

Issue 309

Tuesday 13 December, 2016

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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

Arch Soc Esp Oftalmol. 2016 Nov 29. [Epub ahead of print]

Intravitreal therapies for non-neovascular age-related macular degeneration with intraretinal or subretinal fluid. [Article in English, Spanish]

Cuesta-Lasso M, Vieira-Barros A, Dolz-Marco R, Roig-Revert MJ, Badal J, Amselem L, Díaz-Llopis M, Gallego-Pinazo R.

OBJECTIVE: To evaluate the efficacy of intravitreal therapies in cases of atrophic age-related macular degeneration (AMD) with subretinal or intraretinal fluid.

METHODS: A retrospective review was made of the clinical charts of patients diagnosed with atrophic AMD with subretinal or intraretinal fluid. Fundus photographs and spectral-domain optical coherence tomography images were examined, and an analysis was made on the presence of fluid and its density. Neovascularisation was ruled out by fluorescein and/or indocyanine green angiography.

RESULTS: The study included 14 eyes from 13 patients with a mean age of 72.64 years and a mean follow-up of 80.5 weeks. Intraretinal fluid was observed in 6 eyes (42.9%), while subretinal fluid was shown in 8 eyes (57.1%), with high density in 4 eyes (28.5%), and low density in 4 eyes (28.5%). Snellen best-corrected visual acuity improved from 0.37 at baseline to 0.56 at the final visit ($P=.002$). Central subfield thickness (microns) significantly decreased ($P<.001$) from 291.0 at baseline to 228.9 at the final visit. Eight eyes received ranibizumab, 5 eyes received bevacizumab, and one case received triamcinolone.

CONCLUSIONS: Cases of atrophic AMD may present with subretinal or intraretinal fluid in the absence Neovascularisation. Further studies are required to analyse the value of this finding as a risk factor of developing advanced forms of AMD, as well as the efficacy of intravitreal therapies.

PMID: 27912913

J Med Life. 2016 Oct-Dec;9(4):392-398.

The remote effects of intravitreal anti-VEGF therapy.

F B, M M, C T, G N, A M, D M, D B, V J.

Objective: To study the effects of intravitreal anti-Vascular Endothelial Growth Factor (VEGF) therapy with Avastin for wet Age-Related Macular Degeneration (AMD) on Benign Prostatic Hyperplasia (BPH)-related symptoms.

Methods: An exploratory trial was conducted from August 1, 2013 to February 1, 2014, that included 14 male patients previously diagnosed with BPH, who were aged between 59 and 69 years. The trial was performed in Bucharest and involved two medical institutions: the Clinical Hospital of Eye Emergencies and the "Prof. Dr. Theodor Burghel" Hospital. This prospective study utilized both objective and subjective

indicators to analyze the link between intravitreal anti-VEGF therapy for wet AMD and BPH. The evaluations consisted of uroflowmetry and International Prostate Symptom Score (I-PSS) assessments.

Results: The maximum flow rate (Qmax) improved by an average of 5.05 ml/ sec in 9 patients, whereas the remaining 5 patients showed a slight decrease in Qmax (mean 1.6 ml/ sec). The I-PSS score improved, with an overall decrease of 1.18 points at follow-up compared to the initial score (mean initial score = 2.42; mean follow-up score = 1.24).

Conclusion: The analysis revealed that anti-VEGF therapy for wet AMD had a significant positive effect on all BPH-related symptoms; patients reported improved urinary streams and decreased nocturia.

PMID: 27928444

Ophthalmic Res. 2016 Dec 8. [Epub ahead of print]

Dexamethasone Implant in Chronic Diabetic Macular Edema Resistant to Intravitreal Ranibizumab Treatment.

Eski Yucel O, Can E, Eser Ozturk H, Birinci H, Sullu Y.

PURPOSE: The aim of this study was to assess the efficacy of a single intravitreal dexamethasone implant (IDI) over 6 months in eyes with chronic diabetic macular edema (DME) that were resistant to intravitreal ranibizumab (IR) treatment.

METHODS: This retrospective study was conducted at the Ondokuz Mayıs University Hospital, Samsun, Turkey. Efficacy outcomes were considered as the change from baseline in best corrected visual acuity (BCVA) and central macular thickness (CMT).

RESULTS: Thirty eyes of 20 patients with a mean age of 61.6 ± 8.8 (45-85) years were included in the study. The mean BCVA significantly increased from 0.68 ± 0.27 to 0.56 ± 0.30 logMAR ($p = 0.001$) and 0.57 ± 0.30 logMAR ($p = 0.002$) at months 1 and 2, respectively. The proportion of patients who gained 3 or more lines in BCVA was 20%. The mean CMT significantly decreased from 578.93 ± 17.95 μ m at baseline to 282.10 ± 21.42 , 292.26 ± 19.69 , 371.70 ± 21.23 , and 463.60 ± 23.16 μ m at months 1, 2, 3, and 4, respectively ($p = 0.001$). Intraocular pressure (IOP) increase occurred in 5 (16.7%) eyes. Cataract surgery was required in 3 (13%) out of 23 phakic eyes.

CONCLUSION: IDI provides significant benefits in visual acuity gains and anatomic improvements in eyes with chronic DME that are resistant to IR treatment. Increases in IOP and cataract progression can be observed in IDI-treated patients. However, its safety profile is acceptable.

PMID: 27926909

Br J Ophthalmol. 2016 Dec 2. [Epub ahead of print]

Comparison of anti-VEGF therapies on fibrovascular pigment epithelial detachments in age-related macular degeneration.

Au A, Parikh VS, Singh RP, Ehlers JP, Yuan A, Rachitskaya AV, Sears JE, Srivastava SK, Kaiser PK, Schachat AP, Martin DF, Modi Y.

BACKGROUND: The aim is to compare the therapeutic effects of three anti-vascular endothelial growth factor (VEGF) drugs (bevacizumab, aflibercept and ranibizumab) on fibrovascular pigment epithelial detachments (fvPEDs) in age-related macular degeneration (AMD).

METHODS: This was a retrospective, comparative, consecutive case series of 88 unique eyes with fvPEDs in neovascular AMD treated with anti-VEGF monotherapy for a minimum of 6 months. All eyes were treatment naive. Diagnosis was confirmed retrospectively by fluorescein angiography and spectral-domain

optical coherence tomography. Exclusion criteria included serous/drusenoid PEDs or patients who switched anti-VEGF. Mean follow-up across all therapies was 313.9±85.3 days.

RESULTS: Average age of all patients was 80.6 years. Baseline maximum subfoveal PED height was 326.8±185.1 µm, 394.5±238.6 µm and 258.0±145.3 µm for bevacizumab, aflibercept and ranibizumab, respectively ($p=0.05$). All patients had subretinal fluid, intraretinal fluid or a combination of the two at an initial presentation. Central retinal thickness decreased at all time points compared with baseline across all three anti-VEGF therapies. Subfoveal PED height decreased in patients treated with aflibercept at all time points and decreased in patients treated with bevacizumab at 1-month, 3-month and 6-month time points. Aflibercept reduced PED height more than bevacizumab at 1-month and 12-month follow-ups ($p=0.02$ and $p=0.03$, respectively) and ranibizumab at 1-month and 6-month follow-ups ($p=0.03$ and $p=0.02$, respectively). No differences in best-corrected visual acuity were appreciated at any time point between drugs.

CONCLUSIONS: There was a significant reduction in subfoveal PED height for aflibercept and bevacizumab compared with baseline. A direct comparison of drugs demonstrated a beneficial reduction of PED height, albeit inconsistently, favouring aflibercept. There were no differences in visual acuity across the groups at any time point.

PMID: 27913442

Am J Ophthalmol. 2016 Nov 30. [Epub ahead of print]

Real-World Outcomes of Ranibizumab Treatment for Diabetic Macular Edema in a United Kingdom National Health Service Setting.

Patrao NV, Antao S, Egan C, Omar A, Hamilton R, Hykin PG, Sivaprasad S, Rajendram R; For Moorfields Diabetic Macular Edema Study Group.

PMID: 27914628

Graefes Arch Clin Exp Ophthalmol. 2016 Dec 3. [Epub ahead of print]

Ranibizumab for vascularized pigment epithelial detachment: 1-year anatomic and functional results.

Chevreaud O, Oubraham H, Cohen SY, Jung C, Blanco-Garavito R, Gherdaoui F, Souied EH.

PURPOSE: To assess the anatomical and functional efficacy of ranibizumab on vascularized pigment epithelial detachment (V-PED) secondary to neovascular age-related macular degeneration (nAMD).

METHODS: One hundred and nine patients (116 eyes) were retrospectively selected from medical records of 2097 patients who benefited from intravitreal injection between January 2011 and June 2013 in a tertiary-care University-based Department of Ophthalmology. Inclusion criteria were: nAMD, treatment-naïve eyes, presence of V-PED higher than 250 µm, intravitreal ranibizumab with a loading phase, followed by a pro-re-nata regimen, and 1-year follow-up. Baseline characteristics and type of choroidal neovascularization (CNV) were analyzed. PED height, central macular thickness (CMT) and best-corrected visual acuity (BCVA, logMAR) were measured at baseline, months 3, 6 and 12.

RESULTS: CNV was of type 1 in 91 eyes (78.4 %), type 2 in seven (6 %), type 3 in six (5.2 %), and polypoidal choroidal vasculopathy in 12 (10.3 %). Mean CMT at baseline was 572.1 µm and decreased to 396.6 µm ($p < 0.0001$) at 12 months. Mean height of PED was 458.2 µm at baseline and 306.8 µm ($p < 0.0001$) at 12 months. Mean BCVA improved from 0.46 at baseline to 0.39 at 12 months ($p = 0.013$).

CONCLUSIONS: Treatment with ranibizumab improved visual and anatomical outcome in nAMD patients with V-PED.

PMID: 27913869

Am J Ophthalmol. 2016 Dec 5. [Epub ahead of print]

Comparison of Time to Retreatment and Visual Function Between Ranibizumab and Aflibercept in Age-Related Macular Degeneration.

Călugăru D, Călugăru M.

PMID: 27931718

Other treatment & diagnosis

Angew Chem Int Ed Engl. 2016 Dec 5. [Epub ahead of print]

Photo-Modulated Therapeutic Protein Release from a Hydrogel Depot Using Visible Light.

Basuki JS, Qie F, Mulet X, Suryadinata R, Vashi AV, Peng YY, Li L, Hao X, Tan T, Hughes TC.

Abstract: The use of biomacromolecular therapeutics has revolutionized disease treatment, but frequent injections are required owing to their short half-life in vivo. Thus there is a need for a drug delivery system that acts as a reservoir and releases the drug remotely "on demand". Here we demonstrate a simple light-triggered local drug delivery system through photo-thermal interactions of polymer-coated gold nanoparticles (AuNPs) inside an agarose hydrogel as therapeutic depot. Localized temperature increase induced by the visible light exposure caused reversible softening of the hydrogel matrix to release the pre-loaded therapeutics. The release profile can be adjusted by AuNPs and agarose concentrations, light intensity and exposure time. Importantly, the biological activity of the released bevacizumab was highly retained. In this study we demonstrate the potential application of this facile AuNPs/hydrogel system for ocular therapeutics delivery through its versatility to release multiple biologics, compatibility to ocular cells and spatiotemporal control using visible light.

PMID: 27918129

Invest Ophthalmol Vis Sci. 2016 Dec 1;57(15):6604-6609.

Ocular Perfusion Pressure and Choroidal Thickness in Early Age-Related Macular Degeneration Patients With Reticular Pseudodrusen.

Yun C, Ahn J, Kim M, Hwang SY, Kim SW, Oh J.

PURPOSE: The purpose of this study was to investigate the relationship between the ocular perfusion pressure (OPP) and subfoveal choroidal thickness (CT) in eyes with early age-related macular degeneration (AMD) with or without reticular pseudodrusen (RPD).

METHODS: We evaluated the clinical history, blood pressure parameters, fundus photography, and optical coherence tomography images of consecutive patients with early AMD. We calculated the mean OPP from blood pressure and intraocular pressure.

RESULTS: We included 103 eyes from 103 patients, classifying 45 as the RPD group and 58 as the non-RPD group. The mean OPP of the RPD group (46.1 ± 6.5 mm Hg) did not differ from that of the non-RPD group (45.1 ± 5.1 mm Hg, $P = 0.325$), but the RPD group showed a thinner mean subfoveal CT (158.3 ± 73.0 μ m) than the non-RPD group (220.9 ± 67.0 μ m, $P < 0.001$). Among 64 patients who underwent follow-up examination, the rate of change in subfoveal CT in the RPD group (-4.74 ± 0.86 μ m/y) was greater than that in the non-RPD group (-2.46 ± 0.75 μ m/y, $P = 0.028$). In the RPD group, a history of systemic hypertension and lower baseline OPP were associated with a higher rate of change in subfoveal CT ($P = 0.019$ and $P = 0.010$, respectively).

CONCLUSIONS: Subfoveal CT was thinner in early AMD patients with RPD than in those without RPD.

Lower baseline mean OPP and a history of systemic hypertension could be risk factors associated with the progression of choroidal thinning in early AMD patients with RPD.

PMID: 27926751

Diabet Med. 2016 Dec 5. [Epub ahead of print]

Visual complications in diabetes mellitus: beyond retinopathy.

Khan A, Petropoulos IN, Ponirakis G, Malik RA.

Abstract: Diabetic retinopathy is the most common cause of vision loss in people with diabetes mellitus; however, other causes of visual impairment/loss include other retinal and non-retinal visual problems, including glaucoma, age-related macular degeneration, non-arteritic anterior ischaemic optic neuropathy and cataracts. Additionally, when a person with diabetes complains of visual disturbance despite a visual acuity of 6/6, abnormalities in refraction, contrast sensitivity, straylight and amplitude of accommodation should be considered. We review and highlight these visual problems for physicians who manage people with diabetes to ensure timely referral and treatment to limit visual disability, which can have a significant impact on daily living, especially for those participating in sports and driving. This article is protected by copyright. All rights reserved.

PMID: 27917530

Adv Drug Deliv Rev. 2016 Nov 29. [Epub ahead of print]

Gene delivery nanoparticles to modulate angiogenesis.

Kim J, Mirando AC, Popel AS, Green JJ.

Abstract: Angiogenesis is naturally balanced by many pro- and anti-angiogenic factors while an imbalance of these factors leads to aberrant angiogenesis, which is closely associated with many diseases. Gene therapy has become a promising strategy for the treatment of such a disordered state through the introduction of exogenous nucleic acids that express or silence the target agents, thereby engineering neovascularization in both directions. Numerous non-viral gene delivery nanoparticles have been investigated towards this goal, but their clinical translation has been hampered by issues associated with safety, delivery efficiency, and therapeutic effect. This review summarizes key factors targeted for therapeutic angiogenesis and anti-angiogenesis gene therapy, non-viral nanoparticle-mediated approaches to gene delivery, and recent gene therapy applications in pre-clinical and clinical trials for ischemia, tissue regeneration, cancer, and wet age-related macular degeneration. Enhanced nanoparticle design strategies are also proposed to further improve the efficacy of gene delivery nanoparticles to modulate angiogenesis.

PMID: 27913120

Pathogenesis

J Am Soc Nephrol. 2016 Dec 8. [Epub ahead of print]

Moss-Produced, Glycosylation-Optimized Human Factor H for Therapeutic Application in Complement Disorders.

Michelfelder S, Parsons J, Bohlender LL et al

Abstract: Genetic defects in complement regulatory proteins can lead to severe renal diseases, including atypical hemolytic uremic syndrome and C3 glomerulopathies, and age-related macular degeneration. The majority of the mutations found in patients with these diseases affect the glycoprotein complement factor H,

the main regulator of the alternative pathway of complement activation. Therapeutic options are limited, and novel treatments, specifically those targeting alternative pathway activation, are highly desirable. Substitution with biologically active factor H could potentially treat a variety of diseases that involve increased alternative pathway activation, but no therapeutic factor H is commercially available. We recently reported the expression of full-length recombinant factor H in moss (*Physcomitrella patens*). Here, we present the production of an improved moss-derived recombinant human factor H devoid of potentially immunogenic plant-specific sugar residues on protein N-glycans, yielding approximately 1 mg purified moss-derived human factor H per liter of initial *P. patens* culture after a multistep purification process. This glycosylation-optimized factor H showed full in vitro complement regulatory activity similar to that of plasma-derived factor H and efficiently blocked LPS-induced alternative pathway activation and hemolysis induced by sera from patients with atypical hemolytic uremic syndrome. Furthermore, injection of moss-derived factor H reduced C3 deposition and increased serum C3 levels in a murine model of C3 glomerulopathy. Thus, we consider moss-produced recombinant human factor H a promising pharmaceutical product for therapeutic intervention in patients suffering from complement dysregulation.

PMID: 27932477

MAbs. 2016 Dec 8:0. [Epub ahead of print]

Generation and characterization of ABBV642, a dual variable domain immunoglobulin molecule (DVD-Ig) that potently neutralizes VEGF and PDGF-BB and is designed for the treatment of exudative age-related macular degeneration.

Ding K, Eaton L, Bowley D, et al

Abstract: Exudative age-related macular degeneration (AMD) is the most common cause of moderate and severe vision loss in developed countries. Intraocular injections of vascular endothelial growth factor (VEGF or VEGF-A)-neutralizing proteins provide substantial benefit, but frequent, long-term injections are needed. In addition, many patients experience initial visual gains that are ultimately lost due to subretinal fibrosis. Preclinical studies and early phase clinical trials suggest that combined suppression of VEGF and platelet-derived growth factor-BB (PDGF-BB) provides better outcomes than suppression of VEGF alone, due to more frequent regression of neovascularization (NV) and suppression of subretinal fibrosis. We generated a dual variable domain immunoglobulin molecule, ABBV642 that specifically and potently binds and neutralizes VEGF and PDGF-BB. ABBV642 has been optimized for treatment of exudative AMD based on the following design characteristics: 1) high affinity binding to all VEGF-A isoforms and both soluble and extracellular matrix (ECM)-associated PDGF-BB; 2) potential for extended residence time in the vitreous cavity to decrease the frequency of intraocular injections; 3) rapid clearance from systemic circulation compared to molecules with wild type Fc region for normal FcRn binding, which may reduce the risk of systemic complications; and 4) low risk of potential effector function. The bispecificity of ABBV642 allows for a single injection of a single therapeutic agent, and thus a more streamlined development and regulatory path compared to combination products. In a mouse model of exudative AMD, ABBV642 was observed to be more effective than aflibercept. ABBV642 has potential to improve efficacy with reduced injection frequency in patients with exudative AMD, thereby reducing the enormous disease burden for patients and society.

PMID: 27929753

J Clin Invest. 2016 Dec 5. [Epub ahead of print]

VEGF regulates local inhibitory complement proteins in the eye and kidney.

Keir LS, Firth R, Aponik L, Feitelberg D, Sakimoto S, Aguilar E, Welsh GI, Richards A, Usui Y, Satchell SC, Kuzmuk V, Coward RJ, Goult J, Bull KR, Sharma R, Bharti K, Westenskow PD, Michael IP, Saleem MA, Friedlander M.

Abstract: Outer retinal and renal glomerular functions rely on specialized vasculature maintained by VEGF that is produced by neighboring epithelial cells, the retinal pigment epithelium (RPE) and podocytes, respectively. Dysregulation of RPE- and podocyte-derived VEGF is associated with neovascularization in wet age-related macular degeneration (ARMD), choriocapillaris degeneration, and glomerular thrombotic microangiopathy (TMA). Since complement activation and genetic variants in inhibitory complement factor H (CFH) are also features of both ARMD and TMA, we hypothesized that VEGF and CFH interact. Here, we demonstrated that VEGF inhibition decreases local CFH and other complement regulators in the eye and kidney through reduced VEGFR2/PKC- α /CREB signaling. Patient podocytes and RPE cells carrying disease-associated CFH genetic variants had more alternative complement pathway deposits than controls. These deposits were increased by VEGF antagonism, a common wet ARMD treatment, suggesting that VEGF inhibition could reduce cellular complement regulatory capacity. VEGF antagonism also increased markers of endothelial cell activation, which was partially reduced by genetic complement inhibition. Together, these results suggest that VEGF protects the retinal and glomerular microvasculature, not only through VEGFR2-mediated vasculotrophism, but also through modulation of local complement proteins that could protect against complement-mediated damage. Though further study is warranted, these findings could be relevant for patients receiving VEGF antagonists.

PMID: 27918307

Exp Eye Res. 2016 Dec 3. [Epub ahead of print]

Nrf2 protects photoreceptor cells from photo-oxidative stress induced by blue light.

Chen WJ, Wu C, Xu Z, Kuse Y, Hara H, Duh EJ.

Abstract: array of Nrf2 target genes, including antioxidant genes, as indicated by quantitative reverse transcription PCR (qRT-PCR). In order to determine the functional role of Nrf2, siRNA-mediated knockdown studies were performed. Nrf2-knockdown in 661W cells resulted in significant exacerbation of blue light-induced reactive oxygen species levels as well as cell death. Taken together, these findings indicate that Nrf2 is an important endogenous protective factor against oxidative stress in photoreceptor cells. This suggests that drugs targeting Nrf2 could be considered as a neuroprotective strategy for photoreceptors in AMD and other retinal conditions.

PMID: 27923559

Mol Pharmacol. 2017 Jan;91(1):1-13. Epub 2016 Nov 9.

Novel Small Molecule JP-153 Targets the Src-FAK-Paxillin Signaling Complex to Inhibit VEGF-Induced Retinal Angiogenesis.

Toutounchian JJ, Pagadala J, Miller DD, Baudry J, Park F, Chaum E, Yates CR.

Abstract: Targeting vascular endothelial growth factor (VEGF) is a common treatment strategy for neovascular eye disease, a major cause of vision loss in diabetic retinopathy and age-related macular degeneration. However, the decline in clinical efficacy over time in many patients suggests that monotherapy of anti-VEGF protein therapeutics may benefit from adjunctive treatments. Our previous work has shown that through decreased activation of the cytoskeletal protein paxillin, growth factor-induced ischemic retinopathy in the murine oxygen-induced retinopathy model could be inhibited. In this study, we demonstrated that VEGF-dependent activation of the Src/FAK/paxillin signalsome is required for human retinal endothelial cell migration and proliferation. Specifically, the disruption of focal adhesion kinase (FAK) and paxillin interactions using the small molecule JP-153 inhibited Src-dependent phosphorylation of paxillin (Y118) and downstream activation of Akt (S473), resulting in reduced migration and proliferation of retinal endothelial cells stimulated with VEGF. However, this effect did not prevent the initial activation of either Src or FAK. Furthermore, topical application of a JP-153-loaded microemulsion affected the hallmark features of pathologic retinal angiogenesis, reducing neovascular tuft formation and increased avascular

area, in a dose-dependent manner. In conclusion, our results suggest that using small molecules to modulate the focal adhesion protein paxillin is an effective strategy for treating pathologic retinal neovascularization. To our knowledge, this is the first paradigm validating modulation of paxillin to inhibit angiogenesis. As such, we have identified and developed a novel class of small molecules aimed at targeting focal adhesion protein interactions that are essential for pathologic neovascularization in the eye.

PMID: 27913654

Annu Rev Vis Sci. 2016 Oct;2:197-234. Epub 2016 Jul 18.

Retinoids and Retinal Diseases.

Kiser PD, Palczewski K.

Abstract: Recent progress in molecular understanding of the retinoid cycle in mammalian retina stems from painstaking biochemical reconstitution studies supported by natural or engineered animal models with known genetic lesions and studies of humans with specific genetic blinding diseases. Structural and membrane biology have been used to detect critical retinal enzymes and proteins and their substrates and ligands, placing them in a cellular context. These studies have been supplemented by analytical chemistry methods that have identified small molecules by their spectral characteristics, often in conjunction with the evaluation of models of animal retinal disease. It is from this background that rational therapeutic interventions to correct genetic defects or environmental insults are identified. Thus, most presently accepted modulators of the retinoid cycle already have demonstrated promising results in animal models of retinal degeneration. These encouraging signs indicate that some human blinding diseases can be alleviated by pharmacological interventions.

PMID: 27917399 PMCID: PMC5132409

Epidemiology

JAMA Ophthalmol. 2016 Dec 1. [Epub ahead of print]

Association Between Myopia, Ultraviolet B Radiation Exposure, Serum Vitamin D Concentrations, and Genetic Polymorphisms in Vitamin D Metabolic Pathways in a Multicountry European Study.

Williams KM, Bentham GC, Young IS, McGinty A, McKay GJ, Hogg R, Hammond CJ, Chakravarthy U, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Fletcher AE.

IMPORTANCE: Myopia is becoming increasingly common globally and is associated with potentially sight-threatening complications. Spending time outdoors is protective, but the mechanism underlying this association is poorly understood.

OBJECTIVE: To examine the association of myopia with ultraviolet B radiation (UVB; directly associated with time outdoors and sunlight exposure), serum vitamin D concentrations, and vitamin D pathway genetic variants, adjusting for years in education.

DESIGN, SETTING, AND PARTICIPANTS: A cross-sectional, population-based random sample of participants 65 years and older was chosen from 6 study centers from the European Eye Study between November 6, 2000, to November 15, 2002. Of 4187 participants, 4166 attended an eye examination including refraction, gave a blood sample, and were interviewed by trained fieldworkers using a structured questionnaire. Myopia was defined as a mean spherical equivalent of -0.75 diopters or less. Exclusion criteria included aphakia, pseudophakia, late age-related macular degeneration, and vision impairment due to cataract, resulting in 371 participants with myopia and 2797 without.

EXPOSURES: Exposure to UVB estimated by combining meteorological and questionnaire data at different ages, single-nucleotide polymorphisms in vitamin D metabolic pathway genes, serum vitamin D3

concentrations, and years of education.

MAIN OUTCOMES AND MEASURES: Odds ratios (ORs) of UVB, serum vitamin D3 concentrations, vitamin D single-nucleotide polymorphisms, and myopia estimated from logistic regression.

RESULT: Of the included 3168 participants, the mean (SD) age was 72.4 (5) years, and 1456 (46.0%) were male. An SD increase in UVB exposure at age 14 to 19 years (OR, 0.81; 95% CI, 0.71-0.92) and 20 to 39 years (OR, 0.7; 95% CI, 0.62-0.93) was associated with a reduced adjusted OR of myopia; those in the highest tertile of years of education had twice the OR of myopia (OR, 2.08; 95% CI, 1.41-3.06). No independent associations between myopia and serum vitamin D3 concentrations nor variants in genes associated with vitamin D metabolism were found. An unexpected finding was that the highest quintile of plasma lutein concentrations was associated with a reduced OR of myopia (OR, 0.57; 95% CI, 0.46-0.72).

CONCLUSIONS AND RELEVANCE: Increased UVB exposure was associated with reduced myopia, particularly in adolescence and young adulthood. The association was not altered by adjusting for education. We found no convincing evidence for a direct role of vitamin D in myopia risk. The relationship between high plasma lutein concentrations and a lower risk of myopia requires replication.

PMID: 27918775

Acta Ophthalmol. 2016 Dec 9. [Epub ahead of print]

Analysis of antioxidative factors related to AMD risk development in Polish patients.

Mrowicka M, Mrowicki J, Szaflik JP, Szaflik M, Ulinska M, Szaflik J, Majsterek I.

PURPOSE: Age-related macular degeneration (AMD) is a major cause of blindness in developed countries. Oxidative mechanisms may play a key role in the aetiology of AMD. The main aim of this study was to investigate antioxidative markers in the pathogenesis of AMD.

METHODS: A total of 510 subjects including 240 patients with AMD (mean age 77.9 ± 8.5 year) and 270 controls (mean age 74.0 ± 10.4 year) were allowed in this study. We measured activity of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) and examined their association with the SNPs of respective genes (SOD1 + 35A/C, CAT C-262T and GPx Pro197Leu). Restriction fragment length polymorphism (RFLP) technique was used to determine the selected gene polymorphisms. Sixty subjects including 30 patients with AMD (mean age 69.4 ± 9.3) and 30 controls (mean age 64.6 ± 8.2) were enrolled to determine the activity of antioxidant enzymes by spectrometry method.

RESULTS: A significant decrease in enzymes, SOD ($p = 0.011$), CAT ($p = 0.002$) and GPx ($p \leq 0.001$) in AMD patients compared to controls, was indicated. The risk of susceptibility to AMD was significantly higher in patients with AMD who had Pro197Leu C/T genotype of GPx (OR = 2.78; 95% CI = 1.78-4.35). The A/C genotype and the C allele frequencies of A/C polymorphism of SOD1 gene significantly reduce the risk of AMD (OR=0.48; 95% CI 0.27; 0.85).

CONCLUSION: In conclusion, our data showed that insufficient antioxidant capacity may have an important role in age-related macular degeneration. The polymorphism of GPx Pro197Leu may reduce the ability to scavenge free radicals in retina and contribute to the development of AMD.

PMID: 27935234

Ophthalmology. 2016 Nov 30. [Epub ahead of print]

β-blockers and Neovascular Age-related Macular Degeneration.

Yeung L, Huang TS, Lin YH, Hsu KH, Chien-Chieh Huang J, Sun CC.

PMID: 27914835

Genetics

JAMA Ophthalmol. 2016 Dec 1. [Epub ahead of print]

The Functional Effect of Rare Variants in Complement Genes on C3b Degradation in Patients With Age-Related Macular Degeneration.

Geerlings MJ, Kremlitzka M, Bakker B, Nilsson SC, Saksens NT, Lechanteur YT, Pauper M, Corominas J, Fauser S, Hoyng CB, Blom AM, de Jong EK, den Hollander AI.

IMPORTANCE: In age-related macular degeneration (AMD), rare variants in the complement system have been described, but their functional consequences remain largely unexplored.

OBJECTIVES: To identify new rare variants in complement genes and determine the functional effect of identified variants on complement levels and complement regulation in serum samples from carriers and noncarriers.

DESIGN, SETTING, AND PARTICIPANTS: This study evaluated affected (n = 114) and unaffected (n = 60) members of 22 families with AMD and a case-control cohort consisting of 1831 unrelated patients with AMD and 1367 control individuals from the European Genetic Database from March 29, 2006, to April 26, 2013, in Nijmegen, the Netherlands, and Cologne, Germany. Exome sequencing data of families were filtered for rare variants in the complement factor H (CFH), complement factor I (CFI), complement C9 (C9), and complement C3 (C3) genes. The case-control cohort was genotyped with allele-specific assays. Serum samples were obtained from carriers of identified variants (n = 177) and age-matched noncarriers (n = 157). Serum concentrations of factor H (FH), factor I (FI), C9, and C3 were measured, and C3b degradation ability was determined.

MAIN OUTCOMES AND MEASURES: Association of rare variants in the CFH, CFI, C9, and C3 genes with AMD, serum levels of corresponding proteins, and C3b degradation ability of CFH and CFI variant carriers.

RESULTS: The 1831 unrelated patients with AMD had a mean (SD) age of 75.0 (9.4) years, and 60.5% were female. The 1367 unrelated control participants had a mean (SD) age of 70.4 (7.0), and 58.7% were female. All individuals were of European descent. Rare variants in CFH, CFI, C9, and C3 contributed to an increased risk of developing AMD (odds ratio, 2.04; 95% CI, 1.47-2.82; P < .001). CFI carriers had decreased median FI serum levels (18.2 µg/mL in Gly119Arg carriers and 16.2 µg/mL in Leu131Arg carriers vs 27.2 and 30.4 µg/mL in noncarrier cases and controls, respectively; both P < .001). Elevated C9 levels were observed in Pro167Ser carriers (10.7 µg/mL vs 6.6 and 6.1 µg/mL in noncarrier cases and controls, respectively; P < .001). The median FH serum levels were 299.4 µg/mL for CFH Arg175Gln and 266.3 µg/mL for CFH Ser193Leu carriers vs 302.4 and 283.0 µg/mL for noncarrier cases and controls, respectively. The median C3 serum levels were 943.2 µg/mL for C3 Arg161Trp and 946.7 µg/mL for C3 Lys155Gln carriers vs 874.0 and 946.7 µg/mL for noncarrier cases and controls, respectively. The FH and FI levels correlated with C3b degradation in noncarriers (R² = 0.35 and R² = 0.31, respectively; both P < .001).

CONCLUSIONS AND RELEVANCE: Reduced serum levels were associated with C3b degradation in carriers of CFI but not CFH variants, suggesting that CFH variants affect functional activity of FH rather than serum levels. Carriers of CFH (Arg175Gln and Ser193Leu) and CFI (Gly119Arg and Leu131Arg) variants have an impaired ability to regulate complement activation and may benefit more from complement-inhibiting therapy than patients with AMD in general.

PMID: 27918759

Curr Pharm Des. 2016 Dec 8. [Epub ahead of print]

Hot Topics in Pharmacogenetics of Age-Related Macular Degeneration.

Schwartz SG, Brantley MA, Kovach JL, Grzybowski A.

Abstract: Age-related macular degeneration (AMD) is a leading cause of irreversible visual loss and is primarily treated with nutritional supplementation as well as with anti-vascular endothelial growth factor (VEGF) agents for certain patients with neovascular disease. AMD is a complex disease with both genetic and environmental risk factors. In addition, treatment outcomes from nutritional supplementation and anti-VEGF agents vary considerably. Therefore, it is reasonable to suspect that there may be pharmacogenetic influences on these treatments. Many series have reported individual associations with variants in complement factor H (CFH), age-related maculopathy susceptibility 2 (ARMS2), and other loci. However, at this time there are no validated associations. With respect to AMD, pharmacogenetics remains an intriguing area of research but is not helpful for routine clinical management.

PMID: 27928964

Stem cells

Transl Vis Sci Technol. 2016 Nov 22;5(6):7. eCollection 2016.

ROCK Inhibition Promotes Attachment, Proliferation, and Wound Closure in Human Embryonic Stem Cell-Derived Retinal Pigmented Epithelium.

Croze RH, Thi WJ, Clegg DO.

PURPOSE: Nonexudative (dry) age-related macular degeneration (AMD), a leading cause of blindness in the elderly, is associated with the loss of retinal pigmented epithelium (RPE) cells and the development of geographic atrophy, which are areas devoid of RPE cells and photoreceptors. One possible treatment option would be to stimulate RPE attachment and proliferation to replace dying/dysfunctional RPE and bring about wound repair. Clinical trials are underway testing injections of RPE cells derived from pluripotent stem cells to determine their safety and efficacy in treating AMD. However, the factors regulating RPE responses to AMD-associated lesions are not well understood. Here, we use cell culture to investigate the role of RhoA coiled coil kinases (ROCKs) in human embryonic stem cell-derived RPE (hESC-RPE) attachment, proliferation, and wound closure.

METHODS: H9 hESC were spontaneously differentiated into RPE cells. hESC-RPE cells were treated with a pan ROCK1/2 or a ROCK2 only inhibitor; attachment, and proliferation and cell size within an in vitro scratch assay were examined.

RESULTS: Pharmacological inhibition of ROCKs promoted hESC-RPE attachment and proliferation, and increased the rate of closure of in vitro wounds. ROCK inhibition decreased phosphorylation of cofilin and myosin light chain, suggesting that regulation of the cytoskeleton underlies the mechanism of action of ROCK inhibition.

CONCLUSIONS: ROCK inhibition promotes attachment, proliferation, and wound closure in H9 hESC-RPE cells. ROCK isoforms may have different roles in wound healing.

TRANSLATIONAL RELEVANCE: Modulation of the ROCK-cytoskeletal axis has potential in stimulating wound repair in transplanted RPE cells and attachment in cellular therapies.

PMID: 27917311 PMCID: PMC5132148

Diet, lifestyle and low vision

BMJ Open. 2016 Dec 2;6(12):e011504.

How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review.

Taylor DJ, Hobby AE, Binns AM, Crabb DP.

Macular Disease Foundation Australia Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.

Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: research@mdfoundation.com.au | W: www.mdfoundation.com.au

OBJECTIVES: To review systematically the evidence of age-related macular degeneration (AMD) affecting real-world visual ability and quality of life (QoL). To explore trends in specific topics within this body of the literature.

DESIGN: Systematic review.

METHODS: A systematic literature search was carried out using MEDLINE, EMBASE, CINAHL, PsycINFO, PsychARTICLES and Health and Psychosocial Instruments for articles published up to January 2015 for studies including people diagnosed with AMD, assessing real-world visual ability or QoL as an outcome. Two researchers screened studies for eligibility. Details of eligible studies including study design, characteristics of study population and outcomes measured were recorded in a data extraction table. All included studies underwent quality appraisal using the Mixed Methods Appraisal Tool 2011 Version (MMAT).

RESULTS: From 5284 studies, 123 were eligible for inclusion. A range of approaches were identified, including performance-based methods, quantitative and qualitative patient-reported outcome measures (PROMs). AMD negatively affects tasks including mobility, face recognition, perception of scenes, computer use, meal preparation, shopping, cleaning, watching TV, reading, driving and, in some cases, self-care. There is evidence for higher rates of depression among people with AMD than among community dwelling elderly. A number of adaptation strategies have been associated with AMD of varying duration. Much of the research fails to report the type of AMD studied (59% of included studies) or the duration of disease in participants (74%). Of those that do report type studied, the breakdown is as follows: wet AMD 20%, dry AMD 4% and both types 17%.

CONCLUSIONS: There are many publications highlighting the negative effects of AMD in various domains of life. Future research should focus on delivering some of this research knowledge into patient management and clinical trials and differentiating between the types of AMD.

PMID: 27913556

Clin Exp Ophthalmol. 2016 Dec 7. [Epub ahead of print]

Self-care tools to treat depressive symptoms in patients with age-related eye disease: a randomized controlled clinical trial.

Kamga H, McCusker J, Yaffe M, Sewitch M, Sussman T, Strumpf E, Olivier S, Wittich W, Moghadaszadeh S, Freeman EE.

BACKGROUND: Depression is very common in people with age-related eye disease. Our goal was to determine if self-care tools plus limited telephone support could reduce depressive symptoms in patients with age-related macular degeneration (AMD) or diabetic retinopathy (DR).

DESIGN: A single-blind randomized controlled clinical trial was conducted at Maisonneuve-Rosemont Hospital in Montreal, Canada.

PARTICIPANTS: Eighty participants were recruited **METHODS:** To be eligible, participants must have had either late stage AMD or DR, at least mild depressive symptoms, and visual acuity better than 20/200. Half were randomized to the intervention arm and half to delayed intervention/usual care. The intervention consisted of large print written and audio tools incorporating cognitive-behavioral principles plus three 10-minute telephone calls from a lay coach. Eight-week follow-up data were collected by telephone.

MAIN OUTCOME MEASURES: The primary outcome was the 8-week change in depressive symptoms as measured by the Patient Health Questionnaire (PHQ-9). Secondary outcomes included anxiety, life space, and self-efficacy.

RESULTS: The baseline mean logMAR visual acuity was 0.37 (SD = 0.20) and the baseline mean PHQ-9 score was 9.5 (SD = 3.9) indicating moderate depressive symptoms. After adjusting for baseline imbalances in visual acuity, the intervention reduced depressive symptoms by 2.1 points more than usual care (P =

0.040). The intervention was not associated with the secondary outcomes ($P > 0.05$).

CONCLUSIONS: Self-care tools plus telephone coaching led to a modest improvement in depressive symptoms in patients with age-related eye disease. Additional research on how to maximize their effect is necessary.

PMID: 27928888

PLoS One. 2016 Dec 9;11(12):e0167828. eCollection 2016.

Lutein Attenuates Both Apoptosis and Autophagy upon Cobalt (II) Chloride-Induced Hypoxia in Rat Müller Cells.

Fung FK, Law BY, Lo AC.

Abstract: Retinal ischemia/reperfusion injury is a common feature of various retinal diseases such as glaucoma and diabetic retinopathy. Lutein, a potent anti-oxidant, is used to improve visual function in patients with age-related macular degeneration (AMD). Lutein attenuates apoptosis, oxidative stress and inflammation in animal models of acute retinal ischemia/hypoxia. Here, we further show that lutein improved Müller cell viability and enhanced cell survival upon hypoxia-induced cell death through regulation of intrinsic apoptotic pathway. Moreover, autophagy was activated upon treatment of cobalt (II) chloride, indicating that hypoxic injury not only triggered apoptosis but also autophagy in our in vitro model. Most importantly, we report for the first time that lutein treatment suppressed autophagosome formation after hypoxic insult and lutein administration could inhibit autophagic event after activation of autophagy by a pharmacological approach (rapamycin). Taken together, lutein may have a beneficial role in enhancing glial cell survival after hypoxic injury through regulating both apoptosis and autophagy.

PMID: 27936094

Disclaimer: This newsletter is provided as a free service to eye care professionals by the Macular Disease Foundation Australia. The Macular Disease Foundation cannot be liable for any error or omission in this publication and makes no warranty of any kind, either expressed or implied in relation to this publication.