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Drug treatment

Ophthalmology. 2012 May 10. [Epub ahead of print]

Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial.

The IVAN Study Investigators(□) Writing Committee:, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Wordsworth S, Reeves BC.

Institute of Clinical Science, The Queen's University of Belfast, Belfast, Ireland.

PURPOSE: To compare the efficacy and safety of ranibizumab and bevacizumab intravitreal injections to treat neovascular age-related macular degeneration (nAMD).

DESIGN: Multicenter, noninferiority factorial trial with equal allocation to groups. The noninferiority limit was 3.5 letters. This trial is registered (ISRCTN92166560).

PARTICIPANTS: People >50 years of age with untreated nAMD in the study eye who read ≥ 25 letters on the Early Treatment Diabetic Retinopathy Study chart.

METHODS: We randomized participants to 4 groups: ranibizumab or bevacizumab, given either every month (continuous) or as needed (discontinuous), with monthly review.

MAIN OUTCOME MEASURES: The primary outcome is at 2 years; this paper reports a prespecified interim analysis at 1 year. The primary efficacy and safety outcome measures are distance visual acuity and arteriothrombotic events or heart failure. Other outcome measures are health-related quality of life, contrast sensitivity, near visual acuity, reading index, lesion morphology, serum vascular endothelial growth factor (VEGF) levels, and costs.

RESULTS: Between March 27, 2008 and October 15, 2010, we randomized and treated 610 participants. One year after randomization, the comparison between bevacizumab and ranibizumab was inconclusive (bevacizumab minus ranibizumab -1.99 letters, 95% confidence interval [CI], -4.04 to 0.06). Discontinuous treatment was equivalent to continuous treatment (discontinuous minus continuous -0.35 letters; 95% CI, -2.40 to 1.70). Foveal total thickness did not differ by drug, but was 9% less with continuous treatment (geometric mean ratio [GMR], 0.91; 95% CI, 0.86 to 0.97; $P = 0.005$). Fewer participants receiving bevacizumab had an arteriothrombotic event or heart failure (odds ratio [OR], 0.23; 95% CI, 0.05 to 1.07; $P = 0.03$). There was no difference between drugs in the proportion experiencing a serious systemic adverse event (OR, 1.35; 95% CI, 0.80 to 2.27; $P = 0.25$). Serum VEGF was lower with bevacizumab (GMR, 0.47; 95% CI, 0.41 to 0.54; $P < 0.0001$) and higher with discontinuous treatment (GMR, 1.23; 95% CI, 1.07 to 1.42; $P = 0.004$). Continuous and discontinuous treatment costs were £9656 and £6398 per patient per

year for ranibizumab and £1654 and £1509 for bevacizumab; bevacizumab was less costly for both treatment regimens ($P<0.0001$).

CONCLUSIONS: The comparison of visual acuity at 1 year between bevacizumab and ranibizumab was inconclusive. Visual acuities with continuous and discontinuous treatment were equivalent. Other outcomes are consistent with the drugs and treatment regimens having similar efficacy and safety.

PMID: 22578446 [PubMed - as supplied by publisher]

Eye (Lond). 2012 May 18. doi: 10.1038/eye.2012.97. [Epub ahead of print]

Long-term outcome of intravitreal anti-vascular endothelial growth factor therapy with bevacizumab or ranibizumab as primary treatment for subfoveal myopic choroidal neovascularization.

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Purpose: To evaluate the long-term efficacy of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy as primary treatment for subfoveal myopic choroidal neovascularization (CNV).

Methods: In all, 37 treatment-naïve eyes of 37 patients with subfoveal myopic CNV who received intravitreal bevacizumab ($n=22$) or ranibizumab ($n=15$) injections with at least 2 years of follow-up were reviewed. All eyes received initial three loading doses of anti-VEGF at monthly intervals and retreatment was performed in persistent or recurrent CNV. Multivariate regression analyses were performed to determine the prognostic factors for visual outcome.

Results: The mean age was 57.3 years and the mean refractive error was -11.7 D. For all eyes, the mean logMAR best-corrected visual acuity improved from 0.86 (20/145) at baseline to 0.48 (20/60) at 2 years ($P<0.001$). The mean visual improvement for the bevacizumab and ranibizumab groups at 2 years was 2.8 and 5.1 lines, respectively ($P=0.073$). There was no significant difference in the proportion of eyes having visual gain of three or more lines or visual loss of three or more lines between the two groups. The mean number of injections was 3.8 for both bevacizumab and ranibizumab groups. Multivariate analyses showed that eyes with higher myopic refractive error were less likely to have visual gain after treatment ($P=0.043$), while size of CNV was negatively correlated with mean change in vision ($P=0.046$).

Conclusions: Intravitreal anti-VEGF therapy resulted in long-term visual improvement in myopic CNV. The treatment efficacy in terms of visual gain and number of retreatment appeared to be similar between bevacizumab and ranibizumab. Eye advance online publication, 18 May 2012; doi:10.1038/eye.2012.97.

PMID: 22595908 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2011 May 9;129(5):580-4.

Pattern Electrophoretography in Age-Related Macular Degeneration PERG in AMD.

Sheybani A, Brantley MA, Apte RS.

OBJECTIVE: To determine whether prolonged vascular endothelial growth factor inhibition is toxic to the retina by using pattern electrophoretographic imaging in participants with neovascular age-related macular degeneration (AMD).

METHODS: We performed a prospective, single-arm clinical trial of 17 eyes in 17 treatment-naïve participants with subfoveal choroidal neovascularization from AMD. On-label intravitreal ranibizumab was

injected monthly for 6 months. Then pattern electroretinographic imaging was performed before and at 1 month, 3 months, and 6 months after first treatment, and results were interpreted by a trained reader masked to the clinical data. The primary outcome measure was the change in pattern electroretinographic imaging (positive wave peaking at 50 milliseconds [P50] and negative wave peaking at 95 milliseconds [N95] values) from baseline at 6 months. The secondary outcome measure was the change in visual acuity at 6 months.

RESULTS: The mean participant age was 79.6 years (range, 69.5-90.4 years). At baseline, mean (SD) P50 and N95 amplitudes were 1.3 (0.69) μ V and 1.5 (0.71) μ V, respectively. By 6 months, no decrease in P50 or N95 amplitudes from baseline was observed (1.4 [0.47] μ V, $P = .46$; and 1.8 [0.96] μ V, $P = .14$, respectively). Mean visual acuity before treatment was 20/85 with improvement to a mean of 20/55 ($P = .004$) at 6 months.

CONCLUSIONS: This study found no decrease in P50 and N95 amplitudes in participants treated with ranibizumab for neovascular AMD. These findings indicate that vascular endothelial growth factor inhibition with monthly injections of ranibizumab for 6 months likely does not lead to retinal damage.

PMID: 22605013 [PubMed - in process]

Ophthalmologe. 2012 May;109(5):474-8.

[Access to healthcare services for elderly patients with neovascular age-related macular degeneration].

[Article in German]

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BACKGROUND: Neovascular (nv) age-related macular degeneration (AMD) is the leading cause of blindness in Germany and is usually treated with monthly injections of anti-VEGF agents. The current level and the estimated need of service provision for nv-AMD were assessed.

METHODS: Current levels of service provision with ranibizumab (Lucentis) were documented in 3,633 patients in the WAVE study, the currently largest observational study in Germany on the use of anti-VEGF agents. The expected need was calculated using German population figures for 2010 and available prevalence data. Both were stratified by age and gender and descriptively analyzed.

RESULTS: A larger number of younger patients with nv-AMD (< 75 years) than expected were treated in the WAVE study. Expected need in the age groups 75-84 years and 84 years and older was much higher than the proportion of patients actually treated in these age groups (up to 3 times). Based on expected need, women accessed treatment less often than men.

CONCLUSION: In the WAVE study, less elderly persons and in particular elderly women seemed to access treatment for nv-AMD than expected. Future studies should investigate barriers in accessing treatment for nv-AMD and how to address these problems.

PMID: 22581049 [PubMed - in process]

Other treatment & diagnosis

Mol Vis. 2012;18:1045-1054. Epub 2012 Apr 26.

In vivo imaging of choroidal angiogenesis using fluorescence-labeled cationic liposomes.

Hua J, Gross N, Schulze B, Michaelis U, Bohnenkamp H, Guenzi E, Hansen LL, Martin G, Agostini HT.

PURPOSE: Precise monitoring of active angiogenesis in neovascular eye diseases such as age-related macular degeneration (AMD) enables sensitive use of antiangiogenic drugs and reduces adverse side effects. So far, no in vivo imaging methods are available to specifically label active angiogenesis. Here, we report such a technique using fluorophore-labeled cationic liposomes (CL) detected with a standard clinical in vivo scanning laser ophthalmoscope (SLO).

METHODS: C57Bl/6 mice underwent laser coagulations at day 0 (d0) to induce choroidal neovascularization (CNV). Liposomes labeled with Oregon green, rhodamine (Rh), or indocyanine green (ICG) were injected into the tail vein at various time points after laser coagulation, and their fluorescence was observed in vivo 60 min later using an SLO, or afterwards in choroidal flatmounts or cryosections.

RESULTS: SLO detected accumulated fluorescence only in active CNV lesions with insignificant background noise. The best signal was obtained with CL-ICG. Choroidal flatmounts and cryosections of the eye confirmed the location of retained CL in CNV lesions. Neutral liposomes, in contrast, showed no accumulation.

CONCLUSIONS: These results establish fluorophore-labeled CL as high affinity markers to selectively stain active CNV. This novel, non-invasive SLO imaging technique could improve risk assessment and indication for current intraocular antiangiogenic drugs in neovascular eye diseases, as well as monitor therapeutic outcomes. Labeling of angiogenic vessels using CL can be of interest not only for functional imaging in ophthalmology but also for other conditions where localization of active angiogenesis is desirable.

PMID: 22605917 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 Apr 29. [Epub ahead of print]

Confocal scanning laser ophthalmoscope in the retromode imaging modality in exudative age-related macular degeneration.

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PURPOSE: To evaluate the ability of confocal scanning laser ophthalmoscope (cSLO) in the retromode imaging modality in detecting retinal changes secondary to exudative age-related macular degeneration (AMD).

METHODS: Seventeen eyes of 13 consecutive patients affected by CNV secondary to AMD were evaluated with optical coherence tomography (OCT) to detect neuroretinal detachment (NRD), pigment epithelial detachment (PED), cystoid macular edema (CME), and epiretinal membranes (ERM). All eyes were examined with a cSLO equipped with infrared retromode (RM) imaging modality. Infrared and fundus autofluorescence images were also obtained (IR and FAF). The intermethod agreement between OCT and cSLO was evaluated considering single cSLO imaging modality separately (IR, FAF, and RM), and all imaging modalities together.

RESULTS: Eight eyes (47 %) had NRD at OCT; intermethod agreement was poor for any single cSLO imaging modality considered separately (k : 0.14, 0.01, and 0.29 for cSLO IR, FAF, and RM, respectively).

Four eyes had PED at OCT (24 %); intermethod agreement was mild for cSLO RM, poor for IR and FAF (k: 0.51, 0.16, and 0.00, respectively). CME was present in eight eyes (47 %); intermethod agreement was excellent for cSLO RM, poor for IR and FAF (k: 0.88, 0.38, and 0.26, respectively). ERM was present in three eyes (18 %); intermethod agreement was mild for cSLO IR, poor for FAF, and excellent for RM (k: 0.59, 0.00, and 0.76, respectively).

CONCLUSIONS: cSLO RM imaging is a useful and reproducible technique in detecting retinal features associated with CNV, particularly CME.

PMID: 22580948 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 May 11. doi: 10.1111/j.1755-3768.2012.02434.x. [Epub ahead of print]

Peripheral autofluorescence findings in age-related macular degeneration.

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Purpose: To describe the peripheral autofluorescent findings in patients with age-related macular degeneration (AMD) using ultrawide-field imaging.

Methods: We retrospectively reviewed the ultra-wide-field autofluorescent images of all patients diagnosed with AMD or macular drusen at the Department of Ophthalmology of Weill Cornell Medical College from July 2010 to September 2011. Peripheral autofluorescent phenotypes included normal autofluorescence, focal pinpoint hyperfluorescence, granular fluorescent changes, patchy hypofluorescence, and reticular hypofluorescence.

Results: One hundred and ten consecutive patients (220 eyes) with a diagnosis of AMD or macular drusen were imaged using ultra-wide-field autofluorescent technology during the study period. Eighty-three patients (157 eyes) were included in the final analysis. Peripheral autofluorescent abnormalities were present in 63.6% of eyes with AMD versus 35.7% of control eyes ($p = 0.049$). Granular fluorescent changes ($p = 0.0001$) and patchy hypofluorescence ($p = 0.0015$) were more common in eyes with advanced AMD than in eyes with early AMD or control eyes. Granular fluorescent changes were also more common in eyes with choroidal neovascularization ($p = 0.026$) or geographic atrophy ($p = 0.0001$). Patchy hypofluorescence ($p = 0.0001$) was more common in eyes with geographic atrophy.

Conclusions: Peripheral autofluorescent abnormalities are common in eyes with AMD. The peripheral findings in eyes with AMD may represent different phenotypes, which may indicate different environmental or genetic factors in the development of AMD. Characterizing the different peripheral phenotypes may have implications for diagnosis and treatment of AMD subtypes.

PMID: 22578271 [PubMed - as supplied by publisher]

Regen Med. 2012 May;7(3):291-4.

Conference Scene: Trends in the stem cells marketplace - report from Select Biosciences Stem Cells 2012 Conference.

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Abstract

Select Biosciences hosted a three-track conference in San Diego (CA, USA) focusing on stem cells,

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circulating tumor cells and cell culture. In this article, I present a snapshot of selected presentations from the Stem Cells conference track and frame them in the big picture of the trajectory of this field and expectations for the coming years. This conference track focused on three themes: cellular therapy translational development and clinical trials in this space; biobanking; and stem cells in research, drug discovery and development. Even though all of the above segments of the stem cells marketplace are undergoing vigorous growth and expansion, perhaps the most vigorous growth exists in the translational research space, wherein various adult stem cell populations are being developed to address different important disease classes such as cardiovascular disease, CNS diseases, diabetes, HIV and various types of cancer, as well as macular degeneration and other disorders. This segment of the conference will be a key subject of this article.

PMID: 22594323 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2012 May 15. [Epub ahead of print]

The Dark Atrophy with Indocyanine Green Angiography in Stargardt Disease.

Giani A, Pellegrini M, Carini E, Peroglio Deiro A, Bottoni F, Staurenghi G.

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Purpose: To evaluate differences in fluorescein and indocyanine green angiography (FA and ICGA) findings between subjects affected by Stargardt disease (STGD) and atrophic age-related macular degeneration (AMD)

Methods: Consecutive, cross-sectional case series. A total of 24 eyes of 12 patients with STGD and 23 eyes of 14 patients with atrophic AMD were enrolled in the study. Patients underwent dynamic simultaneous FA and ICGA using Spectralis HRA+OCT. Images were recorded from the initial filling of choroidal and retinal vessels throughout all the phases of the angiogram. Spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence were also executed. FA and ICGA findings in the two groups were evaluated

Results: In 92% (22/24) of eyes affected by STGD, ICGA showed hypocyanescence from the areas of atrophy, more evident in the late phases. This finding, defined as ICGA-imaged "dark atrophy", was present in only 13% (3/23) of the eyes affected by atrophic AMD. The remaining eyes in both groups showed iso- or mild hypercyanescence from the areas of atrophy. Eyes with ICGA-imaged dark atrophy, both in STGD and atrophic AMD groups, did not show early obscuration of the choroidal vessels by FA. SD-OCT revealed morphologically intact choroid in STGD patients with ICGA-imaged dark atrophy. In atrophic AMD eyes with ICGA-imaged dark atrophy, SD-OCT revealed a severely thinned choroid

Conclusions: Hypocyanescence by ICGA from the areas of atrophy was more frequent in STGD compared to atrophic AMD. This finding, along with SD-OCT evidence of intact choroid, suggests a possible selective damage of the choriocapillaris in STGD.

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Invest Ophthalmol Vis Sci. 2012 May 15. [Epub ahead of print]

Spatial correlation between hyperpigmentary changes on color fundus photography and hyperreflective foci on SDOCT in intermediate AMD.

Folgar FA, Chow JH, Farsiu S, Wong WT, Schuman SG, O'Connell RV, Winter KP, Chew EY, Hwang TS, Srivastava SK, Harrington MW, Clemons TE, Toth CA.

Duke University Eye Center, Durham, NC, United States.

Purpose: Macular hyperpigmentation is associated with progression from intermediate to advanced age-related macular degeneration (AMD). The purpose of this study was to accurately correlate hyperpigmentary changes with spectral domain optical coherence tomography (SDOCT) hyperreflective foci in eyes with non-advanced AMD.

Methods: A prospective cross-sectional analysis of 314 eyes (314 subjects) with intermediate AMD was performed in the multicenter AREDS2 Ancillary SDOCT Study to correlate hyperpigmentary changes on color fundus photographs (CFP) with abnormal morphology on SDOCT. Spatial coregistration was performed with an automated algorithm in 2 non-overlapping subsets of 20 study eyes with double-masked CFP and SDOCT grading by certified investigators.

Results: Macular CFP hyperpigmentation was significantly associated with SDOCT intraretinal hyperreflective foci in 314 study eyes ($p < 0.001$). In a sub-study of 40 eyes, automated intermodality spatial correlation was successfully achieved in all 136 (100%) retinal regions selected for CFP and SDOCT grading. In a subset of 20 study eyes, 28 of 39 (72%) retinal CFP regions with hyperpigmentation were correlated with focal hyperreflectivity on SDOCT, versus 7 of 39 (17.9%) control regions ($p < 0.001$). In another subset of 20 eyes, 21 of 29 (72.4%) SDOCT regions with hyperreflective foci were correlated with hyperpigmentary changes on CFP, versus 2 of 29 (6.9%) control regions ($p < 0.001$).

Conclusions: A novel algorithm achieves automated intermodality spatial correlation for masked grading of regions selected on CFP and SDOCT. In intermediate AMD, macular hyperpigmentation has high spatial correlation to SDOCT hyperreflective foci and often represents the same anatomical lesion.

PMID: 22589439 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging. 2012 May 3;43(3):e38-40. doi: 10.3928/15428877-20120426-01.

Dramatic Regression of Amelanotic Choroidal Melanoma With PDT Following Poor Response to Brachytherapy.

Tuncer S, Kir N, Shields CL.

Abstract

Photodynamic therapy (PDT) has been used for treatment of choroidal neovascular membrane from exudative macular degeneration. Other applications include treatment of some intraocular tumors, such as choroidal hemangioma, vasoproliferative tumor, and choroidal osteoma. The authors report the effect of PDT for amelanotic choroidal melanoma. A 40-year-old woman with an amelanotic choroidal melanoma of 6.5 mm thickness showed poor response to iodine brachytherapy (80 Gy apical dose) with no reduction in thickness at 16 months of follow-up. There was prominent residual tumor. The amelanotic tumor was treated with verteporfin PDT using three overlapping spots (8,600 microns), with avoidance of the optic disc using standard treatment parameters. Dramatic tumor regression over 2 months to a completely flat scar (1.3 mm thickness) was documented and remained stable at 50 months of follow-up. Amelanotic choroidal melanoma with incomplete response following conventional plaque radiotherapy can be treated with verteporfin PDT for consolidation.

PMID: 22589358 [PubMed - in process]

Pathogenesis and pre-clinical

Curr Eye Res. 2012 Jun;37(6):500-7.

Interaction between VEGF and Calcium-Independent Phospholipase A(2) in Proliferation and Migration of Retinal Pigment Epithelium.

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Purpose: Inhibition of VEGF in the eye is an important treatment modality for reducing proliferation and migration of retinal pigment epithelium (RPE) in age-related macular degeneration (AMD). Additionally, previous studies suggest calcium-independent phospholipase A(2) group VIA (iPLA(2)-VIA) to be a potential regulator of cell proliferation and migration, and evidence show abundant expression of iPLA(2)-VIA in RPE cells. The aim of the present study was to evaluate the potential role of iPLA(2)-VIA in VEGF-induced proliferation and migration of RPE cells.

Materials and methods: The human RPE cell line, ARPE-19, was used in all assays. To explore the role of iPLA(2)-VIA in VEGF-induced RPE proliferation and migration, iPLA(2)-VIA inhibition by the iPLA(2)-VIA specific inhibitor, bromoenol lactone, was done. RPE cell proliferation and migration were evaluated by measurements of incorporated radioactive thymidine in DNA and by a Boyden chamber technique, respectively. A luciferase assay monitored the VEGF-induced iPLA(2)-VIA transcriptional activity. Western blot analysis and an activity assay were used to detect the protein levels and activity of iPLA(2)-VIA respectively after treatment with VEGF.

Results: RPE cells treated with VEGF showed significant increased proliferation and migration. Furthermore, inhibition of iPLA(2)-VIA significantly reduced the spontaneous proliferation and migration as well as the VEGF-induced proliferation and migration. Finally, inhibition of iPLA(2)-VIA reduced the VEGF-induced iPLA(2)-VIA-activity, -protein level, and -promoter activity.

Conclusions: A significant interaction between VEGF and iPLA(2)-VIA in the regulation of RPE cells appears to be relevant in elucidating the exact mechanisms of action in the proliferative and migratory phenotype of RPE cells in AMD.

PMID: 22577768 [PubMed - in process]

Clin Experiment Ophthalmol. 2012 May 18. doi: 10.1111/j.1442-9071.2012.02809.x. [Epub ahead of print]

Ocular rigidity: bio-mechanical role, in vivo measurements and clinical significance.

Detorakis ET, Pallikaris IG.

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Abstract

Ocular rigidity (OR) refers to the relationship between pressure and volume changes in the eyeball and is associated with the bio-mechanical behaviour of the eye. Since the description of the differential tonometry method for the calculation of an OR coefficient by Friedenwald, several other methodologies have been proposed to measure OR for an individual eye, including the anterior chamber manometry, axial length (AL) changes, measurement of pulse amplitude and fundus pulse, ultrasound elastography and evaluation of corneal hysteresis. However, most of these methodologies suffer from deficiencies, such as invasive nature, poor accuracy or reproducibility or technical complexity, which compromise their wide-spread application in clinical practice. Nevertheless, it is possible that OR affects the pathogenesis and clinical course of a variety of ocular conditions, including glaucoma, age-related macular degeneration, presbyopia and corneal changes following refractive surgery. The accuracy of IOP measurements by many tonometers, including the gold-standard Goldmann applanation tonometry, is also affected by OR. The importance of incorporating OR in clinical decision making justifies further research towards the development of non-invasive and easy-to-use methodologies for the accurate measurement of OR in the

every-day practice.

PMID: 22594543 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 May 17. [Epub ahead of print]

Redox Proteomic Identification of Visual Arrestin Dimerization in Photoreceptor Degeneration After Photic Injury.

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Purpose: Light-induced oxidative stress is an important risk factor for age-related macular degeneration, but the downstream mediators of photoreceptor and retinal pigment epithelium cell death after photic injury are unknown. Given our previous identification of sulfhydryl/disulfide redox status as a factor in photoreceptor survival, we hypothesized that formation of one or more disulfide-linked homo- or hetero-dimeric proteins might signal photoreceptor death after light-induced injury.

Methods: Two-dimensional (non-reducing/reducing) gel electrophoresis of Wistar rat retinal homogenates after 10 hours of 10,000 lux (4200°K) light in vivo, followed by mass spectrometry identification of differentially oxidized proteins.

Results: The redox proteomic screen identified homodimers of visual arrestin (Arr1; S antigen) after toxic levels of light injury. Immunoblot analysis revealed a light duration-dependent formation of Arr1 homodimers, as well as other Arr1 oligomers. Immunoprecipitation studies revealed that the dimerization of Arr1 due to photic injury was distinct from association with its physiological binding partners, rhodopsin and enolase1. Systemic delivery of tris(2-carboxyethyl)phosphine, a specific disulfide reductant, both decreased Arr1 dimer formation and protected photoreceptors from light-induced degeneration in vivo.

Conclusions: These findings suggest a novel arrestin-associated pathway by which oxidative stress could result in cell death, and identify disulfide-dependent dimerization as a potential therapeutic target in retinal degeneration.

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Clin Experiment Ophthalmol. 2012 May 18. doi: 10.1111/j.1442-9071.2012.02813.x. [Epub ahead of print]

Effect of cediranib, an inhibitor of vascular endothelial growth factor receptor tyrosine kinase, in a mouse model of choroidal neovascularization.

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Background: This study was conducted to evaluate the effect of cediranib, an inhibitor of vascular endothelial growth factor receptor tyrosine kinase, in a mouse model of laser-induced choroidal neovascularization (CNV).

Methods: CNV was induced in C57BL/6 mice by rupturing Bruch's membrane using laser photocoagulation. Following laser injury, the mice were divided into three groups and administered either vehicle, 1 mg/kg or 5 mg/kg of cediranib daily by oral gavage for two weeks. Two weeks after laser injury,

the area of CNV lesions were measured by choroidal flat mounts using fluorescein-labeled dextran. Immunofluorescence staining with isolectin IB4 was also used to quantify the CNV lesions.

Results: Choroidal flat mount analysis revealed that orally administered cediranib reduced the extent of CNV. The groups treated with 1 and 5 mg/kg/day showed 57.2 and 66.0 % reduction of CNV lesions, respectively, compared to the control group treated with vehicle alone ($P = 0.012$). The size of the fluorescently labeled CNV complex in cediranib-treated groups was much smaller than that from vehicle-treated group ($P = 0.035$).

Conclusions: Cediranib inhibited laser-induced CNV in mice and may have therapeutic potential for patients with neovascular age-related macular degeneration.

PMID: 22594647 [PubMed - as supplied by publisher]

Prog Retin Eye Res. 2012 May 3. [Epub ahead of print]

Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease.

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Abstract

We review the cellular and physiological mechanisms responsible for the regulation of blood flow in the retina and choroid in health and disease. Due to the intrinsic light sensitivity of the retina and the direct visual accessibility of fundus blood vessels, the eye offers unique opportunities for the non-invasive investigation of mechanisms of blood flow regulation. The ability of the retinal vasculature to regulate its blood flow is contrasted with the far more restricted ability of the choroidal circulation to regulate its blood flow by virtue of the absence of glial cells, the markedly reduced pericyte ensheathment of the choroidal vasculature, and the lack of intermediate filaments in choroidal pericytes. We review the cellular and molecular components of the neurovascular unit in the retina and choroid, techniques for monitoring retinal and choroidal blood flow, responses of the retinal and choroidal circulation to light stimulation, the role of capillaries and pericytes in regulating blood flow, putative signaling mechanisms mediating neurovascular coupling in the retina, and changes that occur in the retinal and choroidal circulation during diabetic retinopathy, age-related macular degeneration, glaucoma, and Alzheimer's disease. We close by discussing issues that remain to be explored.

PMID: 22580107 [PubMed - as supplied by publisher]

Free Radic Biol Med. 2012 May 1. [Epub ahead of print]

Systemic administration of the iron chelator deferiprone protects against light-induced photoreceptor degeneration in the mouse retina.

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Abstract

Oxidative stress plays a key role in a light-damage (LD) model of retinal degeneration as well as in age-related macular degeneration (AMD). Since iron can promote oxidative stress, the iron chelator deferiprone (DFP) was tested for protection against light-induced retinal degeneration. To accomplish this, A/J mice were treated with or without DFP in drinking water, and then were placed in constant bright white fluorescent light (10,000 lx) for 20h. Retinas were evaluated at several time points after light exposure. Photoreceptor apoptosis was assessed using the TUNEL assay. Retinal degeneration was assessed by histology 10 days after exposure to damaging white light. Two genes upregulated by oxidative stress, heme oxygenase 1 (Hmox1) and ceruloplasmin (Cp), as well as complement component 3 (C3) were quantified by RT-qPCR. Cryosections were immunolabeled for oxidative stress marker (nitrotyrosine), a microglial marker (Iba1), as well as both heavy (H) and light (L) ferritin. Light exposure resulted in substantial photoreceptor-specific cell death. Dosing with DFP protected photoreceptors, decreasing the numbers of TUNEL-positive photoreceptors and increasing the number of surviving photoreceptors. The retinal mRNA levels of oxidative stress-related genes and C3 were upregulated following light exposure and diminished by DFP treatment. Immunostaining for nitrotyrosine indicated that DFP reduced the oxidative stress caused by light exposure. Robust H/L-ferritin-containing microglial activation and migration to the outer retina occurred after light exposure and DFP treatment reduced microglial invasion. DFP is protective against light-induced retinal degeneration and has the potential to diminish oxidative stress in the retina.

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Epidemiology

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The Relationship of Cataract and Cataract Extraction to Age-related Macular Degeneration: The Beaver Dam Eye Study.

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OBJECTIVE: To examine the associations of cataract and cataract surgery with early and late age-related macular degeneration (AMD) over a 20-year interval.

DESIGN: Longitudinal population-based study of age-related eye diseases.

PARTICIPANTS: Beaver Dam Eye Study participants.

METHODS: Persons aged 43 to 86 years participated in the baseline examination in 1988-1990. Participants were followed up at 5-year intervals after the baseline examination. Examinations consisted of ocular examination with lens and fundus photography, medical history, measurements of blood pressure, height, and weight. Values of risk variables were updated, and incidences of early and late AMD were calculated for each 5-year interval. Odds ratios were computed using discrete linear logistic regression modeling with generalized estimating equation methods to account for correlation between the eyes and multiple intervals.

MAIN OUTCOME MEASURES: Age-related macular degeneration.

RESULTS: After adjusting for age and sex, neither cataract nor cataract surgery was associated with increased odds for developing early AMD. Further adjusting for high-risk gene alleles (CFH and ARMS2) and other possible risk factors did not materially affect the odds ratio (OR). However, cataract surgery was associated with incidence of late AMD (OR 1.93; 95% confidence interval [CI], 1.28-2.90). This OR was not materially altered by further adjusting for high-risk alleles (CFH Y402H, ARMS2) or other risk factors. The OR for late AMD was higher for cataract surgery performed 5 or more years prior compared with less than

5 years prior.

CONCLUSIONS: These data strongly support the past findings of an association of cataract surgery with late AMD independent of other risk factors, including high-risk genetic status, and suggest the importance of considering these findings when counseling patients regarding cataract surgery. These findings should provide further impetus for the search for measures to prevent or delay the development of age-related cataract.

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Projected prevalence of age-related macular degeneration in Scandinavia 2012-2040.

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Purpose: To project the number of persons with late age-related macular degeneration (AMD) in Scandinavia through 2040.

Methods: Age- and sex-specific prevalence rates of late AMD (choroidal neovascularization and geographic atrophy) from the European Eye Study and the Eye Diseases Prevalence Research Group were applied to the projected Danish, Norwegian and Swedish population from 2012 to 2040.

Results: A total of 187 000 persons aged ≥ 65 years in Scandinavia are currently affected by late AMD: 47 000 in Denmark, 43 000 in Norway and 97 000 in Sweden. Owing to an ageing population, the number of persons affected by late AMD will increase 75% to 328 000 in 2040.

Conclusion: The number of patients with late AMD in Scandinavia is expected to increase substantially over the next three decades, resulting in increased demand for ophthalmic health services.

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A suggested association between hypothyroidism and age-related macular degeneration.

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Objective: To explore the relationship between age-related macular degeneration (AMD) and hypothyroidism in a population-based sample of adults 50 years and older in the United States. **Study Population:** Participants aged 50 years and older (N = 9,677). Of this total, 356 participants reported having AMD and 9321 reported not having AMD.

Methods: Information pertaining to self-reported thyroid disease (specifically hypothyroidism) and AMD was obtained from the 2008 National Health Interview Survey. The association between self-reported data on hypothyroidism and AMD was estimated using logistic regression adjusting for the potentially confounding influence of demographic, behavioral, and health-related characteristics.

Results: Of the 356 people with AMD, 20.9% reported hypothyroidism compared to 11.2% of those 9,321 without AMD (odds ratio [OR] 2.33; 95% confidence interval [CI] 1.69-3.21). After adjusting for the

confounding influence of age, sex, smoking, and race, the association between AMD and hypothyroidism remained significant (OR 1.59; 95% CI 1.10-2.30).

Conclusions: The results of this study add to the small body of literature indicating a possible relationship between AMD and hypothyroidism. As many of the risk factors for AMD are also risk factors for hypothyroidism, future studies are warranted to ascertain the relationship between the two diseases.

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Genetics

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Association of genetic polymorphisms with response to bevacizumab for neovascular age-related macular degeneration in the Chinese population.

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Aims: To determine whether there is an association between CFH, ARMS2, HTRA1, VEGF, SERPING1 or C3 genotypes and patient response to treatment with intravitreal bevacizumab for neovascular age-related macular degeneration (AMD).

Materials & methods: This was a multicenter prospective study. One hundred and forty four patients with neovascular AMD treated with bevacizumab were recruited from 13 centers. Twelve SNPs were genotyped using Sequenom. Visual acuity score (VAS), central retinal thickness and maximum thickness of lesion were measured at each visit.

Results: For the CFH rs800292 polymorphism, mean VAS changes were 4.4, 8.7 and 15.5 letters in the CC, CT and TT genotype carriers ($p = 0.009$). For ARMS2 rs10490924, mean VAS changes were 3.6, 12.1 and 9.6 letters for the TT, TG and GG genotypes ($p = 0.001$). For HTRA1 rs11200638, mean VAS changes were 3.6, 12.3 and 9.6 letters for the AA, AG and GG genotypes ($p < 0.001$).

Conclusion: CFH, ARMS2 and HTRA1 genotypes may influence patient response to treatment with intravitreal bevacizumab for neovascular AMD.

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Clinical application of exome sequencing in undiagnosed genetic conditions.

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Background: There is considerable interest in the use of next-generation sequencing to help diagnose unidentified genetic conditions, but it is difficult to predict the success rate in a clinical setting that includes patients with a broad range of phenotypic presentations.

Methods: The authors present a pilot programme of whole-exome sequencing on 12 patients with unexplained and apparent genetic conditions, along with their unaffected parents. Unlike many previous studies, the authors did not seek patients with similar phenotypes, but rather enrolled any undiagnosed

proband with an apparent genetic condition when predetermined criteria were met.

Results: This undertaking resulted in a likely genetic diagnosis in 6 of the 12 probands, including the identification of apparently causal mutations in four genes known to cause Mendelian disease (TCF4, EFTUD2, SCN2A and SMAD4) and one gene related to known Mendelian disease genes (NGLY1). Of particular interest is that at the time of this study, EFTUD2 was not yet known as a Mendelian disease gene but was nominated as a likely cause based on the observation of de novo mutations in two unrelated probands. In a seventh case with multiple disparate clinical features, the authors were able to identify homozygous mutations in EFEMP1 as a likely cause for macular degeneration (though likely not for other features).

Conclusions: This study provides evidence that next-generation sequencing can have high success rates in a clinical setting, but also highlights key challenges. It further suggests that the presentation of known Mendelian conditions may be considerably broader than currently recognised.

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