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Drug treatment

Am J Ophthalmol. 2015 Jul 28. [Epub ahead of print]

Baseline Predictors of 12-Month Treatment Response to Ranibizumab in Patients with Wet Age-Related Macular Degeneration.

Regillo CD, Busbee BG, Ho AC, Ding B, Haskova Z.

PURPOSE: To identify baseline characteristics predictive of visual acuity (VA) outcomes at month 12 (M12) and treatment frequency in the first 12 months of the phase III HARBOR study.

DESIGN: Retrospective, exploratory analysis of multi-center, randomized, controlled trial data.

METHODS: Setting: Randomized, multicenter.

STUDY POPULATION: Patients aged ≥ 50 years with subfoveal wet age-related macular degeneration (AMD) who had best-corrected VA (BCVA) values measured at baseline and M12.

INTERVENTION: Intravitreal ranibizumab 0.5-mg administered monthly (n=249) or as-needed (PRN) after 3 monthly loading doses (n=251).

MAIN OUTCOME MEASURES: BCVA change from baseline at M12, percentage of patients who gained ≥ 15 letters (3-lines) in BCVA from baseline at M12, and percentage of patients who achieved $\geq 20/40$ vision (Snellen) at M12 served as the basis for analyzing baseline predictors of observed VA outcomes in the monthly and PRN groups. Total number of ranibizumab PRN injections in the first 12 months was also evaluated. Only variables that were statistically significant ($P < .05$) remained in the final statistical models.

RESULTS: Baseline predictors of BCVA change from baseline at M12 and/or percentage of 3-line gainers included lower BCVA, younger age, smaller total choroidal neovascularization (CNV) leakage area, smaller area of occult CNV, and presence of subretinal fluid (SRF). Baseline predictors of $\geq 20/40$ vision at M12 included higher BCVA, smaller total CNV leakage area, and presence of SRF. SRF thickness $> 118.25\text{-}\mu\text{m}$ at baseline predicted requiring more ranibizumab injections in the first 12 months of treatment.

CONCLUSIONS: Select baseline characteristics have predictive value for visual prognosis and treatment frequency in ranibizumab-treated patients with wet AMD.

PMID: 26231305 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Jul 22;9:1315-1320.

Clinical experience with fixed bimonthly aflibercept dosing in treatment-experienced patients with neovascular age-related macular degeneration.

Khanani AM.

PURPOSE: To evaluate the durability of fixed bimonthly dosing of intravitreal aflibercept for neovascular age-related macular degeneration.

METHODS: Records of 16 patients were retrospectively reviewed. Patients received three initial 2.0 mg monthly doses of aflibercept then 8-weekly doses according to the product label. Best-corrected visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] letters), central macular thickness, fluid on optical coherence tomography, and pigment epithelial detachment (PED) were measured.

RESULTS: Prior to starting aflibercept, 13 patients had subretinal fluid (SRF), five had intraretinal fluid (IRF), four had PED, and baseline visual acuity (VA) was 62 approximate ETDRS letters. Following the monthly dosing, seven patients had no improvement or decreased VA, ten patients still had SRF/IRF, and PED had worsened in one patient. At Visit 4, an average of 6.8 weeks after Visit 3, VA had decreased in seven patients, SRF/IRF had increased in 12 patients, and PED had returned in all patients who initially responded. Based on the presence of fluid after the initial monthly injections, 12 patients could not be extended to fixed bimonthly dosing.

CONCLUSION: This study adds to the growing body of evidence on the need for flexible dosing schedules for the personalized treatment of neovascular age-related macular degeneration.

PMID: 26229424 [PubMed - as supplied by publisher] PMCID: PMC4516180

Eye (Lond). 2015 Jul 31. [Epub ahead of print]

Month-6 primary outcomes of the READ-3 study (Ranibizumab for Edema of the mAcula in Diabetes -Protocol 3 with high dose).

Do DV, Sepah YJ, Boyer D, Callanan D, Gallemore R, Bennett M, Marcus DM, Halperin L, Sadiq MA, Rajagopalan N, Campochiaro PA, Nguyen QD.

Purpose: To compare 2.0 mg ranibizumab (RBZ) injections with 0.5 mg RBZ for eyes with center-involved diabetic macular edema (DME) and a central subfield thickness (CFT) of ≥ 250 μ m on time-domain optical coherence tomography.

Design: Randomized, controlled, multicenter clinical trial.

Methods: Eligible eyes were randomized in a 1:1 ratio to 0.5 mg (n=77) or 2.0 mg (n=75) RBZ. Study eyes received 6-monthly injections.

Main outcome measures: The primary outcome measure was the mean change in best corrected visual acuity (BCVA) at month 6. Secondary outcomes included the incidence and severity of systemic and ocular adverse events and the mean change in CFT from baseline.

Results: In all, 152 eyes (152 patients) were randomized in the study. At month 6, the mean improvement from baseline BCVA was +9.43 letters in the 0.5 mg RBZ group and +7.01 letters in the 2.0 mg RBZ group (P=0.161). At month 6, one death occurred in the 0.5 mg RBZ group and three deaths in the 2.0 mg RBZ group, all due to myocardial infarction in subjects with a prior history of heart disease. Mean CFT was reduced by 168.58 μ m in the 0.5 mg RBZ group and by 159.70 μ m in the 2.0 mg RBZ group (P=0.708).

Conclusions: There was no statistically significant difference in the mean number of letters gained between the 0.5 and 2.0 mg RBZ groups through month 6. In this DME study population, high-dose RBZ does not appear to provide additional benefit over 0.5 mg RBZ.

PMID: 26228291 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2015 Jul 15:0. [Epub ahead of print]

Evaluation of inner and outer retinal thickness in patients receiving intravitreal ranibizumab injections for diabetic macular edema.

Dursun A, Ozec AV, Kirboga K, Dursun FG, Toker MI, Erdogan H, Arici MK.

PURPOSE: To measure inner and outer retinal thickness with optical coherence tomography (OCT) in patients in whom intravitreal ranibizumab was administered due to diabetic macular edema (DME) and to investigate its relation to the visual prognosis.

METHODS: In this retrospective case series, there were 60 consecutive eyes with DME in which intravitreal ranibizumab injection was performed for 3 times in 1-month intervals. All patients underwent full ophthalmic examination and spectral-domain OCT (SD-OCT). The total retinal thickness, the inner thickness, and the outer thickness in 4 parafoveal subfields were measured. The correlation between the retinal thickness and logMAR best-corrected visual acuity (BCVA) was investigated.

RESULTS: No significant correlation was found between the total retinal thickness in the central and other subfields and either the baseline or final visit logMAR BCVA values ($p > 0.05$). There was a significant positive correlation between the final visit logMAR BCVA values and pretreatment inner retinal thickness in the nasal and inferior subfields ($r = 0.270$, $p = 0.037$, and $r = 0.410$, $p = 0.001$, respectively). There was significant negative correlation between the final visit logMAR BCVA values and pretreatment outer retinal thickness in nasal and temporal parafoveal subfields ($r = -0.297$, $p = 0.021$, and $r = -0.268$, $p = 0.038$, respectively).

CONCLUSIONS: It could be beneficial to use inner and outer retinal thickness instead of total retinal thickness in determination of short-term prognosis in patients who had intravitreal ranibizumab injection for DME.

PMID: 26220809 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Hum Gene Ther. 2015 Jul 29. [Epub ahead of print]

Anti-angiogenic Eye Gene Therapy.

Corydon TJ.

Abstract: The idea of treating disease in humans with genetic material was conceived over two decades ago and with that a promising journey involving development and efficacy studies in cells and animals of a large number of novel therapeutic reagents unfolded. In the footsteps of this process, successful gene therapy treatment of genetic conditions in humans has shown clear signs of efficacy. Notably, significant advancements using gene supplementation and silencing strategies have been made in the field of ocular gene therapy, thereby pinpointing ocular gene therapy as one of the compelling 'actors' bringing gene therapy to the clinic. Most of all, this success has been facilitated due to (i) the fact that the eye is an effortlessly accessible, exceedingly compartmentalized and immune-privileged organ offering an unique advantage as a gene therapy target, and (ii) significant progress towards efficient, sustained transduction of cells within the retina having been achieved using non-integrating vectors based on recombinant adeno-associated virus (AAV) and non-integrating lentivirus vectors (LVs). The results from in vivo experiments and trials suggest that treatment of inherited retinal dystrophies, ocular angiogenesis and inflammation with gene therapy can be both safe and effective. Here, the progress of ocular gene therapy is examined with special emphasis on the potential use of RNAi- and protein-based anti-angiogenic gene therapy to treat exudative age-related macular degeneration (AMD).

PMID: 26222377 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Jul 27. [Epub ahead of print]

An evaluation of fundus photography and fundus autofluorescence in the diagnosis of cuticular drusen.

Høeg TB, Moldow B, Klein R, La Cour M, Klemp K, Erngaard D, Ellervik C, Buch H.

PURPOSE: To examine non-mydratic fundus photography (FP) and fundus autofluorescence (FAF) as alternative non-invasive imaging modalities to fluorescein angiography (FA) in the detection of cuticular drusen (CD).

METHODS: Among 2953 adults from the Danish Rural Eye Study (DRES) with gradable FP, three study groups were selected: (1) All those with suspected CD without age-related macular degeneration (AMD) on FP, (2) all those with suspected CD with AMD on FP and (3) a randomly selected group with early AMD. Groups 1, 2 and 3 underwent FA and FAF and group 4 underwent FAF only as part of DRES CD substudy. Main outcome measures included percentage of correct positive and correct negative diagnoses, Cohen's κ and prevalence-adjusted and bias-adjusted κ (PABAK) coefficients of test and grader reliability.

RESULTS: CD was correctly identified on FP 88.9% of the time and correctly identified as not being present 83.3% of the time. CD was correctly identified on FAF 62.0% of the time and correctly identified as not being present 100.0% of the time. Compared with FA, FP has a PABAK of 0.75 (0.60 to 1.5) and FAF a PABAK of 0.44 (0.23 to 0.95).

CONCLUSIONS: FP is a promising, non-invasive substitute for FA in the diagnosis of CD. FAF was less reliable than FP to detect CD.

PMID: 26216869 [PubMed - as supplied by publisher]

Int Ophthalmol. 2015 Jul 28. [Epub ahead of print]

Treatment of massive subretinal hematoma associated with age-related macular degeneration using vitrectomy with intentional giant tear.

Isizaki E, Morishita S, Sato T, Fukumoto M, Suzuki H, Kida T, Ueki M, Ikeda T.

Abstract: The purpose of this study was to report the surgical outcomes after creating a 120° intentional giant retinal tear for use in removing hemorrhage and subretinal proliferative tissue in patients with polypoidal choroidal vasculopathy (PCV) or age-related macular degeneration (ARMD). This study involved 12 eyes of 12 patients (10 eyes: PCV, 2 eyes: ARMD). After removal of the lens in phakic eyes, we performed a vitrectomy with artificial posterior vitreous detachment. Subsequently, a 120° intentional giant retinal tear was created in the temporal periphery, the retina was then turned, and the subretinal hemorrhage and proliferative tissue were removed. In order to preserve as much of the retinal pigment epithelium (RPE) as possible, we used a bimanual technique under direct visualization. After stretching the retina by use of perfluorocarbon liquid (PFCL), we performed endophotocoagulation around the tear followed by PFCL/silicone oil exchange. Except for 1 eye in which extensive loss of the RPE occurred, the fundus findings and the visual acuity (VA) improved in all patients. In addition, postoperative VA improved to $\geq 20/50$ in 3 eyes in which the macular RPE was preserved. This surgical procedure is an effective treatment for PCV or ARMD patients with extensive subretinal hemorrhage and proliferative tissue.

PMID: 26216161 [PubMed - as supplied by publisher]

Case Rep Ophthalmol Med. 2015;2015:728070.

Posterior Chamber Hemorrhage during Fluorescein Angiography.

Vilela MA.

Abstract: This paper provides the first reported case of acute posterior chamber hemorrhage during fluorescein angiography (FA). This is a case review with serial color photographs of the anterior segment. A 76-year-old male was referred for angiographic control of age-related macular degeneration. He was pseudophakic OU, BCVA 20/40 OU. He had mild hypertension, but not diabetes. He had had two previous angiograms without adverse effects. Difficulty was experienced in obtaining the images owing to a progressive reduction in the transparency of the media. A dense hemorrhage in the posterior chamber of the right eye was found, involving the visual axis. Thorough biomicroscopy, gonioscopy, and ultrasonic biomicroscopy showed that part of one of the haptics of the right intraocular lens (IOL) was touching and tearing the posterior face of the iris, without any visible synechiae, iris, or angle neovascularization. Anterior segment FA and posterior ultrasonography were normal. No similar case has been described in the literature involving dense progressive bleeding located in the capsular bag and posterior chamber, without any detectable triggering ocular event other than mydriasis and fluorescein injection. Contact of the iris or sulcus with part of the intraocular lens, aggravated by the intense use of mydriatics during the FA procedure, probably caused bleeding to happen.

PMID: 26221554 [PubMed] PMCID: PMC4499401

Surv Ophthalmol. 2015 Jul 23. [Epub ahead of print]

Submacular hemorrhage in neovascular age-related macular degeneration.

Stanescu-Segall D, Balta F, Jackson TL.

Abstract: Large submacular hemorrhage is an uncommon manifestation of neovascular age-related macular degeneration. It can also occur with idiopathic polypoidal choroidal vasculopathy. Submacular hemorrhage damages photoreceptors owing to iron toxicity, fibrin meshwork contraction, and reduced nutrient flux, with subsequent macular scarring. Clinical and experimental studies support prompt treatment, as tissue damage can occur within 24 hours. Without treatment the natural history is poor, with a mean final visual acuity (VA) of 20/1600. Reported treatments include retinal pigment epithelial patch, macular translocation, pneumatic displacement, intravitreal or subretinal tissue plasminogen activator (TPA), intravitreal anti-vascular endothelial growth factor (VEGF) drugs, and combinations thereof. In the absence of comparative studies, we combined eligible studies to assess the VA change before and after each treatment option. The greatest improvement occurred following combined pars plana vitrectomy, subretinal TPA, intravitreal gas, and anti-VEGF treatment, with VA improving from 20/1000 to 20/400. The best final VA occurred using combined intravitreal TPA, gas and anti-VEGF therapy, with VA improving from 20/200 to 20/100. Both treatments had an acceptable safety profile, but most studies were small, and larger randomized controlled trials are needed to determine both safety and efficacy.

PMID: 26212151 [PubMed - as supplied by publisher]

PLoS One. 2015 Jul 27;10(7):e0134267. eCollection 2015.

Significant Correlation between Retinal Venous Tortuosity and Aqueous Vascular Endothelial Growth Factor Concentration in Eyes with Central Retinal Vein Occlusion.

Yasuda S, Kachi S, Kondo M, Ueno S, Kaneko H, Terasaki H.

PURPOSE: To determine whether the degree of venous tortuosity is significantly correlated with the aqueous vascular endothelial growth factor (VEGF) concentration in eyes with a central retinal vein occlusion (CRVO).

METHODS: We reviewed the medical records of 32 eyes of 32 patients who had macular edema due to a CRVO. All of the patients were examined at the Nagoya University Hospital and were scheduled to receive an intravitreal injection of bevacizumab (IVB) or ranibizumab (IVR) within 12 weeks of the onset of the CRVO to treat the macular edema. Aqueous humor was collected just before the IVB or IVR, and the VEGF

concentration was determined by enzyme-linked immunosorbent assay (ELISA). The venous tortuosity index was calculated by dividing the length of the retinal veins by the chord length of the same segment. The correlation between the mean tortuosity index of the inferotemporal and supratemporal branches of the retinal vein and the aqueous VEGF concentration was determined.

RESULTS: The mean aqueous VEGF concentration was 384 ± 312 pg/ml with a range of 90 to 1077 pg/ml. The degree of venous tortuosity was significantly correlated with the VEGF concentration in the aqueous. ($r = 0.49$, $P = 0.004$), with the foveal thickness ($r = 0.40$, $P = 0.02$), and with the best-corrected visual acuity ($r = 0.38$, $P = 0.03$).

CONCLUSIONS: The significant correlation between the aqueous VEGF concentration and the venous tortuosity indicates that the degree of retinal venous tortuosity can be used to identify eyes that are at a high risk of developing neovascularization.

PMID: 26214803 [PubMed - in process] PMCID: PMC4516354

Pathogenesis

Sci Rep. 2015 Jul 27;5:12364.

Spontaneous Regeneration of Human Photoreceptor Outer Segments.

Horton JC, Parker AB, Botelho JV, Duncan JL.

Abstract: Photoreceptors are damaged in many common eye diseases, such as macular degeneration, retinal detachment, and retinitis pigmentosa. The development of methods to promote the repair or replacement of affected photoreceptors is a major goal of vision research. In this context, it would be useful to know whether photoreceptors are capable of undergoing some degree of spontaneous regeneration after injury. We report a subject who lost retinal function in a wide zone around the optic disc, giving rise to massive enlargement of the physiological blind spot. Imaging with an adaptive optics scanning laser ophthalmoscope (AOSLO) showed depletion of cone outer segments in the affected retina. A year later visual function had improved, with shrinkage of the enlarged blind spot. AOSLO imaging showed repopulation of cone outer segments, although their density remained below normal. There was a one-to-one match between sites of formerly missing outer segments and new outer segments that had appeared over the course of the year's recovery. This correspondence provided direct morphological evidence that damaged cones are capable, under some circumstances, of generating new outer segments.

PMID: 26213154 [PubMed - in process] PMCID: PMC4515765

Eye (Lond). 2015 Jul 31. [Epub ahead of print]

The stereotypical molecular cascade in neovascular age-related macular degeneration: the role of dynamic reciprocity.

Kent D.

Abstract: This review summarises our current understanding of the molecular basis of subretinal neovascularisation (SRNV) in age-related macular degeneration (AMD). The term neovascular AMD (NVAMD) is derived from the dominant early clinical features of haemorrhage, fluid, and lipid in the subretinal space (SRS) and the historical role of fluorescein angiography in detecting the presence of NV tissue. However, at the cellular level, SRNV resembles an aberrant but stereotypical tissue repair response that incorporates both an early inflammatory phase and a late fibrotic phase in addition to the neovascular (NV) component that dominates the early clinical presentation. This review will seek not only to highlight the important molecules involved in each of these components but to demonstrate that the development of SRNV has its origins in the earliest events in non-NV AMD pathogenesis. Current evidence suggests that

this early-stage pathogenesis is characterised by complement-mediated immune dysregulation, leading to a state of chronic inflammation in the retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. These initial events can be seamlessly and inextricably linked to late-stage development of SRNV in AMD by the process of dynamic reciprocity (DyR), the ongoing bidirectional communication between cells, and their surrounding matrix. Moreover, this correlation between disease onset and eventual outcome is reflected in the temporal and spatial correlation between chronic inflammation, NV, and fibrosis within the reparative microenvironment of the SRS. In summary, the downstream consequences of the earliest dysfunctional molecular events in AMD can result in the late-stage entity we recognize clinically as SRNV and is characterized by a spectrum of predictable, related, and stereotypical processes referred to as DyR.

PMID: 26228288 [PubMed - as supplied by publisher]

Photochem Photobiol Sci. 2015 Jul 30. [Epub ahead of print]

A2E and lipofuscin distributions in macaque retinal pigment epithelium are similar to human.

Pallitto P, Ablonczy Z, Jones EE, Drake RR, Koutalos Y, Crouch RK, Donello J, Herrmann J.

Abstract: The accumulation of lipofuscin, an autofluorescent aging marker, in the retinal pigment epithelium (RPE) has been implicated in the development of age-related macular degeneration (AMD). Lipofuscin contains several visual cycle byproducts, most notably the bisretinoid N-retinylidene-N-retinylethanolamine (A2E). Previous studies with human donor eyes have shown a significant mismatch between lipofuscin autofluorescence (AF) and A2E distributions. The goal of the current project was to examine this relationship in a primate model with a retinal anatomy similar to that of humans. Ophthalmologically naive young (<10 years., N = 3) and old (>10 years., N = 4) *Macaca fascicularis* (macaque) eyes, were enucleated, dissected to yield RPE/choroid tissue, and flat-mounted on indium-tin-oxide-coated conductive slides. To compare the spatial distributions of lipofuscin and A2E, fluorescence and mass spectrometric imaging were carried out sequentially on the same samples. The distribution of lipofuscin fluorescence in the primate RPE reflected previously obtained human results, having the highest intensities in a perifoveal ring. Contrarily, A2E levels were consistently highest in the periphery, confirming a lack of correlation between the distributions of lipofuscin and A2E previously described in human donor eyes. We conclude that the mismatch between lipofuscin AF and A2E distributions is related to anatomical features specific to primates, such as the macula, and that this primate model has the potential to fill an important gap in current AMD research.

PMID: 26223373 [PubMed - as supplied by publisher]

Biol Res. 2015 Jul 30;48:42.

Decreased VEGF-A and sustained PEDF expression in a human retinal pigment epithelium cell line cultured under hyperthermia.

Takeyama M, Yoneda M, Gosho M, Iwaki M, Zako M.

BACKGROUND: Previous reports have described a decrease in retinal temperature and clinical improvement of wet age-related macular degeneration (AMD) after vitrectomy. We hypothesized that the retinal temperature decrease after vitrectomy plays a part in the suppression of wet AMD development. To test this hypothesis, we evaluated the temperature dependence of the expression of vascular endothelial growth factor-A (VEGF-A) and in vitro angiogenesis in retinal pigment epithelium (RPE).

RESULTS: We cultured ARPE-19 cells at 37, 35, 33 and 31°C and measured the expression of VEGF-A, VEGF-A splicing variants, and pigment epithelium-derived factor (PEDF). We performed an in vitro tube formation assay. The dehydrogenase activity was also evaluated at each temperature. Expression of VEGF-A significantly decreased with decreased temperature while PEDF expression did not. VEGF165 expression and in vitro angiogenesis also were temperature dependent. The dehydrogenase activity

significantly decreased as the culture temperature decreased.

CONCLUSIONS: RPE cultured under hypothermia that decreased cellular metabolism also had decreased VEGF-A and sustained PEDF expression, creating an anti-angiogenic environment. This mechanism may be associated with a beneficial effect after vitrectomy in patients with wet AMD.

PMID: 26223306 [PubMed - in process] PMCID: PMC4518530

Biochemistry. 2015 Jul 29. [Epub ahead of print]

Vascular Endothelial Growth Factor peptide ligands explored by competition assay and ITC.

Reille-Seroussi M, Gaucher JF, Desole C, Gagey-Eilstein N, Brachet F, Broutin I, Vidal M, Broussy S.

Abstract: The v114* cyclic peptide has been identified as a tight Vascular Endothelial Growth Factor (VEGF) ligand. Here we report on the use of Isothermal Titration Calorimetry, 96-well plate competition assay and Circular Dichroism (CD) to explore the binding determinants of a new set of related peptides. Anti-VEGF antibodies are currently used in the clinic for regulating angiogenesis in cancer and age-related macular degeneration treatment. In this context, our aim is to develop smaller molecular entities with high affinity for the growth factor by a structure activity relationship approach. The cyclic disulfide peptide v114* was modified in several ways, including truncation, substitution, and variation of the size and nature of the cycle. The results indicated that truncation or substitution of the four N-terminal amino acids didn't cause severe loss in affinity, allowing potential peptide labeling. Increase of the cycle size or substitution of the disulfide bridge with a thioether linkage drastically decreased the affinity, due to an enthalpy penalty. The leucine C-terminal residue positively contributed to affinity. Cysteine N-terminal acetylation induced favorable $\Delta\Delta G^\circ$ and $\Delta\Delta H^\circ$ of binding, which correlated with free peptide CD spectra changes. We also propose a biochemical model to extrapolate K_i from IC_{50} values measured in the displacement assay. These calculated K_i correlate well with the K_d values determined by extensive direct and reverse ITC measurements.

PMID: 26222917 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 Jul 26. [Epub ahead of print]

Idiopathic preretinal glia in aging and age-related macular degeneration.

Edwards MM, McLeod DS, Bhutto IA, Villalonga MB, Seddon JM, Luty GA.

Abstract: During analysis of glia in wholemount aged human retinas, frequent projections onto the vitreal surface of the inner limiting membrane (ILM) were noted. The present study characterized these preretinal glial structures. The amount of glial cells on the vitreal side of the ILM was compared between eyes with age-related macular degeneration (AMD) and age-matched control eyes. Retinal wholemounts were stained for markers of retinal astrocytes and activated Müller cells (glial fibrillary acidic protein, GFAP), Müller cells (vimentin, glutamine synthetase) and microglia/hyalocytes (IBA-1). Retinal vessels were labeled with UEA lectin. Images were collected using a Zeiss 710 Meta confocal microscope. Retinas were then cryopreserved. Laminin labeling of cryosections determined the location of glial structures in relation to the ILM. All retinas investigated herein had varied amounts of preretinal glia. These glial structures were classified into three groups based on size: sprouts, blooms, and membranes. The simplest of the glial structures observed were focal "sprouts" of singular GFAP-positive cells or processes on the vitreal surface of the ILM. The intermediate structures observed, glial blooms, were created by multiple cells/processes exiting from a single point and extending along the vitreoretinal surface. The most extensive structures, glial membranes, consisted of compact networks of cells and processes. Preretinal glia were observed in all areas of the retina but they were most prominent over large vessels. While all glial blooms and membranes contained vimentin and GFAP-positive cells, these proteins did not always co-localize. Many areas had no preretinal GFAP but had numerous vimentin only glial sprouts. In double labeled glial sprouts, vimentin

staining extended beyond that of GFAP. Hyalocytes and microglia were detected along with glial sprouts, blooms, and membranes. They did not, however, concentrate in the retina below these structures. Cross sectional analysis identified small breaks in the ILM above large retinal vessels through which glial cells exited the retina. Preretinal glial structures of varied sizes are a common occurrence in aged retinas and, in most cases, are subclinical. While all retinal glia are found in blooms, vimentin labeling suggests that Müller cells form the leading edge. All retinas investigated from eyes with active choroidal neovascularization (CNV) had extensive glial membranes on the vitreal surface of the ILM. Although these structures may be benign, they may exert traction on the retina as they spread along the vitreoretinal interface. In cases with CNV, glial cells in the vitreous could bind intravitreally injected anti-vascular endothelial growth factor. These preretinal glial structures indicate the remodeling of both astrocytes and Müller cells in aged retinas, in particular those with advanced AMD.

PMID: 26220834 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 Jul 26;139:22-36. [Epub ahead of print]

Loss of DJ-1 elicits retinal abnormalities, visual dysfunction, and increased oxidative stress in mice.

Bonilha VL, Bell BA, Rayborn ME, Yang X, Kaul C, Grossman GH, Samuels IS, Hollyfield JG, Xie C, Cai H, Shadrach KG.

Abstract: DJ-1/PARK7 mutations or deletions cause autosomal recessive early onset Parkinson's disease (PD). Thus, DJ-1 protein has been extensively studied in brain and neurons. PD patients display visual symptoms; however, the visual symptoms specifically attributed to PD patients carrying DJ-1/PARK7 mutations are not known. In this study, we analyzed the structure and physiology of retinas of 3- and 6-month-old DJ-1 knockout (KO) mice to determine how loss of function of DJ-1 specifically contributes to the phenotypes observed in PD patients. As compared to controls, the DJ-1 KO mice displayed an increase in the amplitude of the scotopic ERG b-wave and cone ERG, while the amplitude of a subset of the dc-ERG components was decreased. The main structural changes in the DJ-1 KO retinas were found in the outer plexiform layer (OPL), photoreceptors and retinal pigment epithelium (RPE), which were observed at 3 months and progressively increased at 6 months. RPE thinning and structural changes within the OPL were observed in the retinas in DJ-1 KO mice. DJ-1 KO retinas also exhibited disorganized outer segments, central decrease in red/green cone opsin staining, decreased labeling of ezrin, broader distribution of ribeye labeling, decreased tyrosine hydroxylase in dopaminergic neurons, and increased 7,8-dihydro-8-oxoguanine-labeled DNA oxidation. Accelerated outer retinal atrophy was observed in DJ-1 KO mice after selective oxidative damage induced by a single tail vein injection of NaIO₃, exposing increased susceptibility to oxidative stress. Our data indicate that DJ-1-deficient retinas exhibit signs of morphological abnormalities and physiological dysfunction in association with increased oxidative stress. Degeneration of RPE cells in association with oxidative stress is a key hallmark of age-related macular degeneration (AMD). Therefore, in addition to detailing the visual defects that occur as a result of the absence of DJ-1, our data is also relevant to AMD pathogenesis.

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Rejuvenation Res. 2015 Jul 27. [Epub ahead of print]

Role of the cell cycle re-initiation in DNA damage response of postmitotic cells and its implication in the pathogenesis of neurodegenerative diseases.

Tokarz P, Blasiak J, Kaarniranta K.

Abstract: Neurodegenerative diseases are often associated with both normal and premature aging. Resuming of the cell cycle by neurons induced by DNA damage may lead to their apoptosis, which contributes to the degeneration of neuronal tissue. Cell cycle and DNA replication proteins are frequently

found in patients with neurodegenerative diseases. Oxidative stress, which is considered to play an important role in aging and pathogenesis of many neurodegenerative diseases, can induce DNA damage and stimulate cell cycle re-entry by neuronal cells. DNA damage activated ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3 related (ATR), breast cancer 1 (BRCA1), E2F transcription factor 1 (E2F1) and other proteins, which regulate cell cycle, DNA damage repair and apoptosis. Since the E2F complexes associate with histone modifying enzymes, histone modifications, including its acetylation and methylation, are required for cell cycle re-entry and may a regulatory role in DNA repair or apoptosis. Aberrant cell cycle regulation was shown to play a role in age-related macular degeneration (AMD), in which retinal cells are affected and inclusion body myositis which is characterized by the muscle cells dysfunction. There is evidence to suggest that cytostatic chemotherapy could decrease dementia in Alzheimer disease and multiple myeloma, supporting the use of cell cycle inhibitors in the therapy of degenerative diseases.

PMID: 26214710 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 Jul 26. [Epub ahead of print]

Beneficial protective effect of pramipexole on light-induced retinal damage in mice.

Shibagaki K, Okamoto K, Katsuta O, Nakamura M.

Abstract: We investigated the effects of pramipexole, a potent dopamine receptor D2/D3 agonist, on light-induced retinal damage in mice, H₂O₂-induced retinal pigment epithelium ARPE-19 cell injury in humans, and hydroxyl radical scavenging activity in a cell-free system. Pramipexole (0.1 and 1 mg/kg body weight) was orally administered to mice 1 h before light exposure (5000 lux, 2 h). Electrophysiological and morphologic studies were performed to evaluate the effects of the pramipexole on light-induced retinal damage in mice. Pramipexole significantly prevented the reduction of the a- and b-wave electroretinogram (ERG) amplitudes caused by light exposure in a dose-dependent manner. In parallel, damage to the inner and outer segments (IS/OS) of the photoreceptors, loss of photoreceptor nuclei, and the number of Tdt-mediated dUTP nick-end labeling (TUNEL)-positive cells in the outer nuclear layer (ONL) caused by light exposure were notably ameliorated by pramipexole. Additionally, pramipexole suppressed H₂O₂-induced ARPE-19 cell death in vitro in a concentration-dependent manner. The effect of pramipexole was significant at concentrations of 10⁻⁶ M or higher. Pramipexole also significantly prevented H₂O₂-induced activation of caspases-3/7 and the intracellular accumulation of reactive oxygen species (ROS) in a concentration-dependent manner ranging from 10⁻⁵ to 10⁻³ M. Furthermore, pramipexole increased the scavenging activity toward a hydroxyl radical generated from H₂O₂ in a Fenton reaction. Our results suggest that pramipexole protects against light-induced retinal damage as an antioxidant and that it may be a novel and effective therapy for retinal degenerative disorders, such as dry age-related macular degeneration.

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17 β -Estradiol up-regulates Nrf2 via PI3K/AKT and estrogen receptor signaling pathways to suppress light-induced degeneration in rat retina.

Zhu C, Wang S, Wang B, Du F, Hu C, Li H, Feng Y, Zhu R, Mo M, Cao Y, Li A, Yu X.

Abstract: Human age-related retinal diseases, such as age-related macular degeneration (AMD), are intimately associated with decreased tissue oxygenation and hypoxia. Different antioxidants have been investigated to reverse AMD. In the present study, we describe the antioxidant 17 β -estradiol (β E2) and investigate its protective effects on retinal neurons. Fourteen days after ovariectomy, adult Sprague-Dawley rats were exposed to 8000-lux light for 12h to induce retinal degeneration. Reactive oxygen species (ROS) levels were assessed by confocal fluorescence microscopy using 2,7-dichlorofluorescein diacetate. Nuclear factor erythroid 2-related factor 2 (Nrf2) and antioxidant enzyme mRNA expression were detected by real-

time PCR. Western blotting was used to evaluate NRF2 activation. NRF2 translocation was determined by immunohistochemistry, with morphological changes monitored by hematoxylin and eosin staining. Following light exposure, β E2 significantly reduced ROS production. β E2 also up-regulated NRF2 mRNA and protein levels, with maximal expression at 4 and 12h post-exposure, respectively. Interestingly, following β E2 administration, NRF2 was translocated from the cytoplasm to the nucleus, primarily in the outer nuclear layer. β E2 also up-regulated NRF2, which triggered phase-2 antioxidant enzyme expression (superoxide dismutases 1 and 2, catalase, glutaredoxins 1 and 2, and thioredoxins 1 and 2), reduced ROS production, and ameliorated retinal damage. However, the beneficial effects of β E2 were markedly suppressed by pretreatment with LY294002 or ICI182780, specific inhibitors of the phosphatidylinositol 3-kinase-Akt (PI3K/AKT), and estrogen receptor (ER) signaling pathways, respectively. Taken together, these observations suggest that β E2 exerts antioxidative effects following light-induced retinal degeneration potentially via NRF2 activation. This protective mechanism may depend on two pathways: a rapid, non-genomic-type PI3K/AKT response, and a genomic-type ER-dependent response. Our data provide evidence that β E2 is a potentially effective in the treatment of retinal degeneration diseases.

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Epidemiology

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Ancestry of the Timorese: age-related macular degeneration associated genotype and allele sharing among human populations from throughout the world.

Morrison MA, Magalhaes TR, Ramke J, Smith SE, Ennis S, Simpson CL, Portas L, Murgia F, Ahn J, Dardenne C, Mayne K, Robinson R, Morgan DJ, Brian G, Lee L, Woo SJ, Zacharaki F, Tsironi EE, Miller JW, Kim IK, Park KH, Bailey-Wilson JE, Farrer LA, Stambolian D, DeAngelis MM.

Abstract: We observed that the third leading cause of blindness in the world, age-related macular degeneration (AMD), occurs at a very low documented frequency in a population-based cohort from Timor-Leste. Thus, we determined a complete catalog of the ancestry of the Timorese by analysis of whole exome chip data and haplogroup analysis of SNP genotypes determined by sequencing the Hypervariable I and II regions of the mitochondrial genome and 17 genotyped YSTR markers obtained from 535 individuals. We genotyped 20 previously reported AMD-associated SNPs in the Timorese to examine their allele frequencies compared to and between previously documented AMD cohorts of varying ethnicities. For those without AMD (average age > 55 years), genotype and allele frequencies were similar for most SNPs with a few exceptions. The major risk allele of HTRA1 rs11200638 (10q26) was at a significantly higher frequency in the Timorese, as well as 3 of the 5 protective CFH (1q32) SNPs (rs800292, rs2284664, and rs12066959). Additionally, the most commonly associated AMD-risk SNP, CFH rs1061170 (Y402H), was also seen at a much lower frequency in the Korean and Timorese populations than in the assessed Caucasian populations (C ~7 vs. ~40%, respectively). The difference in allele frequencies between the Timorese population and the other genotyped populations, along with the haplogroup analysis, also highlight the genetic diversity of the Timorese. Specifically, the most common ancestry groupings were Oceanic (Melanesian and Papuan) and Eastern Asian (specifically Han Chinese). The low prevalence of AMD in the Timorese population (2 of 535 randomly selected participants) may be due to the enrichment of protective alleles in this population at the 1q32 locus.

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Complement factor H R1210C among Japanese patients with age-related macular degeneration.

Miyake M, Saito M, Yamashiro K, Sekiryu T, Yoshimura N.

PURPOSE: To evaluate the genotype distribution of a rare age-related macular degeneration (AMD)-susceptibility variant, complement factor H (CFH) R1210C, among a large Japanese cohort with AMD.

METHODS: One thousand three hundred and sixty-four Japanese patients with neovascular AMD were evaluated. We screened for CFH R1210C (rs121913059) by genotyping with the Taqman method; the mutation was confirmed by Sanger sequencing. We also searched for this mutation in the human genome variant database, which contains the whole-exome sequencing data for 1208 Japanese individuals. The detailed characteristics of patients with this mutation were reviewed.

RESULTS: The mean age of the patients was 74.5 years (standard deviation 8.7); men accounted for 71.8 % of the patients. The CFH R1210C variant was found in only 1 of the 1364 AMD patients, and was heterozygous (minor allele frequency (MAF) = 0.037 %); it was not found in any of the 1208 individuals in the control group (MAF = 0 %). The patient with CFH R1210C was a 70-year-old woman whose main complaint was visual loss in the right eye. Dilated fundus examination, optical coherence tomography, and fluorescein and indocyanine angiography revealed polypoidal choroidal neovascuopathy (PCV), but no drusen in either eye. Despite treatment, her visual acuity had decreased to 1/50 by 6.8 years after her first visit.

CONCLUSIONS: The CFH R1210C variant was found to be rare among Japanese patients with AMD. The patient with the mutation did have the PCV subtype, but no drusen formation. Considering their ethnicity-specific nature, such rare variants should be studied by use of next-generation sequencing for each ethnicity.

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The Clinical Effectiveness and Cost-Effectiveness of Screening for Age-Related Macular Degeneration in Japan: A Markov Modeling Study.

Tamura H, Goto R, Akune Y, Hiratsuka Y, Hiragi S, Yamada M.

OBJECTIVE: To investigate the cost-effectiveness of screening and subsequent intervention for age-related macular degeneration (AMD) in Japan.

METHODS: The clinical effectiveness and cost-effectiveness of screening and subsequent intervention for AMD were assessed using a Markov model. The Markov model simulation began at the age of 40 years and concluded at the age of 90 years. The first-eye and second-eye combined model assumed an annual state-transition probability, development of prodromal symptoms, choroidal neovascularization (CNV), and reduction in visual acuity. Anti-vascular-endothelial-growth-factor (anti-VEGF) intravitreal injection therapy and photodynamic therapy (PDT) were performed to treat CNV. Intake of supplements was recommended to patients who had prodromal symptoms and unilateral AMD. Data on prevalence, morbidity, transition probability, utility value of each AMD patient, and treatment costs were obtained from published clinical reports.

RESULTS: In the base-case analysis, screening for AMD every 5 years, beginning at the age of 50 years, showed a decrease of 41% in the total number of blind patients. The screening program reduced the incidence of blindness more than did the additional intake of supplements. However, the incremental cost-effectiveness ratio (ICER) of screening versus no screening was 27,486,352 Japanese yen (JPY), or 259,942 US dollars (USD) per quality-adjusted life year (QALY). In the sensitivity analysis, prodromal symptom-related factors for AMD had great impacts on the cost-effectiveness of screening. The lowest ICER obtained from the best scenario was 4,913,717 JPY (46,470 USD) per QALY, which was approximately equal to the willingness to pay in Japan.

CONCLUSIONS: Ophthalmologic screening for AMD in adults is highly effective in reducing the number of patients with blindness but not cost-effective as demonstrated by a Markov model based on clinical data

from Japan.

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Diet, lifestyle and low vision

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Retino-protective effect of Bucida buceras against oxidative stress induced by H₂O₂ in human retinal pigment epithelial cells line.

Iloki-Assanga SB, Lewis-Luján LM, Fernández-Angulo D, Gil-Salido AA, Lara-Espinoza CL, Rubio-Pino JL.

BACKGROUND: Reactive Oxygen Species (ROS) impair the physiological functions of Retinal Pigment Epithelial (RPE) cells, which are known as one major cause of age-related macular degeneration and retinopathy diseases. The purpose of this study is to explore the cytoprotective effects of the antioxidant Bucida buceras extract in co-treatment with hydrogen peroxide (H₂O₂) delivery as a single addition or with continuous generation using glucose oxidase (GOx) in ARPE-19 cell cultures. The mechanism of Bucida buceras extract is believed to be associated with their antioxidant capacity to protect cells against oxidative stress.

METHODS: A comparative oxidative stress H₂O₂-induced was performed by addition and enzymatic generation using glucose oxidase on human retinal pigment epithelial cells line. H₂O₂-induced injury was measured by toxic effects (cell death and apoptotic pathway) and intracellular redox status: glutathione (GSH), antioxidant enzymes (catalase and glutathione peroxidase) and reducing power (FRAP). The retino-protective effect of co-treatment with Bucida buceras extract on H₂O₂-induced human RPE cell injury was investigated by cell death (MTT assay) and oxidative stress biomarkers (H₂O₂, GSH, CAT, GPx and FRAP).

RESULTS: Bucida buceras L. extract is believed to be associated with the ability to prevent cellular oxidative stress. When added as a pulse, H₂O₂ is rapidly depleted and the cytotoxicity analyses show that cells can tolerate short exposure to high peroxide doses delivered as a pulse but are susceptible to lower chronic doses. Co-treatment with Bucida buceras was able to protect the cells against H₂O₂-induced injury. In addition to preventing cell death treatment with antioxidant plant could also reverse the significant decrease in GSH level, catalase activity and reducing power caused by H₂O₂.

CONCLUSION: These findings suggest that Bucida buceras could protect RPE against ocular pathogenesis associated with oxidative stress induced by H₂O₂-delivered by addition and enzymatic generation.

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