

Issue 236

Tuesday 16 June, 2015

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.

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Drug treatment

Ophthalmology. 2015 Jun 4. [Epub ahead of print]

Influence of Glycosylated Hemoglobin on the Efficacy of Ranibizumab for Diabetic Macular Edema: A Post Hoc Analysis of the RIDE/RISE Trials.

Bansal AS, Khurana RN, Wieland MR, Wang PW, Van Everen SA, Tuomi L.

PURPOSE: To investigate the influence of glycosylated hemoglobin (HbA1c) on treatment outcomes in patients with diabetic macular edema (DME) receiving intravitreal ranibizumab.

DESIGN: Post hoc analysis of 2 identical phase III clinical trials assessing the efficacy and safety of intravitreal ranibizumab in DME over 36 months (RIDE: NCT00473382/RISE: NCT00473330).

PARTICIPANTS: A total of 483 adults with vision loss from DME treated with ranibizumab were included in this analysis from RIDE/RISE. Participants received monthly intravitreal ranibizumab (0.3 or 0.5 mg).

MAIN OUTCOME MEASURES: Differences in visual and anatomic outcomes, and diabetic retinopathy (DR) severity score, between subgroups of patients with baseline HbA1c $\leq 7\%$ versus HbA1c $> 7\%$ at 36 months.

RESULTS: There were 195 patients in RIDE/RISE who were treated with ranibizumab with a baseline HbA1c $\leq 7\%$ and 288 patients with a baseline HbA1c $> 7\%$ included in this analysis. The mean improvement in visual acuity (VA) at 36 months was +13 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in patients with baseline HbA1c $\leq 7\%$ compared with +11 ETDRS letters in the patients with a baseline HbA1c $> 7\%$ ($P = 0.17$). After adjustment for baseline central foveal thickness (CFT) and duration of diabetes, the mean CFT reduction was $-268 \mu\text{m}$ in patients with a baseline HbA1c $\leq 7\%$ and $-269 \mu\text{m}$ in patients with a baseline HbA1c $> 7\%$ ($P = 0.98$; 95% confidence interval, -22.93 to 23.54). The proportion of patients with a ≥ 2 -step improvement in DR severity score was 38% in patients with baseline HbA1c $\leq 7\%$ compared with 41% in the patients with a baseline HbA1c $> 7\%$ ($P = 0.53$). There was no correlation of baseline HbA1c with any visual or anatomic parameter.

CONCLUSIONS: The improvement in VA, anatomic reduction of macular edema, and improvement in DR severity score with ranibizumab treatment seem to be independent of baseline HbA1c.

PMID: 26050541 [PubMed - as supplied by publisher]

Transl Vis Sci Technol. 2015 Jun 8;4(3):6. eCollection 2015.

Optimizing the Anti-VEGF Treatment Strategy for Neovascular Age-Related Macular Degeneration: From Clinical Trials to Real-Life Requirements.

Mantel I.

Abstract: This Perspective discusses the pertinence of variable dosing regimens with anti-vascular endothelial growth factor (VEGF) for neovascular age-related macular degeneration (nAMD) with regard to real-life requirements. After the initial pivotal trials of anti-VEGF therapy, the variable dosing regimens pro re nata (PRN), Treat-and-Extend, and Observe-and-Plan, a recently introduced regimen, aimed to optimize the anti-VEGF treatment strategy for nAMD. The PRN regimen showed good visual results but requires monthly monitoring visits and can therefore be difficult to implement. Moreover, application of the PRN regimen revealed inferior results in real-life circumstances due to problems with resource allocation. The Treat-and-Extend regimen uses an interval based approach and has become widely accepted for its ease of preplanning and the reduced number of office visits required. The parallel development of the Observe-and-Plan regimen demonstrated that the future need for retreatment (interval) could be reliably predicted. Studies investigating the observe-and-plan regimen also showed that this could be used in individualized fixed treatment plans, allowing for dramatically reduced clinical burden and good outcomes, thus meeting the real life requirements. This progressive development of variable dosing regimens is a response to the real-life circumstances of limited human, technical, and financial resources. This includes an individualized treatment approach, optimization of the number of retreatments, a minimal number of monitoring visits, and ease of planning ahead. The Observe-and-Plan regimen achieves this goal with good functional results.

Translational Relevance: This perspective reviews the process from the pivotal clinical trials to the development of treatment regimens which are adjusted to real life requirements. The article discusses this translational process which- although not the classical interpretation of translation from fundamental to clinical research, but a subsequent process after the pivotal clinical trials - represents an important translational step from the clinical proof of efficacy to optimization in terms of patients' and clinics' needs. The related scientific procedure includes the exploration of the concept, evaluation of security, and finally proof of efficacy.

PMID: 26069865 [PubMed] PMCID: PMC4461215

Ophthalmic Surg Lasers Imaging Retina. 2015 May 1;46(5):542-9.

Experience With Aflibercept for the Treatment of Neovascular Age-Related Macular Degeneration.

He L, Silva RA, Ayoub N, Moshfeghi DM, Leng T.

BACKGROUND AND OBJECTIVE: Describe visual and anatomic outcomes of eyes with exudative age-related macular degeneration (AMD) after treatment with aflibercept.

PATIENTS AND METHODS: Eyes treated with intravitreal injections of aflibercept for exudative AMD were retrospectively reviewed to compare visual acuity and central subfield thickness (CST) on optical coherence tomography.

RESULTS: A total of 142 eyes receiving aflibercept were previously treated with bevacizumab or ranibizumab intravitreal injections. Baseline vision was $20/73 \pm 5.18$ lines when switched to aflibercept. It improved by 0.2 ± 1.91 lines ($P = .14$) after three injections but decreased by 0.45 ± 2.9 lines ($P = .06$) after 1 year of follow-up. The reduction in CST was $9.9 \pm 46.5 \mu\text{m}$ ($P = .06$) after three injections and grew to $19.3 \pm 50.6 \mu\text{m}$ ($P = .002$), a statistically significant amount, after 1 year.

CONCLUSION: Switching to aflibercept resulted in no clinically significant differences in visual acuity after 1 year. There was a significant reduction in CST, but this may not be clinically significant.

PMID: 26057757 [PubMed - in process]

Asia Pac J Ophthalmol (Phila). 2015 May-Jun;4(3):171-9.

Recent Innovations in Medical and Surgical Retina.

Bhagat N, Zarbin M.

PURPOSE: To summarize major innovations in retinal disease management during fiscal year 2014.

DESIGN: Literature review.

METHODS: A subset of papers published in the peer-reviewed literature were selected.

RESULTS: Major innovations in retina include: (1) advances in the treatment of diabetic macular edema, including the use of aflibercept and sustained delivery dexamethasone intravitreal implants as well as subthreshold micropulse diode laser therapy; (2) reduced progression of age-related macular degeneration (AMD) using zinc, vitamin C, vitamin E, lutein, and zeaxanthin supplements as reported in the Age-Related Eye Disease Study-2; (3) use of enhanced-depth imaging optical coherence tomography for choroidal imaging; (4) use of gene therapy to treat choroideremia; (5) use of combination pharmacotherapy (i.e., squalamine + ranibizumab) and gene therapy to treat the neovascular complications of AMD; and (6) use of stem cell-derived retinal pigment epithelium transplants to treat atrophic AMD and Stargardt macular dystrophy. In addition, we review the ocular and systemic risks associated with sustained intraocular steroid delivery and inhibition of vascular endothelial growth factor signaling pathways. We also review potential applications of gene- versus cell-based therapy for the treatment of retinal degenerative diseases.

CONCLUSIONS: Several treatment approaches are effective in the treatment of diabetic macular edema. Prophylaxis against AMD progression with Age-Related Eye Disease Study-2 supplements seems to reduce the risk of developing neovascular but not atrophic complications of AMD. Enhanced-depth imaging optical coherence tomography data provide new information on the role of the choroid in a variety of conditions. Advances in gene- and cell-based therapy will revolutionize the development of regenerative medicine in ophthalmology.

PMID: 26065505 [PubMed - in process]

PLoS One. 2015 Jun 9;10(6):e0129361. eCollection 2015.

Caregiver Burden in Patients Receiving Ranibizumab Therapy for Neovascular Age Related Macular Degeneration.

Gohil R, Crosby-Nwaobi R, Forbes A, Burton B, Hykin P, Sivaprasad S.

PURPOSE: To assess the caregiver burden and factors determining the burden in patients receiving ranibizumab therapy for neovascular AMD (nAMD).

METHODS: This is a cross-sectional questionnaire survey of 250 matched patient caregiver dyads across three large ophthalmic treatment centres in United Kingdom. The primary outcome was the subjective caregiver burden measured using caregiver reaction assessment scale (CRA). Objective caregiver burden was determined by the caregiver tasks and level of care provided. The factors that may predict the caregiver burden such as the patient's visual acuity of the better eye and vision related quality of life, demographics, satisfaction and support provided by the healthcare and the health status of the dyads were also collected and assessed in a hierarchical regression model.

RESULTS: The mean CRA score was 3.2 ± 0.5 , similar to the score reported by caregivers for atrial fibrillation who require regular hospital appointments for monitoring their thromboprophylaxis. Caregiver tasks including accompanying for hospital appointments for eye treatment and patient's visual acuity in the better eye were the biggest contributors to the caregiver burden hierarchical model explaining 18% and 11% of the variance respectively.

CONCLUSION: Ranibizumab therapy for nAMD is associated with significant caregiver burden. Both disease impact and treatment frequency contributed to the overall burden.

PMID: 26056840 [PubMed - in process]

Clin Ophthalmol. 2015 May 28;9:959-65. eCollection 2015.

Visual outcomes of age-related macular degeneration patients undergoing intravitreal ranibizumab monotherapy in an urban population.

Basheer K, Mensah E, Khanam T, Minakaran N.

AIM: To compare the visual outcomes of an urban population with age-related macular degeneration (AMD) undergoing ranibizumab monotherapy to the results from major clinical trials.

PROCEDURES: Prospective data was collected from 164 wet AMD patients receiving intravitreal ranibizumab. Visual acuities were obtained with the Early Treatment Diabetic Retinopathy Study chart. All patients underwent a loading phase of three monthly treatments of ranibizumab. Patients were monitored monthly using a retreatment criterion. Treatment was further individualized by sequentially lengthening follow-up intervals when stable.

RESULTS: At 12 and 24 months, respectively, the percentage of eyes that maintained vision was 91% and 88.6%. We found that 20.3% of eyes had improved vision at 12 months and 20% at 24 months. At 12 months, 8.3% of eyes' vision worsened and 12% worsened at 24 months.

CONCLUSION: Individualized ranibizumab monotherapy is effective in preserving vision in wet AMD and follows the same trends as the pivotal trials.

PMID: 26060392 [PubMed] PMCID: PMC4454212

Harefuah. 2015 Apr;154(4):270-3, 278.

[The revolution in the treatment of retinal diseases: anti-VEGF treatment at the Assuta Eye Institute]. [Article in Hebrew]

Katz G, Zehavi C, Treister G.

Abstract: The VEGF protein (Vascular Endothelial Growth Factor) was identified in the '80s as a factor which induces proliferation of blood vessels in the body in general and in the retina in particular. Proliferative processes in retinal blood vessels, vascular permeability and induced edema which follows, frequently cause blindness in the diseases of the macula: AMD (Age-related Macular Degeneration) diabetes and retinal vascular occlusions. Since 2006, through treatment using anti-VEGF drugs--Avastin (Bevacizumab) and Lucentis (Ranibizumab) and Eylea (Aflibercept)--blindness in many patients in Israel and elsewhere was prevented. This paper reviews the treatment with anti-VEGF intraocular injections in the above mentioned diseases with reference to the growing activity at the Assuta Eye Institute.

PMID: 26065226 [PubMed - in process]

Drugs. 2015 Jun 9. [Epub ahead of print]

Aflibercept: A Review of Its Use in Diabetic Macular Oedema.

Keating GM.

Abstract: Aflibercept (Eylea®) is an anti-vascular endothelial growth factor agent indicated for intravitreal use in the treatment of diabetic macular oedema. In patients with diabetic macular oedema, significantly greater improvements from baseline to week 52 in visual acuity were seen with intravitreal aflibercept versus macular laser photocoagulation in the phase III VISTA-DME and VIVID-DME trials, and versus intravitreal bevacizumab or ranibizumab in those with worse visual acuity at baseline (i.e. Early Treatment Diabetic Retinopathy Study letter score of <69) in the phase III PROTOCOL-T trial. Intravitreal aflibercept was generally well tolerated in patients with diabetic macular oedema. In conclusion, intravitreal aflibercept is an important new treatment for diabetic macular oedema.

PMID: 26056030 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Jul;160(1):207.

Short-Term Changes in Choroidal Thickness After Aflibercept Therapy for Neovascular Age-Related Macular Degeneration.

Kim JH.

PMID: 26054473 [PubMed - in process]

Other treatment & diagnosis

Ophthalmic Surg Lasers Imaging Retina. 2015 May 1;46(5):531-7.

Combined Nonmydriatic Spectral-Domain Optical Coherence Tomography and Nonmydriatic Fundus Photography for the Detection of Age-Related Macular Degeneration Changes.

Salti H, Antonios RS, Haddad SS, Hamam RN, Bashshur ZF, Ghazi NG.

BACKGROUND AND OBJECTIVE: Nonmydriatic fundus photography (FP) has been a suboptimal tool for detecting age-related macular degeneration (AMD) changes. This study sought to enhance the detection of AMD changes by combining nonmydriatic FP with nonmydriatic spectral-domain optical coherence tomography (SD-OCT).

PATIENTS AND METHODS: The study population included 249 patients aged 65 years and older who were assessed for AMD changes using standard mydriatic biomicroscopic fundus examination. Each eye then underwent nonmydriatic FP in one session followed 1 week later with nonmydriatic FP coupled with nonmydriatic SD-OCT. Images were interpreted for detection of AMD changes, and findings were compared to the original mydriatic biomicroscopic examination.

RESULTS: Nonmydriatic FP had 64% sensitivity, 97% specificity, and a kappa value of 0.67 in detecting AMD changes compared with the traditional mydriatic biomicroscopic examination. Combined nonmydriatic FP and nonmydriatic SD-OCT increased sensitivity to 91.5%, specificity to 98.6%, and kappa to 0.91.

CONCLUSION: The addition of nonmydriatic SD-OCT to nonmydriatic FP enhances the detection of AMD changes.

PMID: 26057756 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2015 May 1;46(5):523-30.

Relationship Between Subretinal Hyperreflective Material Reflectivity and Volume in Patients With Neovascular Age-Related Macular Degeneration Following Anti-Vascular Endothelial Growth Factor Treatment.

Charafeddin W, Nittala MG, Oregon A, Sadda SR.

BACKGROUND AND OBJECTIVE: To assess the relationship between subretinal hyperreflective material (SRHM) reflectivity and volume in patients treated with anti-vascular endothelial growth factor (VEGF) therapy for choroidal neovascularization secondary to exudative age-related macular degeneration (AMD).

PATIENTS AND METHODS: Data from 17 eyes of 16 patients with neovascular AMD undergoing anti-VEGF therapy were collected retrospectively. Optical coherence tomography (OCT) data were obtained using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) 512 × 128 macular cube protocol. Detailed manual segmentation was performed for each case using customized grading software.

RESULTS: The mean macular volume declined from 10.4 mm(3) at baseline to 9.6 mm(3) at 12 months. SRHM volume declined from 0.33 mm(3) to 0.12 mm(3), whereas reflectivity increased from 0.48 to 0.64

units ($P = .012$). SRHM reflectivity correlated positively with logarithm of the minimum angle of resolution (logMAR) acuity ($r = .49$, $P = .04$) but correlated with SRHM volume ($r = -0.50$, $P = .04$) only at baseline.

CONCLUSION: SRHM reflectivity, which correlated partially with SRHM volume, appears to carry independent information regarding disease activity. SRHM reflectivity may be useful for monitoring disease activity and response to therapy.

PMID: 26057755 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2015 May 1;46(5):513-21.

Association Between Subfoveal Choroidal Thickness, Reticular Pseudodrusen, and Geographic Atrophy in Age-Related Macular Degeneration.

Thorell MR, Goldhardt R, Nunes RP, de Amorim Garcia Filho CA, Abbey AM, Kuriyan AE, Modi YS, Gregori G, Yehoshua Z, Feuer W, Sadda S, Rosenfeld PJ.

BACKGROUND AND OBJECTIVE: To compare subfoveal choroidal thickness (CT) measurements in eyes with nonexudative age-related macular degeneration (AMD) in the presence or absence of reticular pseudodrusen (RPD).

PATIENTS AND METHODS: Subfoveal CT measurements obtained from patients with AMD enrolled in the COMPLETE study (30 drusen-only eyes and 30 eyes with geographic atrophy [GA]) were compared with an age-distributed normal control group. Multimodal images were evaluated to detect the presence of RPD.

RESULTS: After controlling for age and axial length, the mean CT was significantly thinner in the GA group with RPD ($213.7 \pm 53.1 \mu\text{m}$) than in the GA group without RPD ($335.3 \pm 123.2 \mu\text{m}$; $P = .001$). The mean CT in the GA group without RPD was not statistically different from the mean CT in the normal control group ($P = .076$) or the drusen group without RPD ($P = .45$). In eyes without RPD, there was a correlation between the increasing size of GA and a decrease in CT measurements.

CONCLUSION: Subfoveal choroidal thinning in eyes with nonexudative AMD was associated with the presence of RPD. In the absence of RPD, CT only decreased as the size of GA increased.

PMID: 26057754 [PubMed - in process]

J Funct Biomater. 2015 Jun 8;6(2):379-94.

Lipid Nanoparticles for Ocular Gene Delivery.

Wang Y, Rajala A, Rajala RV.

Abstract: Lipids contain hydrocarbons and are the building blocks of cells. Lipids can naturally form themselves into nano-films and nano-structures, micelles, reverse micelles, and liposomes. Micelles or reverse micelles are monolayer structures, whereas liposomes are bilayer structures. Liposomes have been recognized as carriers for drug delivery. Solid lipid nanoparticles and lipoplex (liposome-polycation-DNA complex), also called lipid nanoparticles, are currently used to deliver drugs and genes to ocular tissues. A solid lipid nanoparticle (SLN) is typically spherical, and possesses a solid lipid core matrix that can solubilize lipophilic molecules. The lipid nanoparticle, called the liposome protamine/DNA lipoplex (LPD), is electrostatically assembled from cationic liposomes and an anionic protamine-DNA complex. The LPD nanoparticles contain a highly condensed DNA core surrounded by lipid bilayers. SLNs are extensively used to deliver drugs to the cornea. LPD nanoparticles are used to target the retina. Age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy are the most common retinal diseases in humans. There have also been promising results achieved recently with LPD nanoparticles to deliver functional genes and micro RNA to treat retinal diseases. Here, we review recent advances in ocular drug and gene delivery employing lipid nanoparticles.

PMID: 26062170 [PubMed]

Ophthalmic Surg Lasers Imaging Retina. 2015 May 1;46(5):550-9.

Widefield En Face Optical Coherence Tomography Imaging of Subretinal Drusenoid Deposits.

Schaal KB, Legarreta AD, Gregori G, Legarreta JE, Cheng Q, Stetson PF, Cai M, Laron M, Durbin M, Rosenfeld PJ.

BACKGROUND AND OBJECTIVE: To determine whether subretinal drusenoid deposits (SDD) can be detected on widefield en face slab images derived from spectral-domain (SD) and swept-source (SS) optical coherence tomography (OCT) volume scans.

PATIENTS AND METHODS: Retrospective study of patients with dry age-related macular degeneration (AMD) enrolled prospectively in an OCT imaging study using SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA) with a central wavelength of 840 nm, and a prototype 100-kHz SS-OCT instrument (Carl Zeiss Meditec) with a central wavelength of 1,050 nm. Seven en face slabs were evaluated with thicknesses from 20 to 55 μ m and positioned at distances up to 55 μ m above the retinal pigment epithelium (RPE). A montage of 6 $\times$ 6 mm SD-OCT en face images of the posterior pole from each patient was compared with a 9 $\times$ 12 mm SS-OCT single en face slab image and with color, autofluorescence, and infrared reflectance images.

RESULTS: A total of 160 patients (256 eyes) underwent scanning with both OCT instruments; 57 patients (95 eyes) also underwent multimodal fundus imaging. Of 95 eyes, 32 (34%) were diagnosed with reticular pseudodrusen (RPD) using multimodal imaging. All eyes with RPD demonstrated a pattern of SDD on widefield en face OCT similar to that observed for RPD. The en face slab image that consistently identified SDD was the 20- μ m thick slab with boundaries from 35 to 55 μ m above the RPE.

CONCLUSION: Widefield en face slab imaging with SD-OCT and SS-OCT can detect SDD and could replace multimodal imaging for the diagnosis of RPD in the future.

PMID: 26057758 [PubMed - in process]

Am J Ophthalmol. 2015 Jun 4. [Epub ahead of print]

Macular Ganglion Cell Complex and Retinal Nerve Fiber Layer Comparison in Different Stages of Age-Related Macular Degeneration.

Zucchiatti I, Parodi MB, Pierro L, Cicinelli MV, Gagliardi M, Castellino N, Bandello F.

PURPOSE: To employ Optical Coherence Tomography (OCT) to analyze the morphological changes in the inner retina in different categories of Age-related Macular Degeneration (AMD).

DESIGN: Observational, cross-sectional study **METHODS:** Single-center study. Inclusion criteria were age over 50, diagnosis of Age-Related Eye Disease Study (AREDS) category 2 and 3, naïve neovascular AMD and atrophic AMD. Healthy patients of similar age acted as a control group. Primary outcome measures were the changes in ganglion cell complex (GCC) and retinal nerve fiber layer (RNFL). Secondary outcomes included modifications of rim area and cup-to-disk ratio.

RESULTS: One hundred and thirty eyes of 130 patients were recruited: 26 eyes for AREDS category 2, 26 for AREDS category 3, 26 for neovascular AMD, 26 with atrophic AMD and 26 controls. Mean peripapillary RNFL thickness was significantly lower in neovascular AMD, compared to controls ($p=0.004$); peripapillary RNFL did not significantly vary among AREDS category 2 and 3 and atrophic AMD groups, compared to controls. Mean GCC thickness was higher in control group, becoming progressively thinner up to neovascular and atrophic AMD groups ($p<0.0001$). Rim area was significantly thinner in neovascular AMD group compared with controls ($p=0.047$); cup-to-disk ratio was higher in neovascular AMD group compared with control group ($p=0.047$).

CONCLUSIONS: This study demonstrates that eyes with neovascular AMD display reduced RNFL and

GCC thickness. RNFL is partially spared in atrophic advanced AMD. The identification of alteration in RNFL and GCC thickness may reveal useful for future therapeutic implications.

PMID: 26052088 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2015 Jun 11;133(6):e1588. Epub 2015 Jun 11.

Monitoring Age-Related Macular Degeneration Through an Implantable Miniature Telescope Using Ultra-Wide-Field Imaging.

Yonekawa Y, Wolfe JD.

PMID: 26067699 [PubMed - in process]

Pathogenesis

J Ocul Pharmacol Ther. 2015 May 18. [Epub ahead of print]

Thrombospondin-1 and Pathogenesis of Age-Related Macular Degeneration.

Housset M, Sennlaub F.

Abstract: The cardinal features of age-related macular degeneration (AMD) are the accumulation of subretinal debris, subretinal inflammation, neovascularization, and degeneration of the photoreceptors and retinal pigment epithelium (RPE). Thrombospondin-1 (TSP-1) is a major extracellular matrix protein that is physiologically expressed in the RPE and choroid, but severely diminished in eyes with AMD. TSP-1 plays an important role in phagocytosis, potentially inhibits neovascularization, and mediates immune suppression and immune privilege. The lack of TSP-1 could have a central role in the pathogenesis of AMD as it is implicated in the major pathways that seem to be deficient in the disease. We here give an overview of the major functions of TSP-1 and how it could intervene in AMD pathogenesis.

PMID: 26062001 [PubMed - as supplied by publisher]

Epigenetics. 2015 Jun 11:0. [Epub ahead of print]

Differential DNA Methylation Identified in the Blood and Retina of AMD Patients.

Oliver V, Jaffe AE, Song J, Wang G, Zhang P, Branham KE, Swaroop A, Eberhart CG, Zack DJ, Qian J, Merbs SL.

Abstract: Age-related macular degeneration (AMD) is a major cause of blindness in the western world. While genetic studies have linked both common and rare variants in genes involved in regulation of the complement system to increased risk of development of AMD, environmental factors, such as smoking and nutrition, can also significantly affect the risk of developing the disease and the rate of disease progression. Since epigenetics has been implicated in mediating, in part, the disease risk associated with some environmental factors, we investigated a possible epigenetic contribution to AMD. We performed genome-wide DNA methylation profiling of blood from AMD patients and controls. No differential methylation site reached genome-wide significance; however, when epigenetic changes in and around known GWAS-defined AMD risk loci were explored, we found small but significant DNA methylation differences in the blood of neovascular AMD patients near age-related maculopathy susceptibility 2 (ARMS2), a top-ranked GWAS locus preferentially associated with neovascular AMD. The methylation level of one of the CpG sites significantly correlated with the genotype of the risk SNP rs10490924, suggesting a possible epigenetic mechanism of risk. Integrating genome-wide DNA methylation analysis of retina samples with and without AMD together with blood samples, we further identified a consistent, replicable change in DNA methylation

in the promoter region of protease serine 50 (PRSS50). These methylation changes may identify sites in novel genes that are susceptible to non-genetic factors known to contribute to AMD development and progression.

PMID: 26067391 [PubMed - as supplied by publisher]

Crit Rev Food Sci Nutr. 2015 Jun 9:0. [Epub ahead of print]

Modulatory Effects of 1,25-dihydroxyvitamin D3 on Eye Disorders: A Critical Review.

Nebbioso M, Buomprisco G, Pascarella A, Pescosolido N.

Abstract: Many studies have shown that the presence of 1,25-dihydroxyvitamin D3 in the eye is able to modulate inflammatory responses. In fact, it has been demonstrated that topical administration of vitamin D3 inhibits Langerhans cells migration from the central cornea, corneal neovascularization, and production of cytokines (i.e. interleukin-1-6-8) in experimental animals. Moreover, both in vitro and in vivo studies have demonstrated that vitamin D is a potent inhibitor of retinal neovascularization. It has been shown that calcitriol, the biologically active form of vitamin D, inhibits angiogenesis both in cultured endothelial cells and in retinas from guinea pigs with retinoblastoma or oxygen-induced ischemic retinopathy. In addition, it seems that this compound is able to prevent the progression from early to neovascular age-related macular degeneration (AMD) and, at the same time, to down-regulate the characteristic inflammatory cascade at the retinal pigment epithelium-choroid interface due to its anti-inflammatory and immunomodulatory capabilities. Furthermore, 1,25-dihydroxyvitamin D3 and its analogue, 2-methylene-19-nor-1,25-dihydroxyvitamin D3, are able to modulate intraocular pressure (IOP) through gene expression. Several studies have suggested a role in glaucoma and diabetic retinopathy therapies for vitamin D3. In conclusion, this review summarizes our current knowledge on the potential use of vitamin D3 in the protection and treatment of ocular diseases in ophthalmology.

PMID: 26054653 [PubMed - as supplied by publisher]

Macrophage (Houst). 2015;2(1).

Retinal phagocytes in age-related macular degeneration.

Kim SY.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in industrial countries. Vision loss caused by AMD results from geographic atrophy (dry AMD) and/or choroidal neovascularization (wet AMD). Presently, the etiology and pathogenesis of AMD is not fully understood and there is no effective treatment. Oxidative stress in retinal pigment epithelial (RPE) cells is considered to be one of the major factors contributing to the pathogenesis of AMD. Also retinal glia, as scavengers, are deeply related with diseases and could play a role. Therefore, therapeutic approaches for microglia and Müller glia, as well as RPE, may lead to new strategies for AMD treatment. This review summarizes the pathological findings observed in RPE cells, microglia and Müller glia of AMD murine models.

PMID: 26052551 [PubMed] PMCID: PMC4457466

Case Rep Ophthalmol Med. 2015;2015:960950. Epub 2015 Apr 21.

Jugular Vein Insufficiency and Choroidal Neovascularization in Moderate Myopia: A New Unknown Factor of Additional Risk?

Farina M, Ratti C, Novelli E.

Abstract: To date, choroidal blood flow reduction in highly myopic eyes appears to be related to the development of choroidal neovascularization secondary to local reduction of arterial flow. Instead, no evidence of choroidal neovascularization was found in subjects with low or moderate myopia. The authors'

aim has been to encourage new studies regarding the potential role of chronic retinal venous congestion in the pathogenesis of choroidal neovascularization. In December 2011, a 54-year-old woman with moderate bilateral myopia had a sudden block upon swallowing while she was eating. Subsequently (January 2013) metamorphopsia in the left eye revealed macular degeneration with choroidal neovascularization. The related echo-color Doppler study of the neck veins, performed in November 2014, showed an atypical left jugular insufficiency associated with homolateral hypertension of the superior ophthalmic veins. This singular case highlights the necessity to further investigate the potential role of chronic alterations of intra- and extracranial venous drainage in the disruption of choroidal flow in myopic patients.

PMID: 26064738 [PubMed] PMCID: PMC4431598

Cell Transplant. 2015 Jun 10. [Epub ahead of print]

Retinal angiogenesis effects of TGF- β 1, and paracrine factors secreted from human placental stem cells in response to a pathological environment.

Kim KS, Park JM, Kong T, Kim C, Bae SH, Kim HW, Moon J.

Abstract: Abnormal angiogenesis is a primary cause of many eye diseases, including diabetic retinopathy, age-related macular degeneration, and retinopathy of prematurity. Mesenchymal stem cells (MSC) are currently being investigated as a treatment for several such retinal diseases based on their neuroprotective and angiogenic potentials. In this study, we evaluated the role of systemically injected human placental amniotic membrane-derived MSCs (AMSCs) on pathological neovascularization of proliferative retinopathy. We determined that AMSCs secrete higher levels of transforming growth factor beta (TGF- β 1) than other MSCs and the secreted TGF- β 1 directly suppresses the proliferation of endothelial cells under pathological conditions in vitro. Moreover, in a mouse model of oxygen-induced retinopathy, intraperitoneally injected AMSCs migrated into the retina and suppressed excessive neovascularization of the vasculature via expression of TGF- β 1, and the anti-neovascular effect of AMSCs was blocked by treatment with TGF- β 1 siRNA. These findings are the first to demonstrate that TGF- β 1 secreted from AMSCs is one of the key factors to suppress retinal neovascularization in proliferative retinopathy and further elucidate the therapeutic function of AMSCs for the treatment of retinal neovascular diseases.

PMID: 26065854 [PubMed - as supplied by publisher]

Med Hypotheses. 2015 Jun 1. pii: S0306-9877(15)00218-2. doi: 10.1016/j.mehy.2015.05.020. [Epub ahead of print]

Age-related cataract and macular degeneration: Oxygen receptor dysfunction diseases.

Fu Y, Dong Y, Gao Q.

Abstract: Age-related cataract and age-related macular degeneration (AMD) is the leading cause of vision impairment and blindness in developing and developed countries, respectively. Oxidative stress and oxidation products have been verified to play important roles in these two aging diseases. Recent research has demonstrated that there are significant oxygen gradients in the eye. Therefore, we propose a new hypothesis that these two diseases could be summarized as oxygen receptor dysfunction diseases of which the main points are as follows. Oxygen in the retinal and choroidal vasculature is transferred into the vitreous cavity by a special switching valve or oxygen receptor that might exist in the internal limiting membrane, vascular endothelium or posterior vitreous surface. It is then transported from the posterior segment to the anterior segment by vitreous collagen fibrilla networks, which work similar to a gas pipeline. Posterior vitreous detachment is the starting point of these two diseases by inducing formation of the local hyperoxia region, which results in the occurrence of age-related cataract and macular degeneration. Thus, an innovative anti-oxidative therapy should be added to the traditional treatment of age related macular degeneration. Some associated experimental and clinical approaches are suggested in our paper to test this hypothesis.

PMID: 26049822 [PubMed - as supplied by publisher]

Epidemiology

Can J Ophthalmol. 2015 Jun;50 Suppl 1:S29-33.

Reprint of: Aspirin use and early age-related macular degeneration: a meta-analysis.

Kahawita SK, Casson RJ.

OBJECTIVE: The aim of this review was to evaluate the evidence for an association between Aspirin use and early age-related macular degeneration (ARMD).

METHODS: A literature search was performed in 5 databases with no restrictions on language or date of publication. Four studies involving 10292 individuals examining the association between aspirin and ARMD met the inclusion criteria. Meta-analysis was carried out by Cochrane Collaboration Review Manager 5.2 software (Cochrane Collaboration, Copenhagen, Denmark).

RESULTS: The pooled odd ratios showed that Aspirin use was associated with early ARMD (pooled odds ratio 1.43, 95% CI 1.09-1.88).

CONCLUSIONS: There is a small but statistically significant association between Aspirin use and early ARMD, which may warrant further investigation.

PMID: 26049887 [PubMed - in process]

Med Hypothesis Discov Innov Ophthalmol. 2015 Summer;4(2):39-49.

Age-Related Macular Degeneration: A Scientometric Analysis.

Ramin S, Soheilian M, Habibi G, Ghazavi R, Gharebaghi R, Heidary F.

Abstract: Age-related macular degeneration (ARMD) is a major cause of central blindness among working aged adults across the world. Systematic research planning on any subject, including ARMD is in need of solid data regarding previous efforts in this field and to identify the gaps in the research. This study aimed to elucidate the most important trends, directions, and gap in this subject. The data extracted from the Institute for Scientific Information were used to perform a bibliometric analysis of the scientific productions (1993-2013) about ARMD. Specific parameters related to ARMD were analyzed to obtain a view of the topic's structure, history, and document relationships. Additionally, the trends and authors in the most influential publications were analyzed. The number of articles in this field was found constantly increasing. Most highly cited articles addressed genetic epidemiology and clinical research topics in this field. During the past 3 years, there has been a trend toward biomarker research. Through performing the first scientometric survey on ARMD research, we analyzed the characteristics of papers and the trends in scientific production. We also identified some of the critical gaps in the current research efforts that would help in large-scale research strategic planning.

PMID: 26060829 [PubMed] PMCID: PMC4458325

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

PREVALENCE OF SUBTYPES OF RETICULAR PSEUDODRUSEN IN NEWLY DIAGNOSED EXUDATIVE AGE-RELATED MACULAR DEGENERATION AND POLYPOIDAL CHOROIDAL VASCULOPATHY IN KOREAN PATIENTS.

Kim JH, Chang YS, Kim JW, Lee TG, Kim CG.

PURPOSE: To evaluate the prevalence and characteristics of subtypes of pseudodrusen in newly diagnosed exudative age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

METHODS: This retrospective cross-sectional study included 321 eyes of 321 patients who were newly diagnosed with exudative AMD or PCV. Reticular pseudodrusen was classified into dot pseudodrusen and ribbon pseudodrusen; the prevalence of each subtype was estimated and compared between exudative AMD excluding retinal angiomatous proliferation (RAP), PCV, and RAP. Patient age and choroidal thickness were compared between patients with dot pseudodrusen only and those with ribbon pseudodrusen.

RESULTS: The prevalence of reticular pseudodrusen was 13.9% (15 of 108 eyes) in exudative AMD excluding RAP, 3.4% (6 of 175 eyes) in PCV, and 68.4% (27 of 38 eyes) in RAP. Among the eyes with pseudodrusen, dot pseudodrusen and ribbon pseudodrusen were noted in 100% and 40.0%, respectively, in exudative AMD excluding RAP, 100% and 16.7%, respectively, in PCV, and 96.2% and 69.2%, respectively, in RAP. Ribbon pseudodrusen was more frequently observed in RAP ($P = 0.032$). Patients with ribbon pseudodrusen were significantly older (77.3 ± 6.6 years vs. 72.9 ± 8.1 years, $P = 0.042$) than those with dot pseudodrusen only.

CONCLUSION: The markedly higher incidence of ribbon pseudodrusen in RAP may suggest possible influence of ribbon pseudodrusen on the development of RAP.

PMID: 26049615 [PubMed - as supplied by publisher]

Genetics

Mol Ther Methods Clin Dev. 2015 Jan 28;2:14064. doi: 10.1038/mtm.2014.64. eCollection 2015.

Multigenic lentiviral vectors for combined and tissue-specific expression of miRNA- and protein-based antiangiogenic factors.

Askou AL, Aagaard L, Kostic C, Arsenijevic Y, Hollensen AK, Bek T, Jensen TG, Mikkelsen JG, Corydon TJ.

Abstract: Lentivirus-based gene delivery vectors carrying multiple gene cassettes are powerful tools in gene transfer studies and gene therapy, allowing coexpression of multiple therapeutic factors and, if desired, fluorescent reporters. Current strategies to express transgenes and microRNA (miRNA) clusters from a single vector have certain limitations that affect transgene expression levels and/or vector titers. In this study, we describe a novel vector design that facilitates combined expression of therapeutic RNA- and protein-based antiangiogenic factors as well as a fluorescent reporter from back-to-back RNAPolIII-driven expression cassettes. This configuration allows effective production of intron-embedded miRNAs that are released upon transduction of target cells. Exploiting such multigenic lentiviral vectors, we demonstrate robust miRNA-directed downregulation of vascular endothelial growth factor (VEGF) expression, leading to reduced angiogenesis, and parallel impairment of angiogenic pathways by codelivering the gene encoding pigment epithelium-derived factor (PEDF). Notably, subretinal injections of lentiviral vectors reveal efficient retinal pigment epithelium-specific gene expression driven by the VMD2 promoter, verifying that multigenic lentiviral vectors can be produced with high titers sufficient for in vivo applications. Altogether, our results suggest the potential applicability of combined miRNA- and protein-encoding lentiviral vectors in antiangiogenic gene therapy, including new combination therapies for amelioration of age-related macular degeneration.

PMID: 26052532 [PubMed] PMCID: PMC4449022

Diet, lifestyle & low vision

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

METAMORPHOPSIA AND ITS QUANTIFICATION.

Simunovic MP.

PURPOSE: To discuss and analyze the pathophysiologic mechanisms underlying metamorphopsia, the nature of adaptational mechanisms to this symptom, the development and clinical utility of tests of metamorphopsia, and to discuss the cost-effectiveness of screening populations at risk of exudative age-related macular degeneration using such tests.

METHODS: A primary literature search of PubMed and Web of Science was conducted for articles covering the mechanisms and/or tests of metamorphopsia.

RESULTS: A number of possible mechanisms of metamorphopsia were identified in addition to lateral photoreceptor displacement. These included disorders of image formation, changes in effective axial length, and pathology of the visual pathways and centers. The simplest tests of metamorphopsia rely on highly subjective assessments of regular patterns, as exemplified by Amsler grids. Such tests seem to offer poor sensitivity when used in real-life home-monitoring situations. Newer tests such as so-called preferential hyperacuity perimetry may offer more robust paradigms to assess the perception of distortion but suffer from an inherent disadvantage of being unable to precisely correlate function to structure. The recently published findings of the AREDS2-HOME trial suggest that formalized monitoring of visual function using a preferential hyperacuity perimetry task results in detection of exudative age-related macular degeneration when vision is better-preserved. A cost-benefit analysis using the data from the AREDS2-HOME trial suggests that the calculated cost of screening per letter gained/saved is \$3,351 per year.

CONCLUSION: Metamorphopsia is an important symptom in retinal disease and may occur through a variety of mechanisms. Although the human visual system is exquisitely sensitive to metamorphopsia, commonly used tests of this symptom may be unreliable in real-life conditions. Newer tests of metamorphopsia such as preferential hyperacuity perimetry may improve early detection rates of exudative age-related macular degeneration in at-risk populations.

PMID: 26049620 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Apr 1;56(4):2536-40.

Functional Visual Improvement After Cataract Surgery in Eyes With Age-Related Macular Degeneration: Results of the Ophthalmic Surgical Outcomes Data Project.

Stock MV, Vollman DE, Baze EF, Chomsky AS, Daly MK, Lawrence MG.

PURPOSE: To determine if cataract surgery on eyes with AMD confers as much functional visual improvement as surgery on eyes without retinal pathology.

METHODS: This is a retrospective analysis of 4924 cataract surgeries from the Veterans Healthcare Administration Ophthalmic Surgical Outcomes Data Project (OSOD). We included cases of eyes with AMD that had both preoperative and postoperative NEI-VFQ-25 questionnaires submitted and compared their outcomes with controls without retinal pathology. We excluded patients with other retinal pathologies (740 patients). The analyses compared changes in visual acuity and overall functional visual improvement and its subscales using t-tests, multivariate logistic regressions, and linear regression modeling.

RESULTS: Preoperative and postoperative questionnaires were submitted by 58.3% of AMD and 63.8% of no retinal pathology cases (controls). Analysis of overall score showed that cataract surgery on eyes with AMD led to increased visual function (13.8 ± 2.4 NEI-VFQ units, $P < 0.0001$); however, increases were significantly less when compared with controls (-6.4 ± 2.9 NEI-VFQ units, $P < 0.0001$). Preoperative best-corrected visual acuity (preBCVA) in AMD was predictive of postoperative visual function ($r = -0.38$, $P < 0.0001$). In controls, postoperative visual function was only weakly associated with preBCVA ($r = -0.075$, $P = 0.0002$). Patients with AMD with vision of 20/40 or better had overall outcomes similar to controls (-2.2 ± 4.7 NEI-VFQ units, $P = 0.37$).

CONCLUSIONS: Cataract surgery on eyes with AMD offers an increase in functional visual improvement;

however, the amount of benefit is associated with the eye's preBCVA. For eyes with preBCVA of 20/40 or greater, the improvement is similar to that of patients without retinal pathology. However, if preBCVA is less than 20/40, the amount of improvement was shown to be significantly less and decreased with decreasing preBCVA.

PMID: 26066600 [PubMed - in process]

J Vis. 2015 Apr 1;15(5):7.

Stop before you saccade: Looking into an artificial peripheral scotoma.

Janssen CP, Verghese P.

Abstract: We investigated whether adults with healthy vision can move their eyes toward an informative target area that is initially hidden by a gaze-contingent scotoma in the periphery when they are under time pressure. In the experimental task, participants had to perform an object-comparison task requiring a same-different judgment about two silhouettes. One silhouette was visible, whereas the other was hidden under the scotoma. Despite time pressure and the presence of the visible silhouette, most participants were able to move their eyes toward the informative region to reveal the hidden silhouette. Saccades to the hidden stimulus occurred when the visible stimulus was presented directly opposite in either fixed or variable locations and when the visible stimulus was presented at an adjacent location. Older participants were also able to perform this task. First saccades in the direction of the hidden stimulus had longer latencies compared with saccades toward the visible stimulus. This suggests the use of a deliberate, nonreflexive saccade strategy ("stop before you saccade"). A subset of participants occasionally made curved saccades that were aimed first toward the visible stimulus and then toward the hidden stimulus. We discuss the implications of our findings for patients who have a biological scotoma, for example, in macular degeneration.

PMID: 26067525 [PubMed - in process] PMCID: PMC4429928

Invest Ophthalmol Vis Sci. 2015 Apr 1;56(4):2416-22.

The Influence of Coping on Vision-Related Quality of Life in Patients With Low Vision: A Prospective Longitudinal Study.

Sturrock BA, Xie J, Holloway EE, Lamoureux EL, Keeffe JE, Fenwick EK, Rees G.

PURPOSE: To determine the longitudinal impact of specific coping strategies on vision-related quality of life (VRQoL) in patients with low vision.

METHODS: This was a single-group, longitudinal study utilizing telephone-administered interviews conducted at baseline and at 3 and 6 months with patients (visual acuity < 6/12 in the better eye) recruited from low vision services. The Coping Strategy Indicator (CSI) assessed three strategies used specifically in relation to vision-related problems: avoidant coping, problem-solving coping, and seeking social support. Vision-related quality of life was assessed using the Impact of Vision Impairment (IVI) questionnaire, which comprises two domains: vision-related functioning and vision-related emotional well-being. We used multivariable mixed linear regression including time as an independent variable to assess change in VRQoL.

RESULTS: The study comprised 162 patients (mean age = 69.8 years, 66% female), most with age-related macular degeneration (42%) and moderate vision impairment (41%; <6/18-6/60). Multivariable mixed linear regression showed that avoidant coping was a significant determinant of decline in vision-related functioning ($\beta = -0.11$, 95% confidence interval [CI] -0.22 to -0.01, $P = 0.036$) and emotional well-being ($\beta = -0.29$, 95% CI -0.45 to -0.13, $P < 0.001$) over a 6-month period.

CONCLUSIONS: Our findings showed that avoidant coping has a detrimental impact on VRQoL over time.

Low vision specialists should be aware of their patients' coping strategies and encourage them to engage in active rather than avoidant coping to deal with the impact of their vision impairment.

PMID: 26066595 [PubMed - in process]

BMC Geriatr. 2015 Jun 12;15(1):64.

Physical activity restriction in age-related eye disease: a cross-sectional study exploring fear of falling as a potential mediator.

Nguyen AM, Arora KS, Swenor BK, Friedman DS, Ramulu PY.

BACKGROUND: Fear of falling (FoF) is predictive of decreased physical activity. This study sought to determine if FoF mediates the relationship between decreased vision and physical activity restriction in individuals with glaucoma and age-related macular degeneration (AMD).

METHODS: Accelerometers were used to measure physical activity over 1 week in 59 control, 83 glaucoma, and 58 AMD subjects. Subjects completed the University of Illinois at Chicago Fear of Falling Questionnaire, and the extent of FoF was estimated using Rasch analysis. In negative binomial models adjusting for demographic, health, and social factors, FoF was investigated as a potential mediator between the severity of visual field (VF) loss (in glaucoma patients) or the severity of contrast sensitivity (CS) loss (in AMD patients) and decreased engagement in physical activity, defined as minutes spent in moderate-to-vigorous physical activity (MVPA) per day.

RESULTS: In multivariate negative binomial regression models, 5-decibels worse VF mean deviation was associated with 26 % less engagement in MVPA [rate ratio (RR) = 0.74, $p < 0.01$] amongst glaucoma subjects. When FoF was added to the model, the RR increased from 0.74 to 0.78, and VF loss severity remained associated with less MVPA at a statistically significant level ($p < 0.01$). Likewise, 0.1 log units worse CS was associated with 11 % less daily MVPA (RR = 0.89, $p < 0.01$) amongst AMD subjects. When FoF was added to the model, the RR increased from 0.89 to 1.02, and CS loss was no longer associated with MVPA at a statistically significant level ($p = 0.53$).

CONCLUSIONS: FoF may mediate the relationship between vision loss and physical activity restriction amongst patients with AMD. Future work should determine optimal strategies for reducing FoF in individuals with vision loss in order to prevent the deleterious effects of physical activity restriction.

PMID: 26062727 [PubMed - in process] PMCID: PMC4464712

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