, we have defined novel mechanisms of complement activation in oxidatively-stressed RPE, linking molecular events involved in AMD, including the presence of natural antibodies and neoepitopes.

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Cell Struct Funct. 2013 Mar 13. [Epub ahead of print]

Different anti-oxidant effects of thioredoxin 1 and thioredoxin 2 in retinal epithelial cells.

Sugano E, Isago H, Murayama N, Tamai M, Tomita H.

Department of Chemistry and Bioengineering, Faculty of Engineering, Graduate School of Engineering, Iwate University.

Abstract: Age-related macular degeneration (AMD) affects the retina and is the most common cause of blindness in elderly persons in developed countries. The retina is constantly subjected to oxidative stress; to avoid the effects of oxidative stress, retinal pigment epithelial (RPE) cells possess potent anti-oxidant systems. Disruption of these systems leads to dysfunction of RPE cells, which then accelerates the development of AMD. Here, we investigated the role of thioredoxins (TRXs), scavengers of intracellular reactive oxygen species, by assessing the effect of TRX overexpression on cell viability, morphology, NF-<symbol>k</symbol>B expression, and mitochondrial membrane potential, in RPE cells. TRX-overexpressing cell lines were generated by infection of an established human RPE cell line (ARPE) with adeno-associated virus vectors encoding either TRX1 or TRX2. We showed that overexpression of TRXs reduced cell death caused by 4-hydroxynonenal (4-HNE)-induced oxidative stress; TRX2 was more effective than TRX1 in promoting cell survival. 4-HNE caused perinuclear NF-<symbol>k</symbol>B accumulation, which was absent in TRX-overexpressing cells. Moreover, overexpression of TRXs prevented depolarization of mitochondrial membranes; again, TRX2 was more effective than TRX1 in maintaining the membrane potential. The difference in the protective effects of these TRXs against oxidative stress may be due to their expression profile. TRX2 was expressed in the mitochondria, while TRX1 was expressed in the cytoplasm. Thus, TRX2 may directly protect mitochondria by preventing depolarization. These results demonstrate that TRXs are potent antioxidant proteins in RPE cells and their direct effect on mitochondria may be a key to prevent oxidative stress.

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Epidemiology

Br J Ophthalmol. 2013 Mar 13. [Epub ahead of print]

Is aspirin intake associated with early age-related macular degeneration? The Singapore Indian Eye Study.

Cheung N, Tay WT, Cheung GC, Wang JJ, Mitchell P, Wong TY.

Singapore National Eye Centre, Singapore, Singapore.

BACKGROUND/AIMS: To examine the relationship between aspirin intake and early age-related macular degeneration (AMD) among an Asian population.

METHODS: A population based cross sectional study of 3207 ethnic Indians aged 40 years or older residing in Singapore. AMD signs were graded from retinal images following the modified Wisconsin grading system. Information on aspirin intake was obtained from a standardised questionnaire.

RESULTS: The prevalence of early AMD was 5.6%. Aspirin use was reported by 11.4% of participants. Early AMD signs were present among 10.9% of aspirin users and 4.9% of non-aspirin users (p<0.001). After adjusting for potential confounders, including age, smoking and previous cataract surgery, aspirin use was associated with early AMD (OR 1.50; 95% CI: 1.01 to 2.22). The association weakened and was not significant after additional adjustment for cardiovascular disease (OR 1.38; 95% CI 0.89 to 2.14). In stratified analysis, aspirin use was significantly associated with early AMD in participants with (adjusted OR 2.64, 95% CI 1.31 to 5.36) but not without (OR 0.73; 95% CI 0.36 to 1.51) a history of cardiovascular disease (interaction term, p=0.011).

CONCLUSIONS: Aspirin intake overall was not associated with early AMD in this sample of Asian Indians, but in those with a history of cardiovascular disease the association between aspirin intake and early AMD might warrant further investigation.

PMID: 23486919 [PubMed - as supplied by publisher]

Laeknabladid. 2013 Mars;99(1):123-127.

[Visual impairment and blindness in Icelanders aged 50 years and older - The Reykjavík Eye Study.] [Article in Icelandic]

Gunnlaugsdottir E, Arnarsson AM, Jonasson F.

Introduction: The purpose of this study was to examine the cause-specific prevalence and 5-year incidence of visual impairment and blindness among middle-aged and older citizens of Reykjavík.

Material and methods: A random sample of 1045 persons aged 50 years or older underwent a detailed eye examination in 1996 and 846 of the survivors participated in a follow-up examination in 2001. Visual impairment was defined according to World Health Organization definitions as a best-corrected visual acuity of <6/18 but no worse than 3/60, or visual field of ≥5° and <10° around a fixation point in the better eye. Best-corrected visual acuity of <3/60 in the better eye was defined as blindness. The causes of visual impairment or blindness were determined for all eyes with visual loss.

Results: The prevalence of bilateral visual impairment and blindness was 1.0% (95% CI 0.4-1.6) and 0.6% (95% CI 0.1-1.0), respectively and the 5-year incidence was 1.1% (95% CI 0.4-1.8) and 0.4% (95% CI 0.0-0.8), respectively. The prevalence of visual impairment among 60-69 year old participants was 0.6%, but among those aged 80 years or older the prevalence was 7.9%. The major cause of bilateral visual impairment and blindness both at baseline and follow-up was age-related macular degeneration. Cataract accounted for less severe visual loss. The two most common causes of unilateral visual impairment at baseline were amblyopia and cataract. Cataract was the main cause of unilateral visual impairment at 5-year follow-up.

Conclusion: Prevalence and 5-year incidence of both uni- and bilateral visual impairment and blindness increases with age. Age-related macular degeneration was the leading cause of severe visual loss in this population of middle-aged and older Icelanders. Key words: Age-related macular degeneration, blindness, cataract, incidence, prevalence, visual impairment. Correspondence: Elín Gunnlaugsdóttir elingun@gmail.com.

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Genetics

JAMA Ophthalmol. 2013 Mar 1;131(3):383-392.

Risk Alleles in CFH and ARMS2 and the Long-term Natural History of Age-Related Macular Degeneration: The Beaver Dam Eye Study.

Klein R, Myers CE, Meuer SM, Gangnon RE, Sivakumaran TA, Iyengar SK, Lee KE, Klein BE.

OBJECTIVE: To describe the relationships of risk alleles in complement factor H (CFH, rs1061170) and age-related maculopathy susceptibility 2 (ARMS2, rs10490924) to the incidence and progression of age-related macular degeneration (AMD) during a 20-year period.

METHODS: There were 4282 persons aged 43 to 86 years at the baseline examination in 1988-1990 enrolled in a population-based cohort study who participated in at least 1 examination spaced 5 years apart during a 20-year period and had gradable fundus photographs for AMD and genotype information on CFH and ARMS2. Low, intermediate, and high genetic risk for AMD was defined by the presence of 0 to 1, 2, or 3 to 4 risk alleles for CFH and ARMS2, respectively. Multistate models were used to estimate the progression of AMD throughout the entire age range.

RESULTS: There were 2820 (66%), 1129 (26%), and 333 persons (8%) with low, intermediate, and high genetic risk for AMD, respectively. The 5-year incidences of early and late AMD were 9.1% and 1.6%, respectively, and increased with age but did not differ significantly by sex. Using the multistate model, of persons aged 45 years with no AMD in the low, intermediate, and high AMD genetic risk groups, 33.0%, 39.9%, and 46.5%, respectively, were estimated to develop early AMD, and 1.4%, 5.2%, and 15.3% were estimated to develop late AMD by age 80 years.

CONCLUSIONS: These population-based data provide estimates of the long-term risk of the incidence and progression of AMD and its lesions by age and genetic risk alleles for CFH and ARMS2. They also show that when early AMD is present, knowing the phenotype contributes more to risk assessment than knowing the genetic risk based on these 2 AMD genes.

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Innate Immune Network in the Retina Activated by Optic Nerve Crush.

Templeton JP, Freeman NE, Nickerson JM, Jablonski MM, Rex TS, Williams RW, Geisert EE.

Department of Ophthalmology, University of Tennessee Health Science Center, Memphis, TN, 38163, United States.

PURPOSE: Innate immunity plays a role in many diseases, including glaucoma, and age-related macular degeneration (AMD). We have used transcriptome profiling in the mouse to identify a network of genes involved in innate immunity that is present in the normal retina and that is activated by optic nerve crush (ONC).

METHODS: Using a recombinant inbred (RI) mouse strain set (BXD, C57BL/6 crossed with DBA/2J mice), we generate expression datasets (Illumina WG 6.2 arrays) in the normal mouse retina and two days after ONC. The normal dataset is constructed from retinas from 80 mouse strains and the ONC dataset is constructed from 62 strains. These large datasets are hosted by GeneNetwork.org along with a series of powerful bioinformatic tools.

RESULTS: In the retina datasets one intriguing network involves transcripts associated with the innate

immunity. Using C4b to interrogate the normal dataset we can identify a group of genes that are co-regulated across the BXD RI strains. Many of the genes in this network are associated with the innate immune system, including: Serping1, Casp1, C3, Icam1, Tgfbr2, Cfi, Clu, C1qg, Aif1 and Cd74. Following ONC, the expression of these genes is upregulated along with an increase in coordinated expression across the BXD strains. Many of the genes in this network are risk factors for age-related macular degeneration (AMD), including: C3, EFEMP1, MCDR2, CFB, TLR4, HTA1, and C1QTNF5.

CONCLUSIONS: We found a retina-intrinsic innate immunity network that is activated by injury including ONC. Many of the genes in this network are risk factors for retinal disease.

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Mol Cell Biol. 2013 Mar 11. [Epub ahead of print]

AMD-associated silent polymorphisms in HtrA1 impair its ability to antagonize IGF-1.

Jacobo SM, Deangelis MM, Kim IK, Kazlauskas A.

Department of Ophthalmology, Harvard Medical School, The Schepens Eye Research Institute and Massachusetts Eye and Ear Infirmary, 20 Staniford St., Boston, MA 02115, USA.

Abstract: Synonymous single nucleotide polymorphisms (SNPs) within a transcript's coding region produce no change in the amino acid sequence of the protein product, and are therefore intuitively assumed to have neutral effect on protein function. We report that two common variants of HTRA1 that increase inherited risk to neovascular age-related macular degeneration (NvAMD) harbor synonymous SNPs within the exon 1 of HTRA1 that convert common codons for Ala34 and Gly36 to less frequently used codons. The frequent-to-rare codon conversion reduced mRNA translation rate and appeared to compromise HtrA1's conformation and function. The protein product generated from the SNP-containing cDNA displayed enhanced susceptibility to proteolysis and reduced affinity for an anti-HtrA1 antibody. The NvAMD-associated synonymous polymorphisms lie within HtrA1's putative insulin-like growth factor-1 (IGF-1) binding domain. They reduced HtrA1's ability to associate with IGF-1, and to ameliorate IGF-1-stimulated signaling events and cellular responses. These observations highlight the relevance of synonymous codon usage to protein function, and implicate homeostatic protein quality control mechanisms that may go awry in NvAMD.

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Diet

JAMA Ophthalmol. 2013 Mar 1;131(3):365-369.

Electroretinographic Effects of Omega-3 Fatty Acid Supplementation on Dry Age-Related Macular Degeneration.

Gerstenblith AT, Baskin DE, Shah CP, Wolfe JD, Fineman MS, Kaiser RS, Ho AC.

OBJECTIVES: To evaluate the effects of high-dose oral omega-3 fatty acid supplementation on electroretinography and omega-3 index in patients with dry age-related macular degeneration.

DESIGN: Single institution, prospective, nonrandomized, noncomparative interventional case series comprising 34 eyes of 17 patients older than 50 years of age with early to intermediate age-related macular degeneration. Patients received oral supplementation with 4 g of omega-3 fatty acids daily (840 mg eicosapentaenoic acid/2520 mg docosahexaenoic acid) for 6 months. The main outcome measures included Early Treatment Diabetic Retinopathy Study best-corrected visual acuity, change in N1 and P1 peak amplitudes on multifocal electroretinographic testing, and change in serum omega-3 index.

RESULTS: Mean baseline Early Treatment Diabetic Retinopathy Study best-corrected visual acuity letter score was 77 letters (Snellen equivalent of 20/32). There were no statistically significant changes in visual acuity (P = .12) or retinal function by multifocal electroretinographic testing. Serum omega-3 index increased by an average of 7.6% during the course of the study (P < .001). Study limitations included the relatively short duration of the study and small number of participants.

CONCLUSIONS: Short-term supplementation with high doses of omega-3 fatty acids does not result in any measurable changes in visual acuity or retinal function by multifocal electroretinographic testing. Dietary supplementation with 4 g of omega-3 fatty acids results in a significant increase in serum omega-3 index in patients with dry age-related macular degeneration and may provide a useful clinical measure for future studies.

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Discovery of Human Zinc Deficiency: Its Impact on Human Health and Disease.

Prasad AS.

Wayne State University School of Medicine, Department of Oncology, Barbara Ann Karmanos Cancer Institute, Detroit, MI.

Abstract: The essentiality of zinc in humans was established in 1963. During the past 50 y, tremendous advances in both clinical and basic sciences of zinc metabolism in humans have been observed. The major factor contributing to zinc deficiency is high phytate-containing cereal protein intake in the developing world, and nearly 2 billion subjects may be zinc deficient. Conditioned deficiency of zinc has been observed in patients with malabsorption syndrome, liver disease, chronic renal disease, sickle cell disease, and other chronic illnesses. Major clinical problems resulting from zinc deficiency in humans include growth retardation; cell-mediated immune dysfunction, and cognitive impairment. In the Middle East, zinc-deficient dwarfs did not live beyond the age of 25 y, and they died because of intercurrent infections. In 1963, we knew of only 3 enzymes that required zinc for their activities, but now we know of >300 enzymes and >1000 transcription factors that are known to require zinc for their activities. Zinc is a second messenger of immune cells, and intracellular free zinc in these cells participate in signaling events. Zinc has been very successfully used as a therapeutic modality for the management of acute diarrhea in children, Wilson's disease, the common cold and for the prevention of blindness in patients with age-related dry type of macular degeneration and is very effective in decreasing the incidence of infection in the elderly. Zinc not only modulates cell-mediated immunity but is also an antioxidant and anti-inflammatory agent.

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Dietary Omega-3 Fatty Acids, Other Fat Intake, Genetic Susceptibility, and Progression to Incident Geographic Atrophy.

Reynolds R, Rosner B, Seddon JM.

Ophthalmic Epidemiology and Genetics Service, New England Eye Center, Department of Ophthalmology, Tufts Medical Center, Boston, Massachusetts.

OBJECTIVE: To investigate associations between dietary omega-3 fatty acids and other fat intake, genes related to age-related macular degeneration (AMD), and progression to geographic atrophy (GA).

DESIGN: Observational analysis of a prospective cohort.

PARTICIPANTS: A total of 2531 individuals from the Age-Related Eye Disease Study, among which 525 eyes progressed to GA and 4165 eyes did not.

METHODS: Eyes without advanced AMD at baseline were evaluated for progression to GA. Behavioral data, including smoking and body mass index measurements, were collected at baseline using questionnaires. Dietary data were collected from food frequency questionnaires (FFQs) at baseline. Omega -3 fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]), omega-6 fatty acids, monounsaturated, saturated, polyunsaturated, and total fat were adjusted for sex and calories and divided into quintiles (Q). Eight single nucleotide polymorphisms in 7 genes (CFH, ARMS2/HTRA1, CFB, C2, C3, CFI, and LIPC) were genotyped. Cox proportional hazards models were used to test for associations between incident GA and intake of dietary lipids and interaction effects between dietary fat intake and genetic variation on risk of GA.

MAIN OUTCOME MEASURES: Associations between dietary fat intake reported from FFQs, genetic variants, and incident GA.

RESULTS: Increased intake of DHA was significantly associated with reduced risk of progression to GA in models with behavioral factors (model A) plus genetic variants (model B) (P trend = 0.01 and 0.03, respectively). Total omega-3 long chain polyunsaturated (DHA + EPA) fatty acid intake was significantly associated with reduced risk of progression in model B (P trend = 0.02). Monounsaturated fat was associated with increased risk in model A (P trend = 0.05). DHA intake was significantly associated with reduced risk of incident GA among those with the ARMS2/HTRA1 homozygous risk genotype (hazard ratio [HR] Q5 vs Q1, 0.4; P = 0.002; P for interaction between gene and fat intake = 0.05). DHA was not associated with reduced risk of GA among those with the homozygous ARMS2/HTRA1 nonrisk genotype (HR, 1.0; P = 0.90).

CONCLUSIONS: Increased self-reported dietary intake of omega-3 fatty acids is associated with reduced risk of GA and may modify genetic susceptibility for progression to GA.

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