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Drug treatment

Curr Med Res Opin. 2015 Sep 1:1-28. [Epub ahead of print]

Three-year patient-reported visual function outcomes in diabetic macular edema managed with ranibizumab: the RESTORE extension study.

Mitchell P, Massin P, Bressler S, Coon CD, Petrillo J, Ferreira A, Bressler NM.

OBJECTIVE: To determine the impact of ranibizumab 0.5 mg on patient-reported visual function over 36 months in individuals with visual impairment from diabetic macular edema.

METHODS: RESTORE comprises a phase 3, randomized, multicenter, 12-month core study, and a 24-month open-label extension study. Eyes assigned ranibizumab in the core study received ranibizumab for 36 months; eyes assigned laser monotherapy in the core study received ranibizumab during the extension. The primary outcome was least-squares mean change in National Eye Institute 25-item Visual Functioning Questionnaire (NEI VFQ-25) overall composite and subscale scores.

RESULTS: Of 303 core study participants, 240 (79%) entered the extension, comprising 83 (35%) participants initially assigned ranibizumab, 83 (35%) assigned ranibizumab plus laser combination therapy, and 74 (31%) assigned laser monotherapy. Least-squares mean (standard error) change in NEI VFQ-25 composite score from baseline to month 12 (+5.9 [1.5]; +5.0 [1.5], for the ranibizumab and combination therapy groups, respectively) decreased by month 36 (+4.1 [1.7]; +4.0 [1.7], respectively, from baseline to month 36) following reduced injection frequency relative to the core study. At 36 months, the least-squares mean (standard error) change in the laser monotherapy group was similar to that in the ranibizumab groups (+4.1 [1.8]). Most subscale scores showed outcomes similar to that for the composite score. The greatest NEI VFQ-25 gains were consistently observed in participants for whom the study eye was the better-seeing eye.

LIMITATIONS: Patients entering the extension were not randomized, and 21% of the core study participants did not enter the extension, which may have affected the results.

CONCLUSIONS: Gains in patient-reported visual function at month 12 among eyes receiving ranibizumab in the core study decreased slightly by 36 months. Eyes originally receiving laser monotherapy for 12 months, then ranibizumab for 24 months achieved similar gains by 36 months to eyes receiving ranibizumab for 36 months.

PMID: 26327116 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2015 Aug 24. [Epub ahead of print]

[Treatment of age-related macular degeneration: Expert opinion and therapeutic algorithm].[Article in French]

Kodjikian L, Fourmaux E, Coscas F, Dumas S, Français C, Morel C, Oubraham H, Razavi S.

Abstract: Intravitreal injections (IVT) of aflibercept are indicated in France for the treatment of neovascular age-related macular degeneration (AMD). An induction phase consisting of 3 monthly IVTs followed by follow-up visits and IVTs every other month during the first year is recommended. However, it may be necessary to adjust this schedule for some patients who might benefit from a more tailored approach, namely a follow-up visit immediately after the induction phase. The goal was to develop a treatment algorithm that would reflect current clinical experience and the opinions of experts on neovascular AMD.

METHODS: A group of retinologists took positions on therapeutic questions regarding management of AMD using a nominal group technique (NGT). The results were combined to create a treatment algorithm.

RESULTS: Seventy-nine percent of experts considered that the approved schedule was efficacious when fluid was completely resorbed after the induction phase. Ninety-four percent of experts recommended, after a successful induction phase, a monthly follow-up visit for 3 to 6 months in order to determine the rhythm of recurrence for each patient. Ninety-six percent of experts recommended that persistent fluid after the induction phase, even if visual acuity is improved satisfactorily, should be a criterion for systematic retreatment.

CONCLUSION: The proposed algorithm (expert opinion) after the first year of use of aflibercept in France captures the complexity of the clinical cases that exist in daily practice and the necessity for regular follow-ups.

PMID: 26314897 [PubMed - as supplied by publisher]

Retina. 2015 Sep 3. [Epub ahead of print]

POOR LONG-TERM OUTCOME OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY IN NONPROLIFERATIVE MACULAR TELANGIECTASIA TYPE 2.

Kupitz EH, Heeren TF, Holz FG, Charbel Issa P.

PURPOSE: To investigate long-term effects after intravitreal inhibition of vascular endothelial growth factor in nonproliferative macular telangiectasia type 2.

METHODS: Nine patients with macular telangiectasia type 2 treated with 12 monthly intravitreal ranibizumab injections in 1 eye were investigated again after a mean follow-up of 6.0 ± 0.4 years. Functional assessment included best-corrected visual acuity and microperimetry testing. Morphologic investigations included optical coherence tomography imaging and fluorescein angiography.

RESULTS: Mean visual acuity at baseline was similar in treated and control eyes (both 20/50; range: 20/32 -20/125 in the treated eyes and 20/25-20/100 in the untreated eyes). None of the eyes had a neovascular membrane or a paracentral scotoma. At the last follow-up, more eyes of the treatment group had lost 2 or more lines on best-corrected visual acuity testing (4 vs. 1) and more eyes had developed an absolute paracentral scotoma (7 vs. 2). A secondary neovascular membrane had formed in four of the treated and in none of the untreated eyes.

CONCLUSION: Vascular endothelial growth factor inhibition with monthly dosing over 1 year had no beneficial effect 5 years after cessation of therapy. The worse outcome in the treated eyes may be due to selection bias, small sample size, or a potential adverse effect of vascular endothelial growth factor inhibition in a degenerative, primarily nonvascular disease as macular telangiectasia type 2.

PMID: 26340529 [PubMed - as supplied by publisher]

Cutan Ocul Toxicol. 2015 Sep 4:1-3. [Epub ahead of print]

Isolated sixth nerve palsy after intravitreal ranibizumab injection.

Caglar C, Kocamis SI, Durmus M.

Abstract: After intravitreal ranibizumab injection for diabetic macular edema (DME) in a 55-year-old man, the patient was admitted to our ophthalmology clinic with the complaint of diplopia. Given the results of the patient's history, physical exam, and negative magnetic resonance imaging (MRI), we believed that the patient had a sixth nerve palsy related to ranibizumab injection. To the best of our knowledge, this is the first case with isolated abducens palsy after ranibizumab injection.

PMID: 26340018 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2015 Sep 4:1-7. [Epub ahead of print]

Alternating Bi-Weekly Intravitreal Ranibizumab and Bevacizumab for Refractory Neovascular Age-Related Macular Degeneration with Pigment Epithelial Detachment.

Witkin AJ, Rayess N, Garg SJ, Maguire JI, Storey P, Kaiser RS, Hsu J, Vander JF, Ho AC.

OBJECTIVE: To describe visual and anatomical outcomes following bi-weekly intravitreal ranibizumab/bevacizumab injections in eyes with refractory neovascular age-related macular degeneration (AMD) and pigment epithelial detachment (PED).

DESIGN: Retrospective, consecutive, interventional case series.

PARTICIPANTS: Eighteen patients diagnosed with neovascular AMD that were refractory to anti-VEGF therapy and received alternating biweekly ranibizumab/bevacizumab injections were included.

METHODS: Patients with neovascular AMD and PED that were refractory to at least 11 monthly ranibizumab or bevacizumab injections were included in this study at a large, single retina practice. Following inclusion, patients received four bi-weekly alternating ranibizumab/bevacizumab intravitreal injections. After completing a course of four bi-weekly injections, patients were treated with variable regimens of intravitreal anti-vascular endothelial growth factor (VEGF) therapy. The primary outcomes of the study included change in visual acuity (VA) and central foveal thickness (CFT) at eight weeks follow-up.

RESULTS: Study eyes had previously received a mean of 22 intravitreal anti-VEGF injections. At enrollment, mean VA was 20/95 and mean CFT was 455 μm. After four bi-weekly anti-VEGF injections, mean VA improved to 20/65 ($p < 0.001$), and mean CFT decreased to 387 μm ($p = 0.029$). In patients with PED, there was a mean 27.9% reduction in height ($p = 0.046$) at eight weeks' follow-up.

CONCLUSIONS: Four injections of bi-weekly alternating ranibizumab/bevacizumab improved visual acuity and reduced macular thickness in a number of patients with refractory neovascular AMD and PED.

PMID: 26337539 [PubMed - as supplied by publisher]

J Mater Sci Mater Med. 2015 Sep;26(9):5561. Epub 2015 Sep 3.

Application of clotrimazole via a novel controlled release device provides potent retinal protection.

Nezhad ZK, Nagai N, Yamamoto K, Kaji H, Nishizawa M, Saya H, Nakazawa T, Abe T.

Abstract: Age-related macular degeneration is the leading cause of legal blindness among older individuals. Therefore, the development of new therapeutic agents and optimum drug delivery systems for its treatment are crucial. In this study, we investigate whether clotrimazole (CLT) is capable of protecting retinal cells against oxidative-induced injury and the possible inhibitory effect of a sustained CLT-release device against

light-induced retinal damage in rats. In vitro results indicated pretreatment of immortalized retinal pigment epithelium cells (RPE-J cells) with 10-50 μM CLT before exposure to oxygen/glucose deprivation conditions for 48 h decreased the extent of cell death, attenuated the percentage of reactive oxygen species-positive cells, and decreased the levels of cleaved caspase-3. The device consists of a separately fabricated reservoir, a CLT formulation, and a controlled release cover, which are made of poly(ethyleneglycol) dimethacrylate (PEGDM) and tri(ethyleneglycol) dimethacrylate (TEGDM). The release rate of CLT was successfully tuned by changing the ratio of PEGDM/TEGDM in the cover. In vivo results showed that use of a CLT-loaded device lessened the reduction of electroretinographic amplitudes after light exposure. These findings indicate that the application of a polymeric CLT-loaded device may be a promising method for the treatment of some retinal disorders.

PMID: 26335210 [PubMed - in process]

Prim Care. 2015 Sep;42(3):377-91.

Age-Related Macular Degeneration.

Mehta S.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss in the elderly. AMD is diagnosed based on characteristic retinal findings in individuals older than 50. Early detection and treatment are critical in increasing the likelihood of retaining good and functional vision.

PMID: 26319344 [PubMed - in process]

Prim Care. 2015 Sep;42(3):451-64.

Diabetic Retinopathy.

Hendrick AM, Gibson MV, Kulshreshtha A.

Abstract: The prevalence of diabetes is on the rise globally as are the consequences, such as diabetic retinopathy. Diabetic retinopathy is a leading cause of vision loss in working-age adults in developed countries. Visual impairment as a result of diabetic retinopathy has a significant negative impact on the patient's quality of life and their ability to successfully manage their disease. Glycemic control, blood pressure normalization, and lipid management form the basis for long-term diabetes management and protection from worsening eye disease.

PMID: 26319349 [PubMed - in process]

Other treatment & diagnosis

Ophthalmology. 2015 Aug 24. [Epub ahead of print]

Cost-Effectiveness of Screening for Intermediate Age-Related Macular Degeneration during Diabetic Retinopathy Screening.

Chan CK, Gangwani RA, McGhee SM, Lian J, Wong DS.

PURPOSE: To determine whether screening for age-related macular degeneration (AMD) during a diabetic retinopathy (DR) screening program would be cost effective in Hong Kong.

DESIGN: We compared and evaluated the impacts of screening, grading, and vitamin treatment for intermediate AMD compared with no screening using a Markov model. It was based on the natural history of AMD in a cohort with a mean age of 62 years, followed up until 100 years of age or death.

PARTICIPANTS: Subjects attending a DR screening program were recruited.

METHOD: A cost-effectiveness analysis was undertaken from a public provider perspective. It included grading for AMD using the photographs obtained for DR screening and treatment with vitamin therapy for those with intermediate AMD. The measures of effectiveness were obtained largely from a local study, but the transition probabilities and utility values were from overseas data. Costs were all from local sources. The main assumptions and estimates were tested in sensitivity analyses.

MAIN OUTCOME MEASURES: The outcome was cost per quality-adjusted life year (QALY) gained. Both costs and benefits were discounted at 3%. All costs are reported in United States dollars ($).

RESULTS: The cost per QALY gained through screening for AMD and vitamin treatment for appropriate cases was $12 712 after discounting. This would be considered highly cost effective based on the World Health Organization's threshold of willingness to pay (WTP) for a QALY, that is, less than the annual per capita gross domestic product of $29 889. Because of uncertainty regarding the utility value for those with advanced AMD, we also tested an extreme, conservative value for utility under which screening remained cost effective. One-way sensitivity analyses revealed that, besides utility values, the cost per QALY was most sensitive to the progression rate from intermediate to advanced AMD. The cost-effectiveness acceptability curve showed a WTP for a QALY of $29 000 or more has a more than 86% probability of being cost effective compared with no screening.

CONCLUSIONS: Our analysis demonstrated that AMD screening carried out simultaneously with DR screening for patients with diabetes would be cost effective in a Hong Kong public healthcare setting.

PMID: 26315045 [PubMed - as supplied by publisher]

Comput Biol Med. 2015 Jul 9;65:124-136. [Epub ahead of print]

Automated segmentation of geographic atrophy of the retinal epithelium via random forests in AREDS color fundus images.

Feeny AK, Tadarati M, Freund DE, Bressler NM, Burlina P.

BACKGROUND: Age-related macular degeneration (AMD), left untreated, is the leading cause of vision loss in people older than 55. Severe central vision loss occurs in the advanced stage of the disease, characterized by either the in growth of choroidal neovascularization (CNV), termed the "wet" form, or by geographic atrophy (GA) of the retinal pigment epithelium (RPE) involving the center of the macula, termed the "dry" form. Tracking the change in GA area over time is important since it allows for the characterization of the effectiveness of GA treatments. Tracking GA evolution can be achieved by physicians performing manual delineation of GA area on retinal fundus images. However, manual GA delineation is time-consuming and subject to inter-and intra-observer variability.

METHODS: We have developed a fully automated GA segmentation algorithm in color fundus images that uses a supervised machine learning approach employing a random forest classifier. This algorithm is developed and tested using a dataset of images from the NIH-sponsored Age Related Eye Disease Study (AREDS). GA segmentation output was compared against a manual delineation by a retina specialist.

RESULTS: Using 143 color fundus images from 55 different patient eyes, our algorithm achieved PPV of 0.82±0.19, and NPV of 0:95±0.07.

DISCUSSION: This is the first study, to our knowledge, applying machine learning methods to GA segmentation on color fundus images and using AREDS imagery for testing. These preliminary results show promising evidence that machine learning methods may have utility in automated characterization of GA from color fundus images.

PMID: 26318113 [PubMed - as supplied by publisher]

Mol Vis. 2015 Aug 21;21:883-92. eCollection 2015.

Photobiomodulation with 670 nm light increased phagocytosis in human retinal pigment epithelial cells.

Fuma S, Murase H, Kuse Y, Tsuruma K, Shimazawa M, Hara H.

PURPOSE: Photobiomodulation is the treatment with light in the far-red to near-infrared region of the spectrum and has been reported to have beneficial effects in various animal models of disease, including an age-related macular degeneration (AMD) mouse model. Previous reports have suggested that phagocytosis is reduced by age-related increased oxidative stress in AMD. Therefore, we investigated whether photobiomodulation improves phagocytosis caused by oxidative stress in the human retinal pigment epithelial (ARPE-19) cell line.

METHODS: ARPE-19 cells and human primary retinal pigment epithelium (hRPE) cells were incubated and irradiated with near-infrared light (670 nm LED light, 2,500 lx, twice a day, 250 s/per time) for 4 d. Next, hydrogen peroxide (H2O2) and photoreceptor outer segments (POS) labeled using a pH-sensitive fluorescent dye were added to the cell culture, and phagocytosis was evaluated by measuring the fluorescence intensity. Furthermore, cell death was observed by double staining with Hoechst33342 and propidium iodide after photobiomodulation. CM-H2DCFDA, JC-1 dye, and CCK-8 were added to the cell culture to investigate the reactive oxygen species (ROS) production, mitochondrial membrane potential, and cell viability, respectively. We also investigated the expression of phagocytosis-related proteins, such as focal adhesion kinase (FAK) and Mer tyrosine kinase (MerTK).

RESULTS: Oxidative stress inhibited phagocytosis, and photobiomodulation increased the oxidative stress-induced hypoactivity of phagocytosis in ARPE-19 cells and hRPE cells. Furthermore, H2O2 and photobiomodulation did not affect cell death in this experimental condition. Photobiomodulation reduced ROS production but did not affect cell viability or mitochondrial membrane potential. The expression of phosphorylated MerTK increased, but phosphorylated FAK was not affected by photobiomodulation.

CONCLUSIONS: These findings indicate that near-infrared light photobiomodulation (670 nm) may be a noninvasive, inexpensive, and easy adjunctive therapy to help inhibit the development of ocular diseases induced by the activation of phagocytosis.

PMID: 26321863 [PubMed - in process] PMCID: PMC4544713

Pathogenesis

J Immunol. 2015 Aug 31. [Epub ahead of print]

Retinal Pigment Epithelial Cells Mitigate the Effects of Complement Attack by Endocytosis of C5b-9.

Georgiannakis A, Burgoyne T, Lueck K, Futter C, Greenwood J, Moss SE.

Abstract: Retinal pigment epithelial (RPE) cell death is a hallmark of age-related macular degeneration. The alternative pathway of complement activation is strongly implicated in RPE cell dysfunction and loss in age-related macular degeneration; therefore, it is critical that RPE cells use molecular strategies to mitigate the potentially harmful effects of complement attack. We show that the terminal complement complex C5b-9 assembles rapidly on the basal surface of cultured primary porcine RPE cells but disappears over 48 h without any discernable adverse effects on the cells. However, in the presence of the dynamin inhibitor dynasore, C5b-9 was almost completely retained at the cell surface, suggesting that, under normal circumstances, it is eliminated via the endocytic pathway. In support of this idea, we observed that C5b-9 colocalizes with the early endosome marker EEA1 and that, in the presence of protease inhibitors, it can be detected in lysosomes. Preventing the endocytosis of C5b-9 by RPE cells led to structural defects in mitochondrial morphology consistent with cell stress. We conclude that RPE cells use the endocytic pathway to prevent the accumulation of C5b-9 on the cell surface and that processing and destruction of

C5b-9 by this route are essential for RPE cell survival.

PMID: 26324770 [PubMed - as supplied by publisher]

Photochem Photobiol Sci. 2015 Sep 1. [Epub ahead of print]

Determination of N-retinylidene-N-retinylethanolamine (A2E) levels in central and peripheral areas of human retinal pigment epithelium.

Adler L, Boyer NP, Anderson DM, Spraggins JM, Schey KL, Hanneken A, Ablonczy Z, Crouch RK, Koutalos Y.

Abstract: The bis-retinoid N-retinylidene-N-retinylethanolamine (A2E) is one of the major components of lipofuscin, a fluorescent material that accumulates with age in the lysosomes of the retinal pigment epithelium (RPE) of the human eye. Lipofuscin, as well as A2E, exhibit a range of cytotoxic properties, which are thought to contribute to the pathogenesis of degenerative diseases of the retina such as Age-related Macular Degeneration. Consistent with such a pathogenic role, high levels of lipofuscin fluorescence are found in the central area of the human RPE, and decline toward the periphery. Recent reports have however suggested a surprising incongruence between the distributions of lipofuscin and A2E in the human RPE, with A2E levels being lowest in the central area and increasing toward the periphery. To appraise such a possibility, we have quantified the levels of A2E in the central and peripheral RPE areas of 10 eyes from 6 human donors (ages 75-91 years) with HPLC and UV/VIS spectroscopy. The levels of A2E in the central area were on average 3-6 times lower than in peripheral areas of the same eye. Furthermore, continuous accumulation of selected ions (CASI) imaging mass spectrometry showed the presence of A2E in the central RPE, and at lower intensities than in the periphery. We have therefore corroborated that in human RPE the levels of A2E are lower in the central area compared to the periphery. We conclude that the levels of A2E cannot by themselves provide an explanation for the higher lipofuscin fluorescence found in the central area of the human RPE.

PMID: 26323192 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2015 Sep 3. [Epub ahead of print]

Vascular Endothelial Growth Factor Receptor 2 Antibody, BC001, Attenuates Laser-Induced Choroidal Neovascularization in Rhesus Monkeys (Macaca mulatta).

Zhao T, Zhang J, Zhang Y, Huang J, Wang X, Zhang Y, Zhang M, Yuan Y, Xiao K, Li H, Zhong Z.

PURPOSE: A study was conducted to evaluate the inhibitory effects of vascular endothelial growth factor receptor 2 (VEGFR2) monoclonal antibody, BC001, against laser-induced choroidal neovascularization (CNV).

METHODS: We induced the experimental CNV in rhesus monkey eyes using laser photocoagulation. Monkeys were randomly assigned to 4 groups that received a single intravitreal administration of BC001 at 0 (vehicle-treated group), 0.05, 0.2, and 0.5 mg/eye. Fundus fluorescein angiography, optical coherence tomography, and histological studies were used for evaluations. The ocular recovery was determined by comparing changes of fluorescein leaking area and thickness of disrupted retina around the laser burn spot before and after drug administration. Choroidal blood vessels were stained and quantified by lectin staining. Hematoxylin and eosin staining was performed to determine the general histological complications.

RESULTS: An intravitreal injection of BC001 at 0.05, 0.2, and 0.5 mg per eye at 20 days after laser burn significantly reduced the CNV-induced fluorescein leakage, retina pathology, and aberrant choroidal vessel growth and did not change intraocular pressure or induce any immune response.

CONCLUSION: BC001 confers significant inhibitory effects against laser-induced CNV in rhesus monkeys,

thereby suggesting that prevention of VEGFR2 activation may be promising as an alternative therapeutic target for exudative age-related macular degeneration.

PMID: 26334588 [PubMed - as supplied by publisher]

Ophthalmic Genet. 2015 Sep 2:1-7. [Epub ahead of print]

Role of MMP-2 (-1306 C/T) Polymorphism in Age-Related Macular Degeneration.

Liutkeviciene R, Lesauskaite V, Zaliaduonyte-Peksiene D, Sinkunaite-Marsalkiene G, Zaliuniene D, Mizariene V, Gustiene O, Jasinskas V, Tamosiunas A.

PURPOSE: To determine if the frequency of the MMP-2 (-1306 C/T) genotype has an influence on the development of early age-related macular degeneration (AMD).

METHODOLOGY: The study enrolled 387 patients with early AMD and a random sample of 682 healthy persons (control group). The genotyping of MMP-2 (-1306 C/T) was carried out using the real-time polymerase chain reaction method.

RESULTS: The analysis of the MMP-2 (-1306 C/T) gene polymorphism did not reveal any differences in the genotype distribution between the patients with AMD and the control subjects. When the study population was divided into age groups, the C/C genotype was more prevalent in the AMD patients aged <65 years than those aged ≥65 years (65.19% versus 53.88%, p = 0.0294), and the C/T genotype was more frequent in the AMD patients aged ≥65 years when compared with the AMD patients aged <65 years (40.78% versus 26.52%, p = 0.0037). Moreover, in the female group younger than 65 years, the frequency of the C/C genotype was greater in the AMD group than the control group (75% versus 58.91%, p = 0.0232).

CONCLUSIONS: This study showed a significantly greater prevalence of the C/C and C/T genotypes in the patients with AMD younger than 65 years and those aged ≥65 years, respectively. Moreover, the AMD women aged <65 years were the carriers of the C/C genotype significantly more frequently than their control counterparts.

PMID: 26333112 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 Aug 27. [Epub ahead of print]

Lysosomes: regulators of autophagy in the retinal pigmented epithelium.

Sinha D, Valapala M, Shang P, Hose S, Grebe R, Lutty GA, Zigler JS Jr, Kaarniranta K, Handa JT.

Abstract: The retinal pigmented epithelium (RPE) is critically important to retinal homeostasis, in part due to its very active processes of phagocytosis and autophagy. Both of these processes depend upon the normal functioning of lysosomes, organelles which must fuse with (auto)phagosomes to deliver the hydrolases that effect degradation of cargo. It has become clear that signaling through mTOR complex 1 (mTORC1), is very important in the regulation of lysosomal function. This signaling pathway is becoming a target for therapeutic intervention in diseases, including age-related macular degeneration (AMD), where lysosomal function is defective. In addition, our laboratory has been studying animal models in which the gene (Cryba1) for βA3/A1-crystallin is deficient. These animals exhibit impaired lysosomal clearance in the RPE and pathological signs that are similar to some of those seen in AMD patients. The data demonstrate that βA3/A1-crystallin localizes to lysosomes in the RPE and that it is a binding partner of V-ATPase, the proton pump that acidifies the lysosomal lumen. This suggests that βA3/A1-crystallin may also be a potential target for therapeutic intervention in AMD. In this review, we focus on effector molecules that impact the lysosomal-autophagic pathway in RPE cells.

PMID: 26321509 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 Aug 25;140:94-105. [Epub ahead of print]

Systemic treatment with a 5HT1a agonist induces anti-oxidant protection and preserves the retina from mitochondrial oxidative stress.

Biswal MR, Ahmed CM, Ildefonso CJ, Han P, Li H, Jivanji H, Mao H, Lewin AS.

Abstract: Chronic oxidative stress contributes to age related diseases including age related macular degeneration (AMD). Earlier work showed that the 5-hydroxy-tryptamine 1a (5HT1a) receptor agonist 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT) protects retinal pigment epithelium (RPE) cells from hydrogen peroxide treatment and mouse retinas from oxidative insults including light injury. In our current experiments, RPE derived cells subjected to mitochondrial oxidative stress were protected from cell death by the up-regulation of anti-oxidant enzymes and of the metal ion chaperone metallothionein. Differentiated RPE cells were resistant to oxidative stress, and the expression of genes for protective proteins was highly increased by oxidative stress plus drug treatment. In mice treated with 8-OH-DPAT, the same genes (MT1, HO1, NqO1, Cat, Sod1) were induced in the neural retina, but the drug did not affect the expression of Sod2, the gene for manganese superoxide dismutase. We used a mouse strain deleted for Sod2 in the RPE to accelerate age-related oxidative stress in the retina and to test the impact of 8-OH-DPAT on the photoreceptor and RPE degeneration developed in these mice. Treatment of mice with daily injections of the drug led to increased electroretinogram (ERG) amplitudes in dark-adapted mice and to a slight improvement in visual acuity. Most strikingly, in mice treated with a high dose of the drug (5 mg/kg) the structure of the RPE and Bruch's membrane and the normal architecture of photoreceptor outer segments were preserved. These results suggest that systemic treatment with this class of drugs may be useful in preventing geographic atrophy, the advanced form of dry AMD, which is characterized by RPE degeneration.

PMID: 26315784 [PubMed - as supplied by publisher]

Epidemiology

PLoS One. 2015 Sep 3;10(9):e0137342. eCollection 2015.

Comparative Incidence of Conformational, Neurodegenerative Disorders.

de Pedro-Cuesta J, Rábano A, Martínez-Martín P, Ruiz-Tovar M, Alcalde-Cabero E, Almazán-Isla J, Avellanal F, Calero M.

BACKGROUND: The purpose of this study was to identify incidence and survival patterns in conformational neurodegenerative disorders (CNDDs).

METHODS: We identified 2563 reports on the incidence of eight conditions representing sporadic, acquired and genetic, protein-associated, i.e., conformational, NDD groups and age-related macular degeneration (AMD). We selected 245 papers for full-text examination and application of quality criteria. Additionally, data -collection was completed with detailed information from British, Swedish, and Spanish registries on Creutzfeldt-Jakob disease (CJD) forms, amyotrophic lateral sclerosis (ALS), and sporadic rapidly progressing neurodegenerative dementia (sRPNDd). For each condition, age-specific incidence curves, age-adjusted figures, and reported or calculated median survival were plotted and examined.

FINDINGS: Based on 51 valid reported and seven new incidence data sets, nine out of eleven conditions shared specific features. Age-adjusted incidence per million person-years increased from ≤1.5 for sRPNDd, different CJD forms and Huntington's disease (HD), to 1589 and 2589 for AMD and Alzheimer's disease (AD) respectively. Age-specific profiles varied from (a) symmetrical, inverted V-shaped curves for low incidences to (b) those increasing with age for late-life sporadic CNDDs and for sRPNDd, with (c) a suggested, intermediate, non-symmetrical inverted V-shape for fronto-temporal dementia and Parkinson's disease. Frequently, peak age-specific incidences from 20-24 to ≥90 years increased with age at onset and survival. Distinct patterns were seen: for HD, with a low incidence, levelling off at middle age, and long

median survival, 20 years; and for sRPNDd which displayed the lowest incidence, increasing with age, and a short median disease duration.

INTERPRETATION: These results call for a unified population view of NDDs, with an age-at-onset-related pattern for acquired and sporadic CNDDs. The pattern linking age at onset to incidence magnitude and survival might be explained by differential pathophysiological mechanisms associated with specific misfolded protein deposits.

PMID: 26335347 [PubMed - in process]

Ophthalmology. 2015 Sep 1. [Epub ahead of print]

Age-Related Macular Degeneration and Risk of Degenerative Dementia among the Elderly in Taiwan: A Population-Based Cohort Study.

Tsai DC, Chen SJ, Huang CC, Yuan MK, Leu HB.

PURPOSE: To investigate the relationship between age-related macular degeneration (AMD) and future development of Alzheimer's disease (AD) or senile dementia.

DESIGN: A longitudinal case-control study using the Taiwan National Health Insurance Research Database.

PARTICIPANTS: From 2001 to 2009, the newly diagnosed AMD cases aged ≥65 years in the database were recruited as the AMD cohort (n = 4993). Of those, there were 540 with and 4453 without exudative AMD diagnoses. Subjects without any AMD, matched for age, gender, and time of enrollment, were randomly sampled as the control cohort (n = 24 965) for comparison.

METHODS: Alzheimer's disease/senile dementia-free survival analysis was assessed using a Kaplan-Meier method. Cox proportional hazard regressions were performed to calculate the hazard ratios (HR) of AD or senile dementia for the 2 cohorts after adjusting for preexisting comorbidities and number of clinical visits.

MAIN OUTCOME MEASURES: The first-ever diagnosis of AD or senile dementia during the observation period.

RESULTS: Of the 29 958 sampled subjects, 1589 (5.3%) were diagnosed with AD or senile dementia during a mean follow-up period of 4.4 years, including 294 (5.9%) from the AMD cohort and 1295 (5.2%) from the control cohort. The incidence of AD or senile dementia was higher in patients with AMD than in the controls (P = 0.044), with an HR of 1.44 (95% confidence interval [CI], 1.26-1.64) after adjusting for covariates. The stratified analysis showed that the adjusted HR for AD or senile dementia was 1.35 (95% CI, 0.89-2.06) for exudative AMD versus the controls and 1.44 (95% CI, 1.26-1.65) for nonexudative AMD versus the controls.

CONCLUSIONS: This study provides large-scale, population-based evidence that AMD, especially nonexudative AMD, is independently associated with an increased risk of subsequent AD or senile dementia development.

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Genetics

Ophthalmology. 2015 Sep 1. [Epub ahead of print]

MMP20 and ARMS2/HTRA1 Are Associated with Neovascular Lesion Size in Age-Related Macular Degeneration.

Akagi-Kurashige Y, Yamashiro K, Gotoh N, et al, Nagahama Cohort Research Group.

PURPOSE: Age-related macular degeneration (AMD) is the leading cause of severe visual impairment. Despite treatment, a central scotoma often remains. The size of the scotoma depends on the lesion size of the choroidal neovascular membrane and significantly affects the patient's quality of life, and the lesion size of neovascularization also affects response to treatments. The aim of this study was to identify genes associated with the neovascular lesion size in neovascular AMD.

DESIGN: A genome-wide association study (GWAS).

PARTICIPANTS: We included 1146 Japanese patients with neovascular AMD.

METHODS: We performed a 2-stage GWAS for the lesion size of AMD as a quantitative trait among 1146 (first stage: 727, second stage: 419) Japanese patients with neovascular AMD. Lesion size was determined by the greatest linear dimension measured with fluorescein angiography examination before treatment. We examined the association between the genotypic distribution of each single nucleotide polymorphism (SNP) and the trait using an additive model adjusted for age and sex. To evaluate the associations between AMD development and SNPs associated with lesion size, we also performed a case-control study by using the genotype data from these 1146 Japanese patients as case subjects and the fixed dataset from the Nagahama Study as control subjects.

MAIN OUTCOME MEASURES: Genes associated with the lesion size in neovascular AMD.

RESULTS: In the discovery stage, rs10895322 in MMP20 showed a genome-wide significant P value of 6.95×10-8, and rs2284665 in ARMS2/HTRA1 showed a P value of 1.55×10-7. The associations of these 2 SNPs were successfully replicated in the replication stage, and a meta-analysis of both stages showed genome-wide significant P values (2.80×10-9 and 4.41×10-9, respectively). In a case-control study using 3248 Japanese subjects as controls, we could not find contribution of MMP20 rs10895322 for AMD development. Although MMP20 has been thought to be expressed only in dental tissues, we confirmed MMP20 expression in the human retina and retinal pigment epithelium/choroid with polymerase chain reaction.

CONCLUSIONS: The growth of choroidal neovascularization in AMD would be affected by 2 genes: MMP20, a newly confirmed gene expressed in the retina, and ARMS2/HTRA1, a well-known susceptibility gene for AMD.

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Gene expression regulation in retinal pigment epithelial cells induced by viral RNA and viral/ bacterial DNA.

Brosig A, Kuhrt H, Wiedemann P, Kohen L, Bringmann A, Hollborn M.

PURPOSE: The pathogenesis of age-related macular degeneration (AMD) is associated with systemic and local inflammation. Various studies suggested that viral or bacterial infection may aggravate retinal inflammation in the aged retina. We compared the effects of synthetic viral RNA (poly(I:C)) and viral/ bacterial DNA (CpG-ODN) on the expression of genes known to be involved in the development of AMD in retinal pigment epithelial (RPE) cells.

METHODS: Cultured human RPE cells were stimulated with poly(I:C; 500 µg/ml) or CpG-ODN (500 nM). Alterations in gene expression and protein secretion were determined with real-time RT-PCR and ELISA, respectively. Phosphorylation of signal transduction molecules was revealed by western blotting.

RESULTS: Poly(I:C) induced gene expression of the pattern recognition receptor TLR3, transcription factors (HIF-1α, p65/NF-κB), the angiogenic factor bFGF, inflammatory factors (IL-1β, IL-6, TNFα, MCP-1, MIP-2), and complement factors (C5, C9, CFB). Poly(I:C) also induced phosphorylation of ERK1/2 and p38 MAPK proteins, and the secretion of bFGF and TNFα from the cells. CpG-ODN induced moderate gene expression of transcription factors (p65/NF-κB, NFAT5) and complement factors (C5, C9), while it had no effect on the expression of various TLR, angiogenic factor, and inflammatory factor genes. The activities of

various signal transduction pathways and transcription factors were differentially involved in mediating the poly(I:C)-induced transcriptional activation of distinct genes.

CONCLUSIONS: The widespread effects of viral RNA, and the restricted effects of viral/bacterial DNA, on the gene expression pattern of RPE cells may suggest that viral RNA rather than viral/bacterial DNA induces physiologic alterations of RPE cells, which may aggravate inflammation in the aged retina. The data also suggest that selective inhibition of distinct signal transduction pathways or individual transcription factors may not be effective to inhibit viral retinal inflammation.

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Association of gene polymorphism with serum levels of inflammatory and angiogenic factors in Pakistani patients with age-related macular degeneration.

Ambreen F, Ismail M, Qureshi IZ.

PURPOSE: To study the association of serum levels of inflammatory mediators and angiogenic factors with genetic polymorphism in Pakistani age-related macular degeneration (AMD) patients.

METHODS: This was a cross-sectional and case-control study that included 90 AMD patients diagnosed through slit-lamp examination, fundoscopy, and ocular coherence tomography. For reference and comparison purposes, 100 healthy age-matched subjects (controls) were also recruited. IL-6, IL-8, VEGF, and CRP levels were estimated in the serum samples of patients and control subjects. Using restriction fragment length polymorphism, single nucleotide polymorphisms were studied in IL-6 (rs1800795, rs1800796, rs1800797), IL-8 (rs4073, rs2227306, rs2227543), VEGF (rs3025039, rs699947), and CRP genes (rs1205, rs1130864). Since the data were obtained from a sample population, the Box-Cox transformation algorithm was applied to reduce heterogeneity of error. Multivariate analyses of variance (M-ANOVA) were applied on the transformed data to investigate the association of serum levels of IL-6, IL-8, VEGF, and CRP with AMD. Genotype and allele frequencies were compared through $\chi(2)$ tests applying Hardy-Weinberg equilibrium. The serum concentrations of IL-6 and IL-8, VEGF, and CRP between homozygotes and heterozygotes were compared through one-way ANOVA. Significance level was $p<0.05$.

RESULTS: Compared to control subjects, serum IL-6 ($p<0.0001$), IL-8 ($p<0.0001$), VEGF ($p<0.0001$), and CRP ($p<0.0001$) levels were significantly elevated in the AMD patients. For rs1800795, patients with the GG genotype showed significantly raised levels of IL-6 compared to those with GC and CC genotypes ($p<0.0001$). Serum IL-8 levels were significantly higher in patients with the GG genotype compared to the GC and CC genotypes for the single nucleotide polymorphism (SNP) rs2227543 ($p<0.002$). Similarly, significantly higher VEGF levels were detected for genotype TT for rs3025039 SNP ($p<0.038$). However, no significant alteration in serum CRP levels was detected in hetero- or homozygotes for rs1205 and rs1130864 SNPs.

CONCLUSIONS: Serum IL-6, IL-8, and VEGF levels are substantially increased in AMD, and the levels coincide with polymorphism in the respective gene. No such relationship appears to exist with regard to SNPs of CRP.

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Diet, lifestyle & low vision

JAMA. 2015 Aug 25;314(8):774-5.

Lifestyles and Cognitive Health: What Older Individuals Can Do to Optimize Cognitive Outcomes.

Gill SS, Seitz DP.

Comment on:

Effect of a 24-Month Physical Activity Intervention vs Health Education on Cognitive Outcomes in

Sedentary Older Adults: The LIFE Randomized Trial. [JAMA. 2015]

Effect of Omega-3 Fatty Acids, Lutein/Zeaxanthin, or Other Nutrient Supplementation on Cognitive Function: The AREDS2 Randomized Clinical Trial. [JAMA. 2015]

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J Vis. 2015 Sep 1;15(12):987.

Age-related changes in gray and white matter microstucture of patients with macular dystrophies and healthy controls as revealed by DTI.

Beer A, Go SY, Plank T, Greenlee M.

Abstract: Previous research has shown that loss of central vision resulting from macular degeneration not only affects functional processing but also the macroscopic structure of the visual pathway. In particular, magnetic resonance imaging (MRI) showed volumetric reductions of the gray and white matter of patients with macular degeneration in portions of the calcarine sulcus that represent the central visual field. However, the basis of these macrostructural alterations due to partial vision loss is still unclear. Diffusion tensor imaging (DTI) based on MRI is a technique that allows inferences about the microstructure of brain tissue. Here, 25 patients with hereditary and 13 patients with age-related macular degeneration and an equal number of age-matched healthy controls (age range from 19 to 85 years) were examined with DTI. Patients and controls were compared on several diffusion-based quantitative indices including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). A surface-based analysis approach was adopted. In healthy people, diffusivity increased with age in the medial occipital cortex, the cingulate cortex, the temporal cortex, the insular, and the frontal cortex. However, dissociations between AD and RD were observed in several brain regions: Age-related increases of RD were primarily observed in the white matter of the medial occipital cortex, whereas age-related increases of AD were primarily observed in the gray matter of the temporal cortex. Compared to age-matched healthy controls, young but not elderly patients with vision loss showed increased RD in two distinct regions of the posterior calcarine sulcus and the inferior frontal cortex. No reduction in AD was observed. This finding suggests that fiber connections of afferent visual pathways are still preserved in patients with vision loss. However, the white matter microstructure of the visual cortex may be affected by changes in local connectivity or the extra-axonal structure. Meeting abstract presented at VSS 2015.

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Optimal point of fixation to faces for vision with a simulated central scotoma.

Tsank Y, Eckstein M.

Abstract: When identifying a face the majority of humans initially look at a point of fixation (just below the eyes) that optimizes perceptual performance as predicted by a theoretical foveated ideal observer (Peterson & Eckstein, 2012). Here, we use a simulated scotoma paradigm to investigate the potential effects of macular degeneration on human optimal points of fixation (OPF) in face identification and compare these to the predictions of a foveated ideal observer with a central scotoma (S-FIO). We also evaluate observers' ability to adapt to the scotoma and learn new initial fixation strategies to optimize recognition performance.

METHODS: Seven observers completed a 1 of 10 face (15 deg) identification task in luminance noise with a gaze contingent display which simulated a central scotoma (radius = 8 deg). In the first study, observers made free eye movements in eight alternating blocks (1000 trials) with face viewing times of 350ms and 1500ms. In the second study, we assessed the OPFs by having observers fixate 1 out of 4 horizontally centered positions on the face (~375 trials for forehead, eyes, nose, and mouth in random order) for 350ms. Finally, observers repeated the free eye movement study.

RESULTS: The human forced fixation study showed that the simulated scotoma shifted the OPF downwards toward the tip of the nose (p < 0.05) which was predicted by the S-FIO model. However, surprisingly, observers failed to change their eye movement strategy (first and third studies) to initially fixate the new scotoma-induced optimal point of fixation.

CONCLUSIONS: Our findings show unlike object following and search tasks (Kwon et al, 2013), humans have difficulty adapting to the scotoma and re-learning optimal fixations for face identification. Results show the potential use of the S-FIO as a benchmark to evaluate changes in OPFs for humans with low vision disorders. Meeting abstract presented at VSS 2015.

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A computational account on the development of a preferred retinal locus.

Mazyar H, Tjan B.

Abstract: A saccade brings a retinal locus to a target in the visual field. For normally sighted individuals, this retinal locus is the fovea. Central field loss (CFL) caused by macular degeneration often leads to the adoption of a preferred retinal locus (PRL) in the peripheral retina for saccades and fixation. Factors underlying the development of a PRL are not known. Here we show that a conceptually simple computational model can account for the formation of a PRL and its idiosyncrasies. We assume that the visual system always intends to aim the retinal locus with the highest expected post-saccade acuity at the saccade target. The expected post-saccade acuity of a retinal locus is a function of the physiological acuity at and around the locus and the expected saccade error. The expected saccade error is a combination of motor error that is proportional to the saccade amplitude (vector error) and the spatial uncertainties associated with the retinal locus and the saccade target (endpoint errors). We assume that the motor error does not improve, but the spatial uncertainties associated with the neural representation of the endpoints are optimally re-estimated after each saccade from the observed saccade error. A generic forgetting function is assumed to prevent spatial uncertainty from vanishing. Simulations showed that immediately after CFL, the utilized retinal loci are close to the edge of the scotoma on the side nearest to saccade targets. After each saccade, spatial uncertainties associated with the pre-saccade target and utilized retinal locus decrease. Decrease in spatial uncertainty increases the expected post-saccade acuity of the retinal locus. The net effect is that a previously selected retinal locus is more likely to be selected for a future saccade, further reducing its spatial uncertainty, and forming the PRL. Idiosyncrasies at the early stages of CFL strongly influence PRL formation. Meeting abstract presented at VSS 2015.

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Foveal vision loss interferes with visual search guidance by learned spatial contexts in contextual cueing.

Pollmann S, Geringswald F.

Abstract: Visual search is guided by past experience of regularities in our visual environment. In the contextual cueing paradigm, incidental learning of repeated distractor configurations improves search times and eye movement parameters. Both in patients with age-related macular degeneration who suffer from foveal vision loss and in young normal-sighted observers with gaze-contingent central scotoma simulation contextual cueing was severely reduced (Geringswald et al., Front Hum Neurosci 2012, J Vis 2014). Previous work has shown that not the learning of spatial contexts but rather the utilization of previously learned context for efficient search guidance depends on visuospatial working-memory (Manginelli et al., Att Percept Psychophys 2013; Vickery et al., J Exp Psychol Hum Perc Perform 2010). Therefore, increased working memory demands due to top-down controlled visual search in the presence of foveal vision loss could lead to reduced contextual cueing. To test this hypothesis, we let normal-sighted observers search

with simulated foveal scotoma during a learning phase but without scotoma in a subsequent transfer phase. Contextual cueing was absent during learning, but reinstated in the transfer phase. This indicated that context learning occured in the presence of foveal vision loss, but learning could not be utilized for more efficient search while the scotoma was present. However, in a further experiment, after few hours of search training with central scotoma simulation, contextual cueing was reinstated during scotomatous search, indicating that contextual cueing can be regained when the exploration of the environment becomes more automatic. Thus, foveal vision loss leads to inefficient use of implicitly learned contextual cues for the guidance of visual search. Automatization of search with a simulated scotoma leads to reinstatement of contextual cueing in normal-sighted observers. This may show a promising way for training programs in patients with foveal vision loss. Meeting abstract presented at VSS 2015.

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J Vis. 2015 Sep 1;15(12):1015.

Heading Perception with Simulated Visual Defects.

Vinnikov M, Palmisano S, Allison R.

Abstract: Heading perception depends on the ability of different regions of the visual field to extract accurate information about the direction of the visual flow. Hence due to its ability to extract the most accurate information, the central visual field plays a major role in heading estimation. With experience people learn to utilize other regions especially if there is central field loss/impairment. Nevertheless, it is not clear what happens when information in central vision becomes altered or cannot be picked up. In the present study, we examined the effects of gaze-contingent alteration of regions of the visual field on heading. On each trial, one of six different directions of self-motion were simulated (headings ±7.5°, ±5.0° and ±2.5° from the centre of the screen). The simulated defects were analogous to two typical visual field disturbances resulting from macular degeneration, either metamorphopsia or scotomas. Specifically, with a force choice procedure we compared performance with no visual defects to that with five different simulated defects (either 5° or 10° horizontal perturbations, 5° or 10° Gaussian perturbations, or a 10° scotoma). We also looked at three gaze conditions - free viewing, directional viewing and tracking features in the scene. Heading performance was not significantly different in the two environments examined (translation over a plane covered with blue particles or through a forest). Performance declined in the presence of simulated visual defects, as well as when they were instructed to visually track specific scene features. Performance was most accurate for all heading directions during the free view conditions. We conclude that when people are free to direct their gaze in the scene they are able to minimize the impact of simulated central visual field loss/distortion. Meeting abstract presented at VSS 2015.

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Quality of Life in Patients Suffering from Active Exudative Age-Related Macular Degeneration: The EQUADE Study.

Matamoros E, Maurel F, Léon N, Solomiac A, Bardoulat I, Joubert M, Hermans M, Moser E, Le Picard S, Souied EH, Leveziel N.

PURPOSE: Age-related macular degeneration (AMD) is the main cause of visual loss in the elderly population. With the use of anti-vascular endothelial growth factor, the visual outcomes of exudative AMD patients have been improved. This study was aimed at assessing the quality of life (QoL) of exudative AMD patients treated with ranibizumab and at determining its drivers in a real-life setting.

METHODS: We performed a national, cross-sectional, observational survey based on questionnaires sent to members of French associations relative to AMD between December 2012 and March 2013. Patients suffering from exudative AMD with at least one intravitreal injection of ranibizumab within the last 6 months were included. Demographics, AMD characteristics, visual acuity (VA) and past and ongoing treatments

were collected. The 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ-25) was self-administered. A multivariate model was used to identify QoL drivers.

RESULTS: 416 questionnaires fulfilled the complete criteria for both QoL and cost analyses. The mean age of exudative AMD patients was 78.0 years and bilateral involvement was reported in 60.4%. The overall mean QoL score was 53.4. Mental health, driving and role difficulties were the most widely affected domains. After bivariate analyses, long-term illness status, worse VA and higher number of unpaid aids were associated with worse QoL, with odds ratios of 2.4, 5.2 and 11.6, respectively. The mean cost per year and per patient was 1,741 EUR. The main components of costs were aids and services and the purchase of visual equipment.

CONCLUSIONS: The main predictors of QoL in exudative AMD patients treated with ranibizumab are VA outcomes, home healthcare and social services provided to the patients.

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Role of ZnS Nanoparticles on Endoplasmic Reticulum Stress-mediated Apoptosis in Retinal Pigment Epithelial Cells.

Karthikeyan B, Arun A, Harini L, Sundar K, Kathiresan T.

Abstract: Age-related macular degeneration (AMD) is the leading cause for irreversible visual impairment affecting 30-50 million individuals every year. Oxidative stress and endoplasmic reticulum stress have been identified as crucial factors for the pathogenesis of AMD. Current treatments do not focus on underlying stimuli responsible for the disease like AMD. Zinc is an important trace metal in retina and its deficiency leads to AMD. Recent studies on zinc sulphide nanoparticles (ZnS-NPs) are gaining attention in the field of physical and biological research. In this present study, in investigating the role of ZnS-NPs on hydrogen peroxide and thapsigargin-treated primary mice retinal pigment epithelial (MRPE) cells, we synthesized ZnS-NPs and characterized using atomic force microscope (AFM) and SEM-EDX. The ZnS-NPs abrogate the primary MRPE cell death through inhibition of oxidative stress-induced reactive oxygen species production and cell permeability. Oxidant molecules hydrogen peroxide and thapsigargin alter unfolded protein response such as glucose-regulated protein 78 (GRP78) and C/EBP homology protein (CHOP) expressions, whereas ZnS-NPs-pre-treated primary MRPE cells downregulated the overexpression of such proteins. The expressions of apoptotic proteins caspase 12 and cleaved caspase 9 and caspase 3 were also significantly controlled in ZnS-NPs-treated primary MRPE cells when comparing with thapsigargin- and hydrogen peroxide-treated cells. From these results, ZnS-NPs stabilize reactive oxygen species elevation, when subjected to hydrogen peroxide- and thapsigargin-mediated oxidant injury and helps in maintaining normal homeostasis through regulating endoplasmic reticulum (ER) stress response proteins which is the lead cause for apoptosis-mediated pathogenesis of AMD.

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