Macular Degeneration Foundation
Our focus is your vision

MD Research News

Issue 104

Monday October 29 , 2012

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

Ophthalmology. 2012 Oct 16. pii: S0161-6420(12)00865-2. doi: 10.1016/j.ophtha.2012.09.006. [Epub ahead of print]

Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration.

Heier JS, Brown DM, Chong V, Korobelnik JF, Kaiser PK, Nguyen QD, Kirchhof B, Ho A, Ogura Y, Yancopoulos GD, Stahl N, Vitti R, Berliner AJ, Soo Y, Anderesi M, Groetzbach G, Sommerauer B, Sandbrink R, Simader C, Schmidt-Erfurth U; VIEW 1 and VIEW 2 Study Groups*.

Ophthalmic Consultants of Boston and Tufts University School of Medicine, Boston, Massachusetts.

OBJECTIVE: Two similarly designed, phase-3 studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW 1, VIEW 2]) of neovascular age-related macular degeneration (AMD) compared monthly and every-2-month dosing of intravitreal aflibercept injection (VEGF Trap-Eye; Regeneron, Tarrytown, NY, and Bayer HealthCare, Berlin, Germany) with monthly ranibizumab.

DESIGN: Double-masked, multicenter, parallel-group, active-controlled, randomized trials.

PARTICIPANTS: Patients (n = 2419) with active, subfoveal, choroidal neovascularization (CNV) lesions (or juxtafoveal lesions with leakage affecting the fovea) secondary to AMD.

INTERVENTION: Patients were randomized to intravitreal aflibercept 0.5 mg monthly (0.5q4), 2 mg monthly (2q4), 2 mg every 2 months after 3 initial monthly doses (2q8), or ranibizumab 0.5 mg monthly (Rq4).

MAIN OUTCOME MEASURES: The primary end point was noninferiority (margin of 10%) of the aflibercept regimens to ranibizumab in the proportion of patients maintaining vision at week 52 (losing <15 letters on Early Treatment Diabetic Retinopathy Study [ETDRS] chart). Other key end points included change in best-corrected visual acuity (BCVA) and anatomic measures.

RESULTS: All aflibercept groups were noninferior and clinically equivalent to monthly ranibizumab for the primary end point (the 2q4, 0.5q4, and 2q8 regimens were 95.1%, 95.9%, and 95.1%, respectively, for VIEW 1, and 95.6%, 96.3%, and 95.6%, respectively, for VIEW 2, whereas monthly ranibizumab was 94.4% in both studies). In a prespecified integrated analysis of the 2 studies, all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA; all aflibercept regimens also produced similar improvements in anatomic measures. Ocular and systemic adverse events were similar across treatment groups.

CONCLUSIONS: Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab. These studies demonstrate that

aflibercept is an effective treatment for AMD, with the every-2-month regimen offering the potential to reduce the risk from monthly intravitreal injections and the burden of monthly monitoring.

PMID: 23084240 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 Oct 20. [Epub ahead of print]

Adherence to ranibizumab treatment for neovascular age-related macular degeneration in real life.

Droege KM, Muether PS, Hermann MM, Caramoy A, Viebahn U, Kirchhof B, Fauser S.

Center of Ophthalmology, Department of Vitreo-Retinal Surgery, University of Cologne, 50924, Cologne, Germany.

BACKGROUND: To identify factors and problems influencing treatment adherence in patients undergoing anti-VEGF therapy for neovascular age-related macular degeneration (AMD) under real-life conditions.

METHODS: Cross-sectional study was conducted of 95 patients receiving ranibizumab therapy on a pro re nata (PRN) regimen with monthly controls in a tertiary health care clinic. Monthly controls included best corrected visual acuity, slit-lamp examination and spectral-domain optical coherence tomography. Adherence was measured using Kaplan-Meier time-to-discontinuation analysis. Patients were asked to respond to a 16-item questionnaire covering items such as anxiety, subjective benefit, and financial issues of therapy.

RESULTS: Forty-two men and 53 women were included. After a mean follow-up time of 675 days (range 63 -1008), adherence was 81.1 % (77/95). The mean number of follow-up visits was 19 (3-30), the mean number of intravitreal injections was ten (3-23). Seven patients withdrew from treatment due to subjective dissatisfaction with benefit. Other reasons for loss to follow-up were death in one case, serious general disease in three patients, and treatment options closer to home in five cases. Two patients cancelled further follow-up after treatment cessation due to terminal fibrosis. 62.1 % of patients were afraid of a negative examination result, whereas 19.0 % were afraid of intravitreal injections. A major problem was travel to and from the hospital (46.3 %), with 61.5 % of patients requiring escort.

CONCLUSION: Despite necessary monthly visits, patients showed a high adherence to therapy. The major problem was travel to and from the hospital. From the patients' point of view, anxiety of a negative examination result was more pronounced than fear of intraocular injections, which would be an argument for continuous injections rather than for a PRN regimen.

PMID: 23086225 [PubMed - as supplied by publisher]

Wien Klin Wochenschr. 2012 Oct 24. [Epub ahead of print]

The significance of early treatment of exudative age-related macular degeneration: 12 months' results.

Weingessel B, Hintermayer G, Maca SM, Rauch R, Vecsei-Marlovits PV.

Department of Ophthalmology, Hietzing Hospital, Wolkersbergenstrasse 1, 1130, Vienna, Austria.

BACKGROUND: To assess whether the period between initial symptoms and therapy with ranibizumab in patients with choroidal neovascularization (CNV) influences visual outcome after a follow-up of 12 months.

METHODS: Fifty patients with CNV were retrospectively split into three groups depending on the duration of visual symptoms: group I: < 1 month, group II: 1-6 months, and group III: > 6 months. Best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were recorded at baseline, 2, 6, and 12 months.

Patients received two initial intravitreal injections of 0.5 mg ranibizumab at baseline and reinjections as needed.

RESULTS: The mean time span between initial symptoms and treatment was 66 ± 63 days. A longer duration of visual symptoms was significantly correlated with a lower BCVA at baseline, but also after 6 and 12 months.

CONCLUSIONS: Shorter duration of visual symptoms prior to treatment is associated with a better visual outcome.

PMID: 23093324 [PubMed - as supplied by publisher]

Jpn J Ophthalmol. 2012 Oct 24. [Epub ahead of print]

Photodynamic therapy combined with intravitreal bevacizumab and sub-tenon triamcinolone acetonide injections for age-related macular degeneration.

Yoshizawa C, Saito W, Hirose S, Kitamei H, Noda K, Ishida S.

Department of Ophthalmology, Hokkaido University Graduate School of Medicine, N-15, W-7, Kita-ku, Sapporo, 060-8638, Japan.

PURPOSE: To report the results of triple therapy with photodynamic therapy (PDT) (PDT combined with intravitreal injection of bevacizumab (IVB) and sub-tenon injection of triamcinolone acetonide (STTA)) for the treatment of age-related macular degeneration (AMD) in Japanese patients.

METHODS: This retrospective case series included 38 eyes of 38 patients with exudative AMD treated with PDT combined with IVB (1.25 mg) and STTA (40 mg). Retreatment was performed in the same manner with intervals of at least 3 months. All patients had been treatment naïve, with a follow-up period of 12 months. Best-corrected visual acuity (BCVA), macular retinal thickness (MRT) on optical coherence tomography, and the number of treatments were analyzed.

RESULTS: The mean logarithm of the minimum angle of resolution BCVA in patients treated with PDT triple therapy was 0.86 ± 0.55 at baseline and 0.62 ± 0.55 at 12 months ($p < 0.001$). The mean MRT was 554.0 ± 202.6 μm at baseline and 205.1 ± 78.6 μm at 12 months ($p < 0.001$). During the 1-year follow-up, the average number of PDT triple therapy (treatments per patient) was 1.1. No complications, for example increase in intraocular pressure, cataract, or endophthalmitis, were observed.

CONCLUSIONS: In AMD patients, PDT triple therapy significantly improved visual acuity with a minimum number of treatments and a low risk of complications during the 1-year follow-up.

PMID: 23093314 [PubMed - as supplied by publisher]

Jpn J Ophthalmol. 2012 Oct 24. [Epub ahead of print]

Intravitreal injection of bevacizumab: changes in intraocular pressure related to ocular axial length.

Cacciamani A, Oddone F, Parravano M, Scarinci F, Di Nicola M, Lofoco G.

Fondazione G.B. Bietti-IRCCS, Via Livenza 3/5, 00198, Rome, Italy.

PURPOSE: To evaluate the immediate and short-term effects of intravitreal injection of 1.25 mg/0.05 ml of bevacizumab on intraocular pressure related to different ocular axial lengths.

DESIGN: A prospective case series of consecutive patients referred to the Department of Ophthalmology, San Pietro-Fatebenefratelli Hospital, from September 2011 through January 2011.

METHODS: Twenty-five patients (10 men and 15 women, mean age 70.2 ± 8.98 years) scheduled for intravitreal injection of bevacizumab for the treatment of neovascular age-related macular degeneration were enrolled in this study. Axial length was measured preoperatively using IOLMaster. Intraocular pressure was measured before injection, after 1 min and after 15 min using Tono-Pen XL tonometry.

RESULTS: The mean intraocular pressure change following the intravitreal bevacizumab injection was 21.92 ± 6.95 mmHg after 1 min and 6.24 ± 3.77 mmHg after 15 min. The mean axial length of the examined eyes was 23.2 ± 1.06 mm. A good correlation was observed between the axial length and intraocular pressure rise after both 1 ($R(2) = 0.752$, $p < 0.001$) and 15 min ($R(2) = 0.559$, $p < 0.001$).

CONCLUSIONS: Patients undergoing intravitreal injection of 0.05 ml of bevacizumab can be exposed to intraocular pressure increases correlated to ocular axial length.

PMID: 23093311 [PubMed - as supplied by publisher]

Retina. 2012 Oct 24. [Epub ahead of print]

SYSTEMIC BETA-BLOCKERS MAY REDUCE THE NEED FOR REPEATED INTRAVITREAL INJECTIONS IN PATIENTS WITH WET AGE-RELATED MACULAR DEGENERATION TREATED BY BEVACIZUMAB.

Montero JA, Ruiz-Moreno JM, Sanchis-Merino E, Perez-Martin S.

*Ophthalmology Unit, Pio del Rio Hortega University Hospital, Valladolid, Spain †VISSUM, Alicante Institute of Ophthalmology, Alicante, Spain ‡Ophthalmology Unit, Albacete Medical School, Castilla La Mancha University, Albacete, Spain §Allergy Unit, Pio del Rio Hortega University Hospital, Valladolid, Spain.

PURPOSE: To evaluate the effect of concomitant systemic therapy in patients with choroidal neovascularization secondary to age-related macular degeneration (AMD) treated by intravitreal bevacizumab and to propose a mechanism for different interindividual response.

METHODS: Retrospective, nonrandomized, single-center, consecutive interventional case series study. Forty-six eyes from 46 patients with choroidal neovascularization secondary to age-related macular degeneration were treated by monthly intravitreal 1.25 mg bevacizumab injections on a pro re nata regime. Patients' files were revised and changes in Early Treatment Diabetic Retinopathy Study best-corrected visual acuity, central foveal thickness as determined by spectral domain optical coherence tomography, number of injections performed, occurrence of severe adverse effects, and systemic concomitant medication were recorded. The effect of systemic medication on final best-corrected visual acuity, central foveal thickness, and number of injections performed was evaluated.

RESULTS: The most frequent systemic medications recorded were angiotensin-converting-enzyme inhibitors in 19 patients, beta-adrenergic blocking agents (n = 18), nonsteroidal antiinflammatory drugs (n = 17), diuretics (n = 16), calcium channel blockers (n = 14), benzodiazepines (n = 11), proton-pump inhibitors (n = 9), and statins (n = 8). Thirty-two patients had arterial hypertension. Average follow-up was 25.1 months (standard deviation [SD] = 8.9). Average gain in best-corrected visual acuity was 0.9 (SD = 13.6) and -2.1 letters (SD = 15.9) at 12 months and 24 months, respectively. The average reduction in central foveal thickness was 111 μm (SD = 54) and 105 μm (SD = 71) at 12 months and 24 months, respectively. The average number of intravitreal injections required was 6.7 (SD = 3.2). Patients on treatment with systemic beta-adrenergic blocking agents required less intravitreal injections (5.2, SD = 2.4 vs. 7.9, SD = 3.4) and this difference was statistically significant (P = 0.0068, multiple linear regression).

CONCLUSION: Concomitant systemic beta-adrenergic blocking agents treatment may reduce the need for repeated intravitreal injections of bevacizumab in patients with choroidal neovascularization associated with age-related macular degeneration.

PMID: 23099497 [PubMed - as supplied by publisher]

BMJ Case Rep. 2012 Oct 22;2012. pii: bcr2012007260. doi: 10.1136/bcr-2012-007260.

Brilliant crystallisation in the anterior chamber and subretinal space following adjunctive intravitreal ranibizumab for diabetic vitrectomy.

Bastion ML, Mustapha M, Ho I.

Department of Ophthalmology, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia.

Abstract

To report a unique case of crystallisation in the anterior chamber and subretinal space in a Malay lady following inadvertent subretinal injection of ranibizumab prior to vitrectomy for proliferative diabetic retinopathy.

PMID: 23093508 [PubMed - in process]

J Clin Invest. 2012 Oct 24. pii: 65509. doi: 10.1172/JCI65509. [Epub ahead of print]

Turning a blind eye to anti-VEGF toxicities.

Quaggin SE.

Abstract: Excessive blood vessel growth is a key feature of many retinal diseases, and recently, anti-VEGF therapy has been successfully applied to treat neovascular age-related macular degeneration (AMD), diabetic macular edema, and retinal vein occlusion. In this issue of the JCI, Kurihara et al. reveal an essential role of Vegfa in maintaining choroid vasculature and cone photoreceptors, critical for central and color vision. Their findings suggest that therapeutic approaches to blocking VEGF signaling in retinal diseases might have unexpected detrimental side effects and that the development of alternative strategies might be necessary.

PMID: 23093785 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 Oct 24. [Epub ahead of print]

Long term follow-up after a single intravitreal ranibizumab injection for choroidal neovascularisation secondary to optic nerve head drusen in a 5-year-old child.

Baillif S, Nguyen E, Colleville-El Hayek A, Bétis F.

Centre Hospitalier, Universitaire Saint Roch, Nice, France, baillif-gostoli.s@chu-nice.fr.

PMID: 23093047 [PubMed - as supplied by publisher]

Eye (Lond). 2012 Oct 26. doi: 10.1038/eye.2012.221. [Epub ahead of print]

Ranibizumab for the management of Sorsby fundus dystrophy.

Balaskas K, Hovan M, Mahmood S, Bishop P.

Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

PMID: 23099917 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Methods Mol Biol. 2013;945:45-65. doi: 10.1007/978-1-62703-125-7_4.

The culture and maintenance of functional retinal pigment epithelial monolayers from adult human eye.

Blenkinsop TA, Salero E, Stern JH, Temple S.

Neural Stem Cell Institute, Rensselaer, NY, USA.

Abstract: The retinal pigment epithelium (RPE) is implicated in many eye diseases, including age-related macular degeneration, and therefore isolating and culturing these cells from recently deceased adult human donors is the ideal source for disease studies. Adult RPE could also be used as a cell source for transplantation therapy for RPE degenerative disease, likely requiring first in vitro expansion of the cells obtained from a patient. Previous protocols have successfully extracted RPE from adult donors; however improvements in yield, cell survival, and functionality are needed. We describe here a protocol optimized for adult human tissue that yields expanded cultures of RPE with morphological, phenotypic, and functional characteristics similar to freshly isolated RPE. These cells can be expanded and cultured for several months without senescence, gross cell death, or undergoing morphological changes. The protocol takes around a month to obtain functional RPE monolayers with accurate morphological characteristics and normal protein expression, as shown through immunohistochemistry analysis, RNA expression profiles via quantitative PCR (qPCR), and transepithelial resistance (TER) measurements. Included in this chapter are steps used to extract RPE from human adult globes, cell culture, cell splitting, cell bleaching, immunohistochemistry, and qPCR for RPE markers, and TER measurements as functional test.

PMID: 23097100 [PubMed - in process]

Klin Monbl Augenheilkd. 2012 Oct;229(10):1030-5. doi: 10.1055/s-0032-1315305. Epub 2012 Oct 24.

[Vitreomacular Interface and Posterior Vitreomacular Adhesion in Exudative Age-Related Macular Degeneration (AMD): An OCT-Based Comparative Study].

[Article in German]

Maier M, Pfrommer S, Burzer S, Feucht N, Winkler von Mohrenfels C, Lohmann CP.

Augenklinik, Klinikum rechts der Isar, Technische Universität München (TUM).

Purpose: The aim of this study was to evaluate posterior vitreomacular adhesion as a risk factor for choroidal neovascularisation (CNV) in age-related macular degeneration (AMD). The vitreoretinal interface was examined using spectralis optical coherence tomography (Spectralis-OCT, Heidelberg Engineering).

Patients and Methods: In a retrospective observational case series 375 consecutive eyes of 375 patients (age 51-90 years) were examined with spectralis OCT and fluorescein angiography (Spectralis-HRA, Heidelberg Engineering). Vitreomacular adhesion was defined when a posterior hyaloid line attached to the inner retinal surface was seen in OCT. In 202 patients with exudative AMD the incidence of posterior vitreomacular adhesion was compared to 173 control eyes (72 with non-exudative AMD and 101 eyes without retinal alterations).

Results: We found posterior vitreomacular adhesions in 151 patients (40.27%). In the control group 53 patients (30.6%) showed vitreomacular adhesions compared to 98 patients (48.5%) with exudative AMD. The difference was statistically significant (p = 0.001). The location of vitreomacular adhesion was observed over the area of the CNV in 87 patients (88%) with exudative AMD.

Conclusions: Spectralis OCT allows a detailed examination of the vitreomacular interface. The frequency of

posterior vitreomacular adhesion is significantly increased in eyes with CNV in AMD. Chronic vitreomacular traction may be a risk factor for the development of exudative AMD.

PMID: 23096146 [PubMed - in process]

J Fr Ophtalmol. 2012 Oct 18. pii: S0181-5512(12)00273-2. doi: 10.1016/j.jfo.2012.06.013. [Epub ahead of print]

[Angioid streaks complicated by choroidal neovascularization secondary to pseudoxanthoma elasticum: Diagnosis and treatment. Case report.]

[Article in French]

Maalej A, Ouederni M, Khallouli A, Gabsi S.

Hôpital militaire de Tunis, 1008 Montfleury, Tunis, Tunisie. Electronic address: afefmaalej@yahoo.fr.

Abstract: Angioid streaks represent linear breaks in Bruch's membrane secondary to a change in the elastic layer. They are often associated with pseudoxanthoma elasticum. We report the case of a 36-year-old man with no prior history who was seen for a macular problem in the left eye, eventually involving the right eye after 3months. He was diagnosed with pseudoxanthoma elasticum, associated with angioid streaks, complicated by choroidal neovascularization in both eyes. He was treated with intravitreal ranibizumab injections (0.5mg/0.05mL). His course in the right eye was remarkable for stable improvement at 3months after the final injection. In the left eye, after initial improvement, recurrence was noted 2.5months after injection, with subfoveal progression of the choroidal neovascularisation, unresponsive to a fourth ranibizumab injection. Angioid streaks represent a degenerative retinal pathology of elastic tissue with the potential for ingrowth of choroidal neovascularization. Various therapeutic approaches such as photodynamic therapy or laser photocoagulation have been proposed, with variable and sometimes limited results. Intravitreal ranibizumab injections currently remain the best treatment and should be studied with a longer-term, larger series.

PMID: 23084437 [PubMed - as supplied by publisher]

J Formos Med Assoc. 2012 Oct;111(10):572-9. doi: 10.1016/j.jfma.2011.09.021. Epub 2012 May 1.

Assessment of quality of life among Taiwanese patients with visual impairment.

Lin JC, Yu JH.

Department of Ophthalmology, Taipei City Hospital, Heping Fuyoy Branch, Taipei, Taiwan; Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan. Electronic address: jclin54@yahoo.com.tw.

BACKGROUND/PURPOSE: This study aims at evaluating the relationship between visual impairment and health-related quality of life (QoL) by identifying factors that affect the EQ-5D index score and Visual Functioning Questionnaire (VFQ) global score, and determining whether the VFQ-25 scores and the European Quality of Life-5 Dimensions (EQ-5D) scores are correlated.

METHODS: This cross-sectional study comprised 318 patients aged 40 years or more presenting with best corrected visual acuity (BCVA) of 20/40 or worse in the better eye.Patients received comprehensive ophthalmologic examinations, and were administered the National Eye Institute VFQ-25 and the EQ-5D instruments. A higher VFQ-25 score indicates a better QoL and, after conversion of the EQ-5D scores to an index score, a higher EQ-5D index score indicates a better QoL.

RESULTS: On multivariate analysis of the EQ-5D index scores, women and those with arthritis were found

to have significantly worse QoL, and the EQ-5D index score was increased by every unit increase in BCVA or mean deviation. Multivariate analysis of the VFQ-25 scores revealed that a history of heart disease, arthritis, and eye diseases, such as age-related macular degeneration or diabetic retinopathy, had significant negative effects on patients' QoL, and VFQ-25 global score was decreased by every unit increase in logMAR. According to this analysis, patients' QoL was improved by each unit increase in BCVA or mean deviation. The correlation between the two questionnaires was only weak to moderate.

CONCLUSION: Visual impairment was associated with lower QoL, as assessed by either questionnaire in Taiwanese patients.

PMID: 23089693 [PubMed - in process]

JAMA. 2012 Oct 24;308(16):1702. doi: 10.1001/jama.2012.4091.

JAMA patient page. Age-related macular degeneration.

Goodman DM, Parmet S, Lynm C, Livingston EH.

PMID: 23093172 [PubMed - indexed for MEDLINE]

Pathogenesis

J Pathol. 2012 Oct 24. doi: 10.1002/path.4128. [Epub ahead of print]

Decreased Membrane Complement Regulators in the Retinal Pigmented Epithelium Contributes to Age-Related Macular Degeneration.

Ebrahimi KB, Fijalkowski N, Cano M, Handa JT.

Wilmer Eye Institute, Johns Hopkins School of Medicine.

Abstract: Dysregulated complement is thought to play a central role in Age-related macular degeneration (AMD) pathogenesis, but the specific mechanisms have yet to be determined. In maculas of AMD specimens, we found that the complement regulatory protein, CD59, was increased in regions of uninvolved retinal pigmented epithelium (RPE) of early AMD, but decreased in the RPE overlying drusen and in geographic atrophy, an advanced form of AMD. While CD46 immunostaining was basolaterally distributed in the RPE of unaffected controls, it was decreased in diseased areas of early AMD samples. Since oxidized low density lipoproteins (oxLDL) collect in drusen of AMD and are a known complement trigger, we treated ARPE-19 cells with oxLDL and found that cellular CD46 and CD59 proteins were decreased by 2.9-fold and 9-fold ($p<0.01$), respectively. OxLDLs increased complement factor B mRNA and Bb protein, but not factor D, I, or H. OxLDLs increased C3b, but not C3a, C5 or C5b-9. C5b-9 was increased by 27% ($p<0.01$) when medium was supplemented with human serum, which was sufficient to induce poly (ADP-ribose) polymerase cleavage, a marker of apoptosis. The decreased levels of CD46 and CD59 were in part explained by their release in exosomal and apoptotic membranous particles. In addition, CD59 was partially degraded through activation of IRE1α. Collectively, these results suggest that a combination of impaired complement regulators results in inadequately controlled complement by the RPE in AMD that induces RPE damage.

PMID: 23097248 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2012 Oct 25. [Epub ahead of print]

In Pursuit of Synthetic Modulators for the Orphan Retina-Specific Nuclear Receptor NR2E3.

Qin Q, Knapinska A, Dobri N, Madoux F, Chase P, Hodder P, Petrukhin K.

Department of Ophthalmology, Columbia University Medical Center , New York, New York.

Abstract Purpose: NR2E3 is an orphan nuclear receptor expressed exclusively in photoreceptor cells of the retina. NR2E3-specific modulators may prolong photoreceptor survival in patients with dry age-related macular degeneration and other forms of retinal degeneration. To definitively establish NR2E3 as a photoreceptor protection target, identification of small-molecule NR2E3 modulators and their testing in animal models of retinal degeneration are required. Development of the high-throughput screen (HTS)-compatible screen for small-molecule NR2E3 modulators is the first step toward this goal.

Methods: Purification protocol for isolation of the functionally competent soluble NR2E3 protein after its expression in the insect Sf9 cells was developed. The time-resolved fluorescence energy-transfer (TR-FRET) assay assessing agonist-sensitive interaction between apo-NR2E3 and transcriptional corepressor RetCOR was used for characterization of the previously reported putative NR2E3 agonist, Compound 11a, and to conduct the HTS for novel small-molecule NR2E3 modulators (direct and inverse agonists). A counterscreen TR-FRET assay that measures the affect of test compounds on PPARγ interaction with corepressor NCOR was used for assessing the specificity of compounds identified in the HTS.

Results: We developed the cell-free TR-FRET assay for small-molecule NR2E3 modulators, which is based on agonist-induced disruption of the interaction between GST-tagged apo-NR2E3 and MBP-tagged fragment of transcriptional corepressor RetCOR. Compound 11a, a putative NR2E3 agonist, did not affect the NR2E3-RetCOR interaction, as was established by its titration in the developed assay. The assay was miniaturized for an ultralow-volume 1,536-well format and automated into 3 simple pipetting steps. Consistent with excellent assay performance, the test runs established a Z'-score within the 0.6-0.8 range. Analysis of the mid-size National Institutes of Health collection of 315,001 structurally diverse drug-like compounds confirmed excellent assay performance, but did not reveal NR2E3-specific agonists or inverse agonists.

Conclusions: A robust and reliable TR-FRET assay for small-molecule NR2E3-specific modulators suitable for the analysis of million compound-strong HTS libraries was developed. A previously described putative NR2E3 agonist, Compound 11a, is unlikely to represent a direct NR2E3 agonist. Application of the developed assay for screening of a more abundant and diverse compound collection be required for identification of synthetic NR2E3 ligands.

PMID: 23098562 [PubMed - as supplied by publisher]

PLoS One. 2012;7(10):e47600. doi: 10.1371/journal.pone.0047600. Epub 2012 Oct 19.

Hyperglycaemia Exacerbates Choroidal Neovascularisation in Mice via the Oxidative Stress-Induced Activation of STAT3 Signalling in RPE Cells.

Li X, Cai Y, Wang YS, Shi YY, Hou W, Xu CS, Wang HY, Ye Z, Yao LB, Zhang J.

Department of Ophthalmology, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi Province, People's Republic of China.

Abstract: Choroidal neovascularisation (CNV) that occurs as a result of age-related macular degeneration (AMD) causes severe vision loss among elderly patients. The relationship between diabetes and CNV remains controversial. However, oxidative stress plays a critical role in the pathogenesis of both AMD and diabetes. In the present study, we investigated the influence of diabetes on experimentally induced CNV and on the underlying molecular mechanisms of CNV. CNV was induced via photocoagulation in the ocular

fundi of mice with streptozotocin-induced diabetes. The effect of diabetes on the severity of CNV was measured. An immunofluorescence technique was used to determine the levels of oxidative DNA damage by anti-8-hydroxy-2-deoxyguanosine (8-OHdG) antibody, the protein expression of phosphorylated signal transducer and activator of transcription 3 (p-STAT3) and vascular endothelial growth factor (VEGF), in mice with CNV. The production of reactive oxygen species (ROS) in retinal pigment epithelial (RPE) cells that had been cultured under high glucose was quantitated using the 2',7'-dichlorofluorescein diacetate (DCFH-DA) method. p-STAT3 expression was examined using Western blot analysis. RT-PCR and ELISA processes were used to detect VEGF expression. Hyperglycaemia exacerbated the development of CNV in mice. Oxidative stress levels and the expression of p-STAT3 and VEGF were highly elevated both in mice and in cultured RPE cells. Treatment with the antioxidant compound N-acetyl-cysteine (NAC) rescued the severity of CNV in diabetic mice. NAC also inhibited the overexpression of p-STAT3 and VEGF in CNV and in RPE cells. The JAK-2/STAT3 pathway inhibitor AG490 blocked VEGF expression but had no effect on the production of ROS in vitro. These results suggest that hyperglycaemia promotes the development of CNV by inducing oxidative stress, which in turn activates STAT3 signalling in RPE cells. Antioxidant supplementation helped attenuate the development of CNV. Thus, our results reveal a potential strategy for the treatment and prevention of diseases involving CNV.

PMID: 23094067 [PubMed - in process]

Epidemiology

Ophthalmology. 2012 Oct 17. pii: S0161-6420(12)00719-1. doi: 10.1016/j.ophtha.2012.07.065. [Epub ahead of print]

Differential Associations of Myopia with Major Age-related Eye Diseases: The Singapore Indian Eye Study.

Pan CW, Cheung CY, Aung T, Cheung CM, Zheng YF, Wu RY, Mitchell P, Lavanya R, Baskaran M, Wang JJ, Wong TY, Saw SM.

Saw Swee Hock School of Public Health, National University of Singapore, Singapore.

PURPOSE: To determine the associations of myopia and axial length (AL) with major age-related eye diseases, including age-related macular degeneration (AMD), diabetic retinopathy (DR), age-related cataract, and primary open-angle glaucoma (POAG).

DESIGN: Population-based, cross-sectional study.

PARTICIPANTS: A total of 3400 Indians (75.6% response rate) aged 40 to 84 years in Singapore.

METHODS: Refractive error was determined by subjective refraction, and AL was determined by noncontact partial coherence laser interferometry. Age-related macular degeneration and DR were defined from retinal photographs according to the Wisconsin Age-Related Maculopathy Grading System and Airlie House classification system, respectively. Age-related cataract was diagnosed clinically using the Lens Opacity Classification System (LOCS) III system. Glaucoma was defined according to International Society for Geographical and Epidemiological Ophthalmology criteria.

MAIN OUTCOME MEASURES: Age-related macular degeneration, DR, age-related cataract, and POAG.

RESULTS: Myopic eyes (spherical equivalent [SE] <-0.5 diopter [D]) were less likely to have AMD (early plus late AMD) (odds ratio [OR], 0.45; 95% confidence interval [CI], 0.25-0.79) or DR (OR, 0.68; 95% CI, 0.46-0.98) compared with emmetropic eyes; each millimeter increase in AL was associated with a lower prevalence of AMD (OR, 0.76; 95% CI, 0.65-0.89) and DR (OR, 0.73; 95% CI, 0.63-0.86). Myopic eyes were more likely to have nuclear (OR, 1.57; 95% CI, 1.13-2.20) and posterior subcapsular (OR, 1.73; 95% CI, 1.10-2.72) cataract, but not cortical cataract (P = 0.64); each millimeter increase in AL was associated

with a higher prevalence of posterior subcapsular cataract (PSC) (OR, 1.29; 95% CI, 1.07-1.55), but not nuclear (P = 0.77) or cortical (P = 0.39) cataract. Eyes with high myopia (SE <-6.0 D) were more likely to have POAG (OR, 5.90; 95% CI, 2.68-12.97); each millimeter increase in AL was associated with a higher prevalence of POAG (OR, 1.43; 95% CI, 1.13-1.80).

CONCLUSIONS: Myopic eyes are less likely to have AMD and DR but more likely to have nuclear cataract, PSC, and POAG. The associations of myopia with AMD, DR, and POAG are mostly explained by longer AL. However, the association between myopia and nuclear cataract is explained by lens refraction rather than AL.

PMID: 23084122 [PubMed - as supplied by publisher]

Genetics

Ophthalmology. 2012 Oct 23. pii: S0161-6420(12)00759-2. doi: 10.1016/j.ophtha.2012.08.004. [Epub ahead of print]

ARMS2 Increases the Risk of Early and Late Age-Related Macular Degeneration in the European Eye Study.

Chakravarthy U, McKay GJ, de Jong PT, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Vingerling JR, Vioque J, Young IS, Sofat R, Hingorani AD, Fletcher AE.

Centre for Vision and Vascular Science, The Queen's University of Belfast, Belfast, United Kingdom. Electronic address: u.chakravarthy@qub.ac.uk.

OBJECTIVE: To study associations between severity stages of early and late age-related macular degeneration (AMD) and genetic variations in age-related maculopathy susceptibility 2 (ARMS2) and complement factor H (CFH) and to investigate potential interactions between smoking and ARMS2.

DESIGN: Population-based, cross-sectional European Eye Study in 7 countries in Europe.

PARTICIPANTS: Four thousand seven hundred fifty participants, 65 years of age and older, recruited through random sampling.

METHODS: Participants were classified on the basis of the more severely affected eye into 5 mutually exclusive AMD severity stages ranging from no AMD, 3 categories of early AMD, and late AMD. History of cigarette smoking was available and allowed classification into never, former, and current smokers, with the latter 2 groups combined into a single category of ever smokers for analysis. Genotyping was performed for single nucleotide polymorphisms rs10490924 and rs4146894 in ARMS2 and rs1061170 in CFH. Associations were analyzed by logistic regression.

MAIN OUTCOME MEASURES: Odds ratios (ORs) for stage of AMD associated with genetic variations in ARMS2 and CFH and interactions between ARMS2 and smoking status.

RESULTS: Early AMD was present in 36.4% and late AMD was present in 3.3% of participants. Data on both genotype and AMD were available for 4276 people. The ORs for associations between AMD stage and ARMS2 increased monotonically with more severe stages of early AMD and were altered little by adjustment for potential confounders. Compared with persons with no AMD, carriers of the TT genotype for rs10490924 in ARMS2 had a 10-fold increase in risk of late AMD (P<3×10(-20)). The ORs for associations with CFH were similar for stage 3 early AMD and late AMD. Interactions between rs10490924 in ARMS2 and smoking status were significant in both unadjusted and adjusted models (P = 0.001). The highest risk was observed in those doubly homozygous for rs10490924 and rs1061170 in CFH (OR, 62.3; 95% confidence interval, 16-242), with P values for trend ranging from 0.03 (early AMD, stage 1) to 1×10(-26) (late AMD).

CONCLUSIONS: A strong association was demonstrated between all stages of AMD and genetic variation in ARMS2, and a significant gene-environment interaction with cigarette smoking was confirmed.

PMID: 23098369 [PubMed - as supplied by publisher]

Exp Eye Res. 2012 Oct 19. pii: S0014-4835(12)00295-3. doi: 10.1016/j.exer.2012.10.003. [Epub ahead of print]

An association of transferrin gene polymorphism and serum transferrin levels with age-related macular degeneration.

Wysokinski D, Danisz K, Blasiak J, Dorecka M, Romaniuk D, Szaflik J, Szaflik JP.

Department of Molecular Genetics, University of Lodz, Pomorska 141/143, 90-236 Lodz, Poland.

Abstract: Age-related macular degeneration (AMD) is a degenerative disease of the eye, triggered by the damage of the macular cells. In the Western world it is the most frequent cause of blindness in the elderly. Oxidative stress is proved to play a key role in AMD pathogenesis and since iron accumulation has been found in AMD maculas, it may accelerate the oxidative processes in this tissue. In the present work we investigated the association between four polymorphisms of the transferrin gene (rs8177178; rs8177179; rs4481157; rs1130459) and AMD in dependence on the transferrin protein and iron serum levels. We employed PCR-RFLP (polymerase chain reaction - restriction fragment length polymorphism) for genotype determination, ELISA assay for serum transferrin evaluation and colorimetric assay for measurement of iron concentration in the serum. We found that advanced age and AMD family history may be independent risk factors for AMD (1.02, $p < 0.05$ and 8.88, $p < 0.001$, respectively). At the rs4481157 site The GG genotype of the rs4481157 polymorphism decreased the risk of dry AMD (OR 0.50; $p < 0.05$), while the GA increased this risk (OR 1.07; $p < 0.05$). Moreover, the GA genotype of this polymorphism decreased the risk of progression to the wet form (OR 0.63; $p < 0.05$). The analysis of the gene-environment interactions showed that the rs4481157 polymorphism modulates the AMD risk among obese (BMI above 30) individuals. In the former smokers group we observed a moderate association between rs4481157 polymorphism and AMD risk while this association in current smokers was stronger. We found also that the serum level of transferrin was higher in the AMD group ($p < 0.001$) than in the control, but the total serum iron levels did not differ between both groups. We found that the serum transferrin was associated with the rs8177178 ($p < 0.001$) and rs4481157 ($p < 0.01$) polymorphisms, and the common variant (GG) of both sites was related to a lower level of transferrin. Presented data may contribute to the involvement of iron homeostasis in AMD risk.

PMID: 23089144 [PubMed - as supplied by publisher]