Macular Disease Foundation AUSTRALIA
Our focus is your vision

MD Research News

Issue 150

Monday 30 September, 2013

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

If you have not already subscribed, please email Rob Cummins at **research@mdfoundation.com.au** with ‘Subscribe to MD Research News’ in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your ‘unsubscribe’ request.

Drug treatment

J Ophthalmol. 2013;2013:676049. doi: 10.1155/2013/676049. Epub 2013 Aug 28.

Predictors of visual response to intravitreal bevacizumab for treatment of neovascular age-related macular degeneration.

Fang K, Tian J, Qing X, Li S, Hou J, Li J, Yu W, Chen D, Hu Y, Li X.

Department of Epidemiology & Biostatistics, School of Public Health, Peking University Health Science Center, Beijing 100191, China.

Purpose: To identify the predictors of visual response to the bevacizumab treatment of neovascular age-related macular degeneration (AMD). Design. A cohort study within the Neovascular AMD Treatment Trial Using Bevacizumab (NATTB).

Methods: This was a multicenter trial including 144 participants from the NATTB study. Visual outcomes measured by change in visual acuity (VA) score, proportion gaining ≥15 letters, and change in central retinal thickness (CRT) were compared among groups according to the baseline, demographic, and ocular characteristics and genotypes.

Results: Mean change in the VA score was 9.2 ± 2.3 SD letters with a total of 46 participants (31.9%) gaining ≥15 letters. Change in median CRT was -81.5 μ m. Younger age, lower baseline VA score, shorter duration of neovascular AMD, and TT genotype in rs10490924 were significantly associated with greater VA score improvement ($P = 0.028$, $P < 0.001$, $P = 0.02$, and $P = 0.039$, resp.). Lower baseline VA score and TT genotype in rs10490924 were significantly associated with a higher likelihood of gaining ≥15 letters ($P = 0.028$, and $P = 0.021$, resp.).

Conclusions: Baseline VA and genotype of rs10490924 were both important predictors for visual response to bevacizumab at 6 months.

PMID: 24069533 [PubMed]

Am J Ophthalmol. 2013 Oct;156(4):693-705.e11. doi: 10.1016/j.ajo.2013.05.039.

Long-term Outcomes in Ranibizumab-Treated Patients With Retinal Vein Occlusion; The Role of Progression of Retinal Nonperfusion.

Sophie R, Hafiz G, Scott AW, Zimmer-Galler I, Nguyen QD, Ying H, Do DV, Solomon S, Sodhi A, Gehlbach P, Duh E, Baranano D, Campochiaro PA.

Department of Ophthalmology, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

PURPOSE: To determine the percentage of ranibizumab-treated patients with retinal vein occlusion (RVO) who had resolution of edema for at least 6 months after the last injection, along with factors and outcomes that correlate with resolution.

DESIGN: Post hoc analysis of open-label clinical trial.

METHODS: Twenty patients with branch RVO (BRVO) and 20 with central RVO (CRVO) received ranibizumab monthly for 3 months and as needed for recurrent/persistent macular edema, no more frequently than every 2 months. Patients still requiring injections after month 40 received scatter and grid laser photocoagulation to try to reduce the need for injections. Main outcome measures included the percentage of patients who had resolution of edema, change in best-corrected visual acuity (BCVA) from baseline, and change in area of retinal nonperfusion in central subfields.

RESULTS: Nine patients with BRVO (45%) had edema resolution from injections alone after a mean of 20.2 months, 4 resolved after addition of laser, 4 were unresolved through 72 months, and 3 exited prior to resolution. Five patients with CRVO (25%) resolved from injections alone after a mean of 14.0 months, 8 remained unresolved through 72 months despite addition of laser, and 7 exited prior to resolution. For BRVO or CRVO, there was a negative correlation between posterior retinal nonperfusion area and BCVA at months 18, 24, and 36 ($P < .05$).

CONCLUSIONS: In patients with RVO, infrequent ranibizumab injections to control edema may not be sufficient to prevent progression of retinal nonperfusion, which may contribute to loss of visual gains.

PMID: 24053892 [PubMed - in process]

J Ocul Pharmacol Ther. 2013 Sep 20. [Epub ahead of print]

One-Year Results of Treatment with Bevacizumab Alone or Ranibizumab Alone for Low Visual Acuity Due to Neovascular Age-Related Macular Degeneration.

Ozkaya A, Alkin Z, Agca A, Satici T, Karakucuk Y, Yazici AT, Demirok A.

Beyoglu Eye Training and Research Hospital , Istanbul, Turkey .

Abstract Purpose: To investigate treatment with bevacizumab alone or ranibizumab alone in neovascular age-related macular degeneration (nAMD) patients with low visual acuity.

Methods: Data were analyzed retrospectively. Inclusion criteria were (1) pretreatment visual acuity of LogMAR 1.3 or worse and (2) treatment duration of at least 12 months. Injections were given monthly for the first 3 months and thereafter as needed. Data collected for each patient included best corrected visual acuity and central retinal thickness measured before treatment, at months 3, 6, 9, and 12 during treatment, and at the last follow-up visit.

Results: In the bevacizumab patients, mean visual acuity was initially 1.70 LogMAR; at months 3, 6, 9, and 12 during treatment it was 1.20, 1.11, 1.14, and 1.10 LogMAR, respectively, and at the last follow-up it was 1.12 LogMAR ($P<0.01$ for all differences with respect to the initial value). Mean injection number in the first 12 months was 5.3. In the ranibizumab patients, mean visual acuity was initially 1.53 LogMAR; at months 3, 6, 9, and 12 during treatment it was 1.18, 1.17, 1.17, and 1.28 LogMAR, respectively, and at the last follow-up it was 1.21 LogMAR ($P<0.01$ for all differences with respect to the initial value). Mean injection number in the first 12 months was 4.2.

Conclusion: Patients with nAMD and low pretreatment visual acuities can benefit from treatment with bevacizumab or ranibizumab.

PMID: 24053539 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2013 Sep 24. [Epub ahead of print]

[Endophthalmitis as a Serious Complication of Intravitreal Drug Delivery.][Article in German]

Lommatzsch AP, Bartels S, Heimes B, Spital G, Dietzel M, Freistühler M, Bornfeld N, Pauleikoff D.

Retinologie, Augenabteilung am St. Franziskus Hospital Münster.

Background: Endophthalmitis, regarded as a severe complication, can occur after intraocular injection of drugs (IVI). At present only few reports exist on the development of this disease, although recently the number of intraocular injections to treat especially age-related macular degenerations is increasing considerably.

Methods: In this paper we present our results of a retrospective study of 27 patients suffering from endophthalmitis after IVI. Treatment had been performed between January 2008 and March 2012. The indications for IVI were as follows: age-related macular degeneration 19, venous branch occlusion 1, diabethic retinopathies 6, uveitis 1. The following drugs were injected: bevacizumab in 8, Rranibizumab in 19 patients. The following data were assessed: incubation time, best corrected visual acuity that had been determined before treatment and later 3, 6 and 9 months after therapeutic vitrectomy. Additionally we describe the ophthalmoscopic changes and the results of bacteriological studies.

Results: Endophthalmitis was diagnosed 5.8 days after IVI on average. The vision of all patients had only been hand movements during the first examination. During the observation time the postoperative visual acuity could be improved only to 1/35 on average. During vitrectomy in 24 out of 27 patients a whitish retinal infiltration could be observed. 18 of 27 patients showed a hypopyon during slit lamp examination. 11 patients developed a retinal detachment and one eye had to be enucleated.

Conclusions: Endophthalmitis must be regarded as a severe complication causing a high risk of retinal detachment with permanent loss of visual acuity. Retinal infiltrations and haemorrhages occur already in the early stages and cause finally a very poor prognosis. The incubation time as a rule amounts to 6 days. The increasing number of IVI and the high risk of damaged retinal structures due to intraocular infections should make postoperative retinal follow-up examinations mandatory, especially during the first 6 days.

PMID: 24065511 [PubMed - as supplied by publisher]

Ophthalmologe. 2013 Sep 25. [Epub ahead of print]

[Tear in the retinal pigment epithelium by intravitreal injection of aflibercept.] [Article in German]

Bertelmann T, Sekundo W, Wenner Y.

Universitätsaugenklinik, Klinik für Augenheilkunde, Philipps-Universität Marburg & UKGM GmbH, Standort Marburg, Baldingerstr., 35043, Marburg, Deutschland, thomas.bertelmann@staff.uni-marburg.de.

Abstract: Development of tears in the retinal pigment epithelium (RIP) has been described as a possible complication following anti-vascular endothelial growth factor (VEGF) antibody therapy with substances which have been available for years when treating pigment epithelium detachment (PED) in eyes affected by age-related macular degeneration (AMD). Aflibercept has become available for the treatment of exsudative AMD since December 2012. This case report describes a further patient in addition to the only other case published so far who developed RIP after aflibercept treatment for PED. Patients have to be thoroughly informed about this potential side effect before initiation of intravitreal aflibercept injection therapy.

PMID: 24062151 [PubMed - as supplied by publisher]

Arq Bras Oftalmol. 2013 Aug;76(4):209-11.

One year results of anti-VEGF treatment in pigment epithelial detachment secondary to macular degeneration.

Yüksel H, Türkcü FM, Sahin A, Sahin M, Cinar Y, Cingü AK, Ari S, Caça I.

PURPOSE: Pigment epithelial detachment (PED) may be seen in all stages of age-related macular degeneration (ARMD) and may lead to poor prognosis. In this study, we retrospectively examined the effect of anti-VEGF treatments in ARMD patients with vascularized PED.

METHODS: Medical records of 15 patients with PED secondary to ARMD were reviewed retrospectively. The diagnosis of PED was made with fundoscopy, fundus fluorescein angiography and optical coherence tomography. Patients were treated with intravitreal ranibizumab or/and bevacizumab and followed up for a minimum of one year. PED height and best corrected visual acuity (BCVA) was obtained before the first intravitreal anti-VEGF injection and again at the 1st, 3rd, 6th and 12th month after the injection.

RESULTS: The mean baseline BCVA was 0.71 ± 0.48 logarithm of the minimal angle of resolution (logMAR) unit and the mean baseline PED height was 361 ± 153 µ. The mean injection count per eye was 3.9 ± 2.9. There was a significant reduce in mean PED height (247 ± 177 µ) also in 2 eyes PED completely resolved at the end of the follow up period. The mean BCVA at 12th month (0,69 ± 0,37) were not different from the baseline record.

CONCLUSIONS: This retrospective case series showed that intravitreal anti-VEGF therapy preserved vision and reduced PED height in PED patients in a one-year follow-up period.

PMID: 24061828 [PubMed - in process]

Arch Soc Esp Oftalmol. 2013 Oct;88(10):380-386. doi: 10.1016/j.oftal.2013.01.016. Epub 2013 May 14.

Responses to ranibizumab in wet age-related macular degeneration patients with vitreomacular traction.[Article in English, Spanish]

Filloy A, Arias L.

Servicio de Oftalmología, Hospital Universitari de Bellvitge-Institut d'Investigació Biomèdica de Bellvitge, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, España. Electronic address: alejandrofilloy@gmail.com.

PURPOSE: The purpose of the present study is to compare the responses to ranibizumab between wet age-related macular degeneration patients, with and without accompanying vitreomacular traction syndrome.

METHODS: Our database of optical coherence tomography files was searched for eyes of age-related macular degeneration patients that had been treated with ranibizumab, and that had evidence of vitreomacular traction. A control group was selected from the same database for comparison. The case history of each selected individual was reviewed for data regarding the evolution of visual acuity in that patient, and the number of intravitreal injections that had been required to date.

RESULTS: From a database of 373 eyes, clear images of vitreomacular traction were obtained for a total of 18 eyes. The mean follow-up period was 20.6 months (SD=10.6, range=10.4-31.7). Patients in the vitreomacular traction group had been given an average of 5.1 injections versus an average of 4.2 injections in patients in the control group. The mean changes in visual acuity (which was measured using ETDRS charts) were -15 letters and -4 letters in the vitreomacular traction and control groups (P=.07), respectively.

CONCLUSIONS: After ranibizumab treatment, age-related macular degeneration patients with

accompanying vitreomacular traction showed a tendency to have a poorer prognosis in terms of visual acuity than patients without this finding. In addition, higher numbers of intravitreal injections were required to obtain clinical responses in patients with vitreomacular traction.

PMID: 24060301 [PubMed - as supplied by publisher]

Int J Immunopathol Pharmacol. 2013 Jul-Sep;26(3):765-8.

Intravitreal infliximab for choroidal neovascularization in patients refractory to conventional treatments.

Semeraro F, Romano MR, Danzi P, Angi M, Costagliola C.

Dipartimento di Oftalmologia, Universita' degli Studi di Brescia, Brescia, Italy.

Abstract: The aim of the study is to evaluate the effectiveness and safety of intravitreal infliximab in the course of compassionate use in patients affected by choroidal neovascularization. This prospective interventional case series includes four eligible patients, affected by exudative age-related macular degeneration (2/4), retinal angiomatous proliferation (1/4) and central retinal vein occlusion (1/4), who were refractory to conventional treatments. The patients received a single intravitreal injection of 0.05 ml of reconstituted infliximab solution (20mg/ml). The main outcomes measure were changes in best-corrected visual acuity and central retinal thickness. Patients were evaluated at baseline, every week for the first month, then every two weeks, and on demand. Morphologic parameters improved after a single infliximab intravitreal injection. However, all patients developed acute uveitis in a period ranging from 4 to 7 weeks after treatment. Control of the intraocular inflammation was achieved with topical and systemic steroids in 3 patients, whereas in one case pars plana vitrectomy was needed. A single intravitreal injection of infliximab does not seem to improve the natural history of CNV from different aetiologies. However, all patients in our series developed a serious inflammatory response that required surgical management in one case. The intravitreal administration of infliximab is hence not safe and not recommended in clinical practice.

PMID: 24067474 [PubMed - in process]

Retina. 2013 Sep 19. [Epub ahead of print]

PHASE 1, DOSE-RANGING STUDY OF EMIXUSTAT HYDROCHLORIDE (ACU-4429), A NOVEL VISUAL CYCLE MODULATOR, IN HEALTHY VOLUNTEERS.

Kubota R, Al-Fayoumi S, Mallikaarjun S, Patil S, Bavik C, Chandler JW.

*Acucela Inc, Seattle, Washington; and †Otsuka Pharmaceutical Development and Commercialization, Inc (OPDC), Princeton, New Jersey.

BACKGROUND: Emixustat hydrochloride (formerly ACU-4429) is a nonretinoid compound with a unique mode of action in the retinal pigment epithelium, where it modulates the biosynthesis of visual chromophore through its effect on retinal pigment epithelium-specific 65 kDa protein isomerase. This study provides clinicians with a background for understanding the pharmacokinetics and safety profile of orally administered emixustat.

METHODS: This randomized, double-masked, placebo-controlled Phase 1b study evaluated the pharmacokinetics, tolerability, and safety of a 14-day course of oral emixustat (5, 10, 20, 30, or 40 mg) or placebo (3:1 ratio) once daily in healthy volunteers.

RESULTS: A total of 40 subjects were enrolled (mean age, 38 years; 75% male). Emixustat (n = 30) was rapidly absorbed (median Tmax, 3.0-5 hours) and readily eliminated (mean t1/2, 4.6-7.9 hours), and mean Cmax and AUC0-24 generally increased in proportion to dose. No significant accumulation of emixustat

was observed with multiple-dose administration. Ocular adverse events occurred in 67% of the subjects who received emixustat; all were considered mild and resolved after study completion. Systemic adverse events were minimal.

CONCLUSION: Oral emixustat was safe and well tolerated when administered once daily for 14 days with minimal systemic adverse events reported. These data support evaluation of emixustat in subjects with geographic atrophy associated with dry age-related macular degeneration.

PMID: 24056528 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2013 Sep 19. [Epub ahead of print]

EVALUATION OF SEMIAUTOMATED MEASUREMENT OF GEOGRAPHIC ATROPHY IN AGE-RELATED MACULAR DEGENERATION BY FUNDUS AUTOFLUORESCENCE IN CLINICAL SETTING.

Panthier C, Querques G, Puche N, Le Tien V, Garavito RB, Béchet S, Massamba N, Souied EH.

*Department of Ophthalmology, University of Paris XII, Centre Hospitalier Intercommunal de Creteil, Creteil, France; and †Centre de Recherche Clinique, CRC, CHI Creteil, Creteil, France.

PURPOSE: To assess intraobserver and interobserver agreement among physicians with different degrees of clinical experience, using a novel fundus autofluorescence semiautomated software for quantification of geographic atrophy in clinical setting.

METHODS: Fundus autofluorescence frames (excitation: 488 nm; emission: 500-700 nm) of 29 eyes (20 patients; mean age, 79.6 ± 6.2 years) with geographic atrophy secondary to age-related macular degeneration, and no signs of choroidal neovascularization, were analyzed using Region Finder, a semiautomated software embedded in Spectralis (Heidelberg Engineering, Heidelberg, Germany). For each study eye, semiautomated atrophy identification and quantification were independently performed, twice (in a 2-week time frame), by 3 readers with different degrees of clinical experience (2 fellows, and 1 resident). Intraobserver and interobserver agreements were assessed.

RESULTS: Mean difference in intraobserver agreement (Bland-Altman statistics) ranged from -0.17 mm to 0.13 mm. Intraobserver agreement was excellent until the geographic atrophy threshold value of 15.72 mm. Variability correlated with the size of atrophy. Mean difference in interobserver agreement (Bland-Altman statistics) ranged from -0.25 mm to 0.27 mm, with no significant difference between senior and junior readers. Multifocal lesion or foveal involvement in atrophy was not the cause of disagreement.

CONCLUSION: Region Finder is a reliable tool for the identification and quantification of geographic atrophy in patients with age-related macular degeneration, in a clinical setting even when performed by junior reader.

PMID: 24056526 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Sep 26. pii: iovs.13-12474v1. doi: 10.1167/iovs.13-12474. [Epub ahead of print]

Reticular Pseudodrusen in Early Age-Related Macular Degeneration is Associated with Choroidal Thinning.

Garg A, Oll M, Yzer S, Chang S, Barile GR, Merriam JC, Tsang SH, Bearelly S.

Ophthalmology, Columbia University, 350 W 37th St, Apartment 19F, New York, NY, 10018, United States.

Purpose: To compare choroidal thickness (CT) measurements in early age-related macular degeneration (AMD) between patients with and without reticular pseudodrusen (RPD) using spectral-domain optical coherence tomography (SD-OCT).

Methods: This cross-sectional study examined 84 age- and sex-matched AMD patients [40 RPD (63 eyes), 44 non-RPD (75 eyes)]. Fundus photographs and scanning laser ophthalmoscopy images were graded to identify RPD and non-RPD groups by three retinal specialists (MO, SY, SB) who were masked to corresponding SD-OCTs. CT at the fovea and 2400 to 3000μm superior and inferior to the fovea was measured on SD-OCT by a grader (AG) and reviewed by a retinal specialist (SB). Only images with a clear posterior choroidal margin were analyzed (6 eyes excluded due to poor image quality), and enhanced depth imaging SD-OCT was used when available (20 of 138 eyes). Greatest retinal thickness (RT) on horizontal foveal SDOCT was also recorded.

Results: Mean CTs in the superior, foveal, and inferior macula in RPD (191.3μm ± 57.9 SD, 176.3μm ± 60.5 SD, 179.7μm ± 56.24 SD) were significantly less than that of non-RPD (228.0μm ± 66.1 SD, 216.5μm ± 70.3 SD, 224.4μm ± 71.9 SD; p=.0010, p=0.0005, p=.0001, respectively), as was greatest RT (p=.0301).

Conclusions: CT was thinner throughout the macula in the RPD group as compared to the non-RPD group. The current analysis supports an association between RPD and a thinned choroidal layer and is consistent with a choroidal etiology of RPD. CT may be integral to understanding RPD, and may be helpful in stratifying AMD progression risk.

PMID: 24071958 [PubMed - as supplied by publisher]

Mol Vis. 2013 Sep 20;19:1985-xxx.

Review: Retinal degeneration: Focus on the unfolded protein response.

Gorbatyuk M, Gorbatyuk O.

Department of Vision Sciences, University of Alabama at Birmingham, Birmingham, AL 35233.

Abstract: Recently published literature has provided evidence that the unfolded protein response (UPR) is involved in the development of retinal degeneration. The scope of these studies encompassed diabetic retinopathy, retinopathy of prematurity, glaucoma, retinal detachment, light-induced retinal degeneration, age-related macular degeneration, and inherited retinal degeneration. Subsequent studies investigating the role of individual UPR markers in retinal pathogenesis and examining the therapeutic potential of reprogramming the UPR as a method for modulating the rate of retinal degeneration have been initiated. Manipulation of UPR markers has been made possible by the use of knockout mice, pharmacological agents, and viral vector-mediated augmentation of gene expression. Future research will aim at identifying specific inhibitors and/or inducers of UPR regulatory markers as well as expand the list of UPR-related animal models. Additionally, adeno-associated virus-mediated gene delivery is a safe and effective method for modulating gene expression, and thus is a useful research tool for manipulating individual UPR markers in affected retinas and a promising delivery vector for gene therapy in retinal degenerative disorders.

PMID: 24068865 [PubMed - as supplied by publisher]

PLoS One. 2013 Sep 12;8(9):e73084. doi: 10.1371/journal.pone.0073084.

Development of a short version of the visual function questionnaire using item-response theory.

Fukuhara S, Wakita T, Yamada M, Hiratsuka Y, Green J, Oki K.

Department of Epidemiology and Healthcare Research, Graduate School of Medicine and Faculty of Medicine, Kyoto University, Kyoto, Japan ; iHope International, Kyoto and Tokyo, Japan.

PURPOSE: In clinical ophthalmology as in other fields, measuring patient-reported outcomes imposes a burden on patients. To decrease that burden, we used item-response theory (IRT) to develop and test a short version of the National Eye Institute's Visual Function Questionnaire (VFQ).

METHODS: We analyzed VFQ data from 276 adults in Japan. Most of them had glaucoma, cataract, or macular degeneration. Their visual acuity (Snellen fraction) averaged 20/120 (range: 20/13 to 20/2000) for the better eye, and 20/200 (range: 20/13 to 20/2000) for the worse eye. We used a polytomous IRT model, the Generalized Partial Credit Model as implemented in software for parameter scaling of rating data (PARSCALE). To select items for inclusion in the short version we examined each item's location on the latent-trait continuum, its slope, and its frequency of missing data. We also ensured representation of all 7 domains that are important in Japan. To examine the characteristics of the resulting scale, we computed its test information (an index of precision that can vary with the value of the latent trait), and carried out validation testing.

RESULTS: From 32 of the original VFQ items, we selected 11. The scale comprising those 11 items (the VFQ-J11) had test information greater than 9 for values of the latent trait between -2.0 and +0.8. The item thresholds were well-targeted for patients with vision problems. Scores on the VFQ-J11 correlated strongly and in the expected direction with measures of visual field and corrected visual acuity. As expected for a valid measure, those scores also improved by a large amount (almost one standard deviation) after cataract surgery.

CONCLUSION: This 11-item instrument can provide reliable and the valid data on visual functioning in patients with ophthalmic problems. It is expected to be less of a burden on respondents, while it maintains good psychometric properties.

PMID: 24069172 [PubMed - in process]

Pathogenesis

Biogerontology. 2013 Sep 22. [Epub ahead of print]

Role of antioxidant enzymes and small molecular weight antioxidants in the pathogenesis of age-related macular degeneration (AMD).

Tokarz P, Kaarniranta K, Blasiak J.

Department of Molecular Genetics, Faculty of Biology and Environmental Protection, University of Lodz, Pomorska 141/143, 90-236, Lodz, Poland, ptokarz@biol.uni.lodz.pl.

Abstract: Cells in aerobic condition are constantly exposed to reactive oxygen species (ROS), which may induce damage to biomolecules, including proteins, nucleic acids and lipids. In normal circumstances, the amount of ROS is counterbalanced by cellular antioxidant defence, with its main components-antioxidant enzymes, DNA repair and small molecular weight antioxidants. An imbalance between the production and neutralization of ROS by antioxidant defence is associated with oxidative stress, which plays an important role in the pathogenesis of many age-related and degenerative diseases, including age-related macular degeneration (AMD), affecting the macula-the central part of the retina. The retina is especially prone to oxidative stress due to high oxygen pressure and exposure to UV and blue light promoting ROS generation. Because oxidative stress has an established role in AMD pathogenesis, proper functioning of antioxidant defence may be crucial for the occurrence and progression of this disease. Antioxidant enzymes play a major role in ROS scavenging and changes of their expression or/and activity are reported to be associated with AMD. Therefore, the enzymes in the retina along with their genes may constitute a perspective target in AMD prevention and therapy.

PMID: 24057278 [PubMed - as supplied by publisher]

PLoS One. 2013 Aug 23;8(8):e71398. doi: 10.1371/journal.pone.0071398.

Phototoxic action spectrum on a retinal pigment epithelium model of age-related macular degeneration exposed to sunlight normalized conditions.

Arnault E, Barrau C, Nanteau C, Gondouin P, Bigot K, Viénot F, Gutman E, Fontaine V, Villette T, Cohen-Tannoudji D, Sahel JA, Picaud S.

Institut de la Vision, UPMC Univ Paris 06, UMR_S 968, Paris, France ; INSERM, U968, Paris, France ; CNRS, UMR_7210, Paris, France.

Abstract: Among the identified risk factors of age-related macular degeneration, sunlight is known to induce cumulative damage to the retina. A photosensitive derivative of the visual pigment, N-retinylidene-N-retinylethanolamine (A2E), may be involved in this phototoxicity. The high energy visible light between 380 nm and 500 nm (blue light) is incriminated. Our aim was to define the most toxic wavelengths in the blue-green range on an in vitro model of the disease. Primary cultures of porcine retinal pigment epithelium cells were incubated for 6 hours with different A2E concentrations and exposed for 18 hours to 10 nm illumination bands centered from 380 to 520 nm in 10 nm increments. Light irradiances were normalized with respect to the natural sunlight reaching the retina. Six hours after light exposure, cell viability, necrosis and apoptosis were assessed using the Apotox-Glo Triplex™ assay. Retinal pigment epithelium cells incubated with A2E displayed fluorescent bodies within the cytoplasm. Their absorption and emission spectra were similar to those of A2E. Exposure to 10 nm illumination bands induced a loss in cell viability with a dose dependence upon A2E concentrations. Irrespective of A2E concentration, the loss of cell viability was maximal for wavelengths from 415 to 455 nm. Cell viability decrease was correlated to an increase in cell apoptosis indicated by caspase-3/7 activities in the same spectral range. No light-elicited necrosis was measured as compared to control cells maintained in darkness. Our results defined the precise spectrum of light retinal toxicity in physiological irradiance conditions on an in vitro model of age-related macular degeneration. Surprisingly, a narrow bandwidth in blue light generated the greatest phototoxic risk to retinal pigment epithelium cells. This phototoxic spectrum may be advantageously valued in designing selective photoprotection ophthalmic filters, without disrupting essential visual and non-visual functions of the eye.

PMID: 24058402 [PubMed - in process] PMCID: PMC3751948

J Vis Exp. 2013 Sep 11;(79). doi: 10.3791/50660.

Retinal detachment model in rodents by subretinal injection of sodium hyaluronate.

Matsumoto H, Miller JW, Vavvas DG.

Retina Service, Angiogenesis Laboratory, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School.

Abstract: Subretinal injection of sodium hyaluronate is a widely accepted method of inducing retinal detachment (RD)(1-15). However, the height and duration of RD or the occurrence of subretinal hemorrhage can affect photoreceptor cell death in the detached retina(16-21). Hence, it is advantageous to create reproducible RDs without subretinal hemorrhage for evaluating photoreceptor cell death. We modified a previously reported method to create bullous and persistent RDs in a reproducible location with rare occurrence of subretinal hemorrhage. The critical step of this modified method is the creation of a self-sealing scleral incision, which can prevent leakage of sodium hyaluronate after injection into the subretinal space. To make the self-sealing scleral incision, a scleral tunnel is created, followed by scleral penetration into the choroid with a 30 G needle. Although choroidal hemorrhage may occur during this step, astriction with a surgical spear reduces the rate of choroidal hemorrhage. This method allows a more reproducible and reliable model of photoreceptor death in diseases that involve RD such as rhegmatogenous RD, retinopathy of prematurity, diabetic retinopathy, central serous chorioretinopathy, and age-related macular

degeneration (AMD).

PMID: 24056325 [PubMed - in process]

Exp Eye Res. 2013 Sep 20. pii: S0014-4835(13)00269-8. doi: 10.1016/j.exer.2013.09.003. [Epub ahead of print]

Retinal pigment epithelium development, plasticity, and tissue homeostasis.

Fuhrmann S, Zou C, Levine EM.

Department of Ophthalmology & Visual Sciences, John A. Moran Eye Center, University of Utah, 65 Mario Capecchi Drive, Salt Lake City, Utah, USA 84132. Electronic address: sabine.fuhrmann@hsc.utah.edu.

Abstract: The retinal pigment epithelium (RPE) is a simple epithelium interposed between the neural retina and the choroid. Although only 1 cell-layer in thickness, the RPE is a virtual workhorse, acting in several capacities that are essential for visual function and preserving the structural and physiological integrities of neighboring tissues. Defects in RPE function, whether through chronic dysfunction or age-related decline, are associated with retinal degenerative diseases including age-related macular degeneration. As such, investigations are focused on developing techniques to replace RPE through stem cell-based methods, motivated primarily because of the seemingly limited regeneration or self-repair properties of mature RPE. Despite this, RPE cells have an unusual capacity to transdifferentiate into various cell types, with the particular fate choices being highly context-dependent. In this review, we describe recent findings elucidating the mechanisms and steps of RPE development and propose a developmental framework for understanding the apparent contradiction in the capacity for low self-repair versus high transdifferentiation.

PMID: 24060344 [PubMed - as supplied by publisher]

Genetics

Ophthalmology. 2013 Sep 23. pii: S0161-6420(13)00686-6. doi: 10.1016/j.ophtha.2013.07.046. [Epub ahead of print]

Pharmacogenetic Associations with Vascular Endothelial Growth Factor Inhibition in Participants with Neovascular Age-Related Macular Degeneration in the IVAN Study.

Lotery AJ, Gibson J, Cree AJ, Downes SM, Harding SP, Rogers CA, Reeves BC, Ennis S, Chakravarthy U; Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation (IVAN) Study Group.

Clinical Neurosciences Research Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom. Electronic address: A.J.Lotery@soton.ac.uk.

PURPOSE: To determine if prespecified genetic polymorphisms influence responsiveness to vascular endothelial growth factor (VEGF) inhibition in neovascular age-related macular degeneration (nAMD). The objectives were to replicate 3 reported pharmacogenetic associations of response in nAMD and to test for novel associations.

DESIGN: Cohort study, combining information about patients' genotypes with information from a randomized controlled trial about responsiveness to anti-VEGF therapy for nAMD.

PARTICIPANTS: Five hundred nine participants with nAMD, enrolled in the Alternative Treatments to Inhibit VEGF in Patients with Age-Related Choroidal Neovascularisation (IVAN) trial.

METHODS: Participants were classified as responders or nonresponders to VEGF inhibition based on the

optical coherence tomography (OCT) metric of total retinal thickness (TRT). We computed the change in TRT from baseline to the latest time point for which OCT data were available (3, 6, 9, or 12 months). Eyes with changes in TRT greater than or equal to the 75th percentile or more were classified as responders, and those with changes less than or equal to the 25th percentile or lower were classified as non-responders. Three previously reported associations of response to VEGF inhibition in nAMD involving single nucleotide polymorphisms (SNPs) at the CFH, FZD4, and HTRA1/ARMS2 loci were tested for replication. An additional 482 SNPs also were tested using a candidate gene approach. Associations were estimated as odds ratios (ORs) with confidence intervals (CIs).

MAIN OUTCOME MEASURES: The primary outcome was evidence of a genetic association with response to VEGF inhibition as measured by change in TRT.

RESULTS: One hundred twenty-six participants were classified as responders and 128 were classified as nonresponders. The SNP rs10490924 in HTRA1/ARMS2 showed a borderline association with responsiveness after Bonferroni correction (OR, 1.53; CI, 0.99-2.36; P = 0.055, Bonferroni correction). None of the other 484 additional SNPs tested for association was significant after Bonferroni correction for multiple testing. The smallest corrected P value was 0.84 (P = 0.002, uncorrected) for rs9679290 in the EPAS1 (HIF2A) gene on chromosome 2. Four of the 10 most significant results were in this gene.

CONCLUSIONS: We estimated pharmacogenetic associations using high-quality phenotype data from a randomized controlled clinical trial of nAMD. No significant association or replication of previous associations were observed. Further investigation of the EPAS1 (HIF2A) gene, however, may, be merited.

PMID: 24070809 [PubMed - as supplied by publisher]

Klin Oczna. 2013;115(2):96-102.

Association between the 25129A > C polymorphism of the nuclear respiratory factor 2 gene and age -related macular degeneration.

Sliwiński T, Kołodziejska U, Szaflik JP, Błasiak J, Szaflik J.

Department of Molecular Genetics, University of Lodz, Poland. tomsliw@biol.uni.lodz.pl

PURPOSE:Oxidative stress belongs to the main factors of pathogenesis of age-related macular degeneration, characterized by the damage to the retinal pigment epithelium cells and photoreceptors. Retinal pigment epithelium cells are rich in mitochondria, producing large amount of reactive oxygen species, which are by-products of the activity of the respiratory chain. The distribution in the activity of the chain may be evoked by the release of cytochrome C from the mitochondrion to the cytoplasm. This process may activated by nuclear respiratory factor 2, Nrf2, which is encoded by a highly polymorphic gene. In this study we examined the association between age-related macular degeneration risk and the 25129A > C polymorphism of the gene encoding nuclear respiratory factor 2 (rs12594956).

MATERIAL AND METHODS: Genotypes were determined in DNA from peripheral blood lymphocytes of 281 patients with age-related macular degeneration (181 with wet form of the disease and 101 with its dry form), and 105 controls by PCR-restriction fragment length polymorphism.

RESULTS: A weak association (OR 1.96; p = 0.023) between the C/C genotype of the 25129A > C polymorphism and the occurrence of age-related macular degeneration was found. A stronger association was observed between dry age-related macular degeneration occurrence and the C/C genotype of the polymorphism (OR 2.23; p = 0.018). The A/C genotype decreased the risk of age-related macular degeneration and its dry form (OR 0.51; p = 0.023 and 0.44; p = 0.018, respectively). Potential risk factors such as age, gender, smoking habit, living environment (rural or urban) and family status of age-related macular degeneration increased the risk of AMD associated with the C/C genotype (OR 2.52; p = 0.012).

CONCLUSIONS: The 25129A > C polymorphism of the NRF2 gene may be associated with age-related

macular degeneration. mitochondria, reactive oxygen species, gene polymorphism, NRF2 gene, age-related macular degeneration - AMD.

PMID: 24059022 [PubMed - in process]

Mutat Res. 2013 Sep 17. pii: S1383-5742(13)00070-7. doi: 10.1016/j.mrrev.2013.09.001. [Epub ahead of print]

Mutations that affect mitochondrial functions and their association with neurodegenerative diseases.

Dhillon VS, Fenech M.

Preventative-Health Flagship, Gate 13, Kintore Avenue, Adelaide, SA 5000, Australia; CSIRO Animal, Food and Health Sciences, Gate 13, Kintore Avenue, Adelaide, SA 5000, Australia. Electronic address: Varinderpal.dhillon@csiro.au.

Abstract: Mitochondria are essential for mammalian and human cell function as they generate ATP via aerobic respiration. The proteins required in the electron transport chain are mainly encoded by the circular mitochondrial genome but other essential mitochondrial proteins such as DNA repair genes, are coded in the nuclear genome and require transport into the mitochondria. In this review we summarize current knowledge on the association of point mutations and deletions in the mitochondrial genome that are detrimental to mitochondrial function and are associated with accelerated ageing and neurological disorders including Alzheimer's, Parkinson's, Huntington's and Amyotrophic lateral sclerosis (ALS). Mutations in the nuclear encoded genes that disrupt mitochondrial functions are also discussed. It is evident that a greater understanding of the causes of mutations that adversely affect mitochondrial metabolism is required to develop preventive measures against accelerated ageing and neurological disorders caused by mitochondrial dysfunction.

PMID: 24055911 [PubMed - as supplied by publisher]

Diet & lifestyle

Antioxid Redox Signal. 2013 Sep 22. [Epub ahead of print]

Role of UPR dysregulation in oxidative injury of retinal pigment epithelial cells.

Chen C, Cano M, Wang JJ, Li J, Huang C, Yu Q, Herbert TP, Handa J, Zhang SX.

University at Buffalo, the State University of New York, Ophthalmology, Buffalo, New York, United States ; chenchenmd@yahoo.cn.

Aims: Age-related macular degeneration (AMD), a major cause of legal blindness in the elderly, is associated with genetic and environmental risk factors, such as cigarette smoking. Recent evidence shows that cigarette smoke (CS) that contains high levels of potent oxidants preferably targets retinal pigment epithelium (RPE) leading to oxidative damage and apoptosis; however, the mechanisms are poorly understood. The present study aimed to investigate the role of ER stress and the unfolded protein response (UPR) in CS-related RPE apoptosis.

Results: ER stress and pro-apoptotic gene CHOP were induced in the RPE/choroid complex from mice exposed to CS for 2 weeks and in human RPE cells treated with hydroquinone, a potent oxidant found at high concentrations in CS. Suppressing ER stress or inhibiting CHOP activation by pharmacological chaperones or genetic approaches attenuated hydroquinone-induced RPE cell apoptosis. In contrast to enhanced CHOP activation, protein level of active XBP1, a major regulator of the adaptive UPR, was

reduced in hydroquinone-treated cells. Conditional knockout of XBP1 gene in the RPE resulted in caspase-12 activation, increased CHOP expression, and decreased anti-apoptotic gene Bcl-2. Furthermore, XBP1-deficient RPE cells are more sensitive to oxidative damage induced by hydroquinone or NaIO3, a CS-unrelated chemical oxidant. Conversely, overexpressing XBP1 protected RPE cells and attenuated oxidative stress-induced RPE apoptosis.

Innovations and conclusions: These findings provide strong evidence suggesting an important role of ER stress and the UPR in CS-related oxidative injury of RPE cells. Thus, modulation of the UPR signaling may provide a promising target for the treatment of AMD.

PMID: 24053669 [PubMed - as supplied by publisher]

Am J Clin Nutr. 2013 Oct;98(4):1144. doi: 10.3945/ajcn.113.071142.

Nutrients related to the incidence of early and late age-related macular degeneration.

Kawada T.

Department of Hygiene and Public Health Nippon Medical School 1-1-5 Sendagi Bunkyo-Ku Tokyo 113-8602 Japan E-mail: kawada@nms.ac.jp.

PMID: 24056822 [PubMed - in process]