

Issue 322

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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

Clin Ophthalmol. 2017 Mar 23;11:567-571. eCollection 2017.

Intravitreal aflibercept versus intravitreal ranibizumab for the treatment of diabetic macular edema.

Fouda SM, Bahgat AM.

PURPOSE: The purpose of this study was to compare the efficacy of intravitreal aflibercept and ranibizumab in the treatment of diabetic macular edema (DME) in eyes with moderate visual loss.

PATIENTS AND METHODS: This study is a randomized prospective study. Seventy eyes with DME were divided into two groups (each containing 35 eyes). Eyes in group I were treated with intravitreal injection of 2 mg/0.05 mL aflibercept and eyes in group II were treated with intravitreal injection of 0.5 mg/0.1 mL ranibizumab. All the eyes had three successive injections as a loading dose (with 1 month interval), and then the patients were followed up monthly for 12 months. The outcomes of the study were visual acuity, central macular thickness (CMT), and the number of re-injections of the drug.

RESULTS: Mean age of the patients in group I was 55.05 ± 4.7 years and in group II was 56.64 ± 5.8 years ($P=0.17$). The mean baseline best corrected visual acuity (BCVA) of eyes treated with aflibercept was 0.17 ± 0.05 and with ranibizumab was 0.18 ± 0.04 ($P=0.9$). BCVA was improved in both the groups at the end of the follow-up period and was found to be 0.42 ± 0.28 and 0.37 ± 0.23 , respectively ($P=0.27$). The mean baseline CMT of eyes in group I was 465.29 ± 33.7 μm and in group II was 471.5 ± 34.4 μm ($P=0.65$). CMT decreased in both the groups to 360.8 ± 85.7 μm and 387.3 ± 87.8 μm , respectively ($P=0.2$). The mean number of drug re-injection was 2.62 ± 0.68 and 3.03 ± 0.95 in both the groups, respectively ($P=0.02$).

CONCLUSION: Aflibercept and ranibizumab have the same efficacy in the treatment of DME in eyes with moderate visual loss but with less number of drug re-injection and less treatment burden with aflibercept (2.62 ± 0.68 versus 3.03 ± 0.95).

PMID: 28356711 PMCID: PMC5367610

Invest Ophthalmol Vis Sci. 2017 Mar 1;58(3):1893-1898.

Intravitreal Anti-VEGF Injections Reduce Aqueous Outflow Facility in Patients With Neovascular Age-Related Macular Degeneration.

Wen JC, Reina-Torres E, Sherwood JM, Challa P, Liu KC, Li G, Chang JY, Cousins SW, Schuman SG, Mettu PS, Stamer WD, Overby DR, Allingham RR.

PURPOSE: We assess the effect of intravitreal anti-VEGF injections on tonographic outflow facility.

METHODS: Patients with age-related macular degeneration who had received unilateral intravitreal anti-VEGF injections were recruited into two groups, those with ≤ 10 and those with ≥ 20 total anti-VEGF

injections. Intraocular pressure and tonographic outflow facility of injected and uninjected fellow eyes were measured and compared between groups. Risk factors for development of reduced outflow facility also were assessed.

RESULTS: Outflow facility was 12% lower in the injected eyes of patients who received ≥ 20 anti-VEGF injections, compared to contralateral uninjected eyes ($P = 0.02$). In contrast, there was no facility reduction for patients with ≤ 10 anti-VEGF injections ($P = 0.4$). In patients with ocular hypertension in the uninjected eye (IOP > 21 mm Hg, $n = 5$), the outflow facility of injected eyes was on average 46% lower ($P = 0.01$) than in the uninjected fellow eyes. This was significantly greater than the difference observed in patients with IOP ≤ 21 mm Hg in the uninjected eye ($P = 2 \times 10^{-4}$). In patients with ocular hypertension in the injected eye ($n = 6$) the differences in facility and IOP between contralateral eyes were significantly greater than in patients with IOP ≤ 21 mm Hg in the injected eye ($P = 2 \times 10^{-4}$ and $P = 7 \times 10^{-4}$, respectively).

CONCLUSIONS: Chronic anti-VEGF injections significantly reduce outflow facility in patients with AMD. The greatest facility reduction is observed in patients with baseline ocular hypertension. Ophthalmologists who administer anti-VEGF injections should be aware of these findings and monitor patients closely for changes in IOP or evidence of glaucoma, especially in those with pre-existing ocular hypertension.

PMID: 28358961

J Ophthalmol. 2017;2017:5632634. Epub 2017 Mar 1.

Switch to Aflibercept in Diabetic Macular Edema Patients Unresponsive to Previous Anti-VEGF Therapy.

Mira F, Paulo M, Henriques F, Figueira J.

Purpose: The aim was to evaluate the efficacy of aflibercept in patients with diabetic macular edema (DME) unresponsive to prior anti-VEGF therapy.

Methods: Retrospective review of DME unresponsive to previous anti-VEGF switched to aflibercept with 3 months of follow-up. Changes in best correct visual acuity (BCVA), central retinal thickness (CRT), and frequency of injections were analyzed. The percentage of subjects who had $\geq 20/40$ (logMAR equivalent 0.3) and $\leq 20/200$ (logMAR equivalent 1) was evaluated.

Results: A total of 32 eyes from 26 patients were included. Mean age was 65 ± 10 years old. The mean number of previous anti-VEGF injections was 5.34 ± 2.38 , and the mean number of aflibercept injections at the end of the study was 2.00 ± 0.00 . The CRT at baseline was $501.47 \pm 150.51 \mu\text{m}$ and $367.97 \pm 124.61 \mu\text{m}$ at 3 months of follow-up ($P < 0.001$). The logMAR BCVA at baseline was 0.71 ± 0.36 and 0.65 ± 0.33 at the end of the follow-up ($P = 0.037$). At baseline, 12.5% of patients had $\geq 20/40$ compared with 25% at the end of follow-up. At baseline, 28.13% of patients had 20/200 or inferior vision compared with 15.63% at the end of the follow-up.

Conclusions: DME patients unresponsive to previous multiple ranibizumab injections demonstrate a significant anatomical and functional improvement with the switch to aflibercept.

PMID: 28348885 PMCID: PMC5350533

J Ophthalmol. 2017;2017:2407037. Epub 2017 Feb 27.

Combination of Anti-VEGF and Laser Photocoagulation for Diabetic Macular Edema: A Review.

Distefano LN, Garcia-Arumi J, Martinez-Castillo V, Boixadera A.

Abstract: Diabetic macular edema (DME) is the most common cause of vision loss in diabetic patients. Thirty years ago, the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that focal/grid

laser photocoagulation reduces moderate vision loss from DME by 50% or more; thus, macular photocoagulation became the gold standard treatment for DME. However, with the development of anti-VEGF drugs (bevacizumab, ranibizumab, and aflibercept), better outcomes were obtained in terms of visual acuity gain and decrease in macular thickness in some studies when antiangiogenic drugs were administered in monotherapy. Macular laser therapy may still play an important role as an adjuvant treatment because it is able to improve macular thickness outcomes and reduce the number of injections needed. Here, we review some of the clinical trials that have assessed the efficacy of macular laser treatment, either as part of the treatment protocol or as rescue therapy.

PMID: 28348882 PMCID: PMC5350536

Invest Ophthalmol Vis Sci. 2017 Mar 1;58(3):1857.

Author Response: Functional and Anatomic Outcomes in Patients With Serous Retinal Detachment in Diabetic Macular Edema Treated With Ranibizumab.

Giocanti-Auregan A, Fajnkuchen F.

PMID: 28358952

Retin Cases Brief Rep. 2017 Mar 29. [Epub ahead of print]

STENOTROPHOMONAS MALTOPHILIA ENDOPHTHALMITIS 1 MONTH AFTER INTRAVITREAL AFLIBERCEPT.

Boeke PS, Gottlieb JL.

PURPOSE: Endophthalmitis caused by *Stenotrophomonas maltophilia* is rare and has been described after cataract surgery and open globe injuries. We report a patient with endophthalmitis caused by this organism after uncomplicated intravitreal aflibercept injection.

METHODS: A 70-year-old man with a history of anti-vascular endothelial growth factor therapy for diabetic macular edema presented 23 days after aflibercept injection with clinical diagnosis of endophthalmitis. The patient initially had mild pain, conjunctival congestion, and anterior chamber cell; 2 days later, the patient returned with hand motion visual acuity, hypopyon, and dense vitritis.

RESULTS: A tap and inject procedure was performed. The aqueous sample confirmed the presence of *S. maltophilia*. Antimicrobial testing showed susceptibility to ceftazidime which was used during the initial treatment. After resolution of the vitritis and hypopyon, the visual acuity returned to 20/70 at his 3-month follow-up examination.

CONCLUSION: *Stenotrophomonas maltophilia* is a rare infectious agent associated with intravitreal injection and may present 1 month after treatment.

PMID: 28358745

Invest Ophthalmol Vis Sci. 2017 Mar 1;58(3):1856.

Functional and Anatomic Outcomes in Patients With Serous Retinal Detachment in Diabetic Macular Edema Treated With Ranibizumab.

Ashraf M.

PMID: 28358951

Other treatment & diagnosis

JAMA Ophthalmol. 2017 Mar 30. [Epub ahead of print]

Economic Evaluation of a Home-Based Age-Related Macular Degeneration Monitoring System.

Wittenborn JS, Clemons T, Regillo C, Rayess N, Liffmann Kruger D, Rein D.

BACKGROUND: Medicare recently approved coverage of home telemonitoring for early detection of incident choroidal neovascularization (CNV) among patients with age-related macular degeneration (AMD), but no economic evaluation has yet assessed its cost-effectiveness and budgetary impact.

OBJECTIVES: To evaluate a home-based daily visual-field monitoring system using simulation methods and to apply the findings of the Home Monitoring of the Eye study to the US population at high risk for wet-form AMD.

DESIGN, SETTING, AND PARTICIPANTS: In this economic analysis, an evaluation of the potential cost, cost-effectiveness, and government budgetary impact of adoption of a home-based daily visual-field monitoring system among eligible Medicare patients was performed. Effectiveness and visual outcomes data from the Age-Related Eye Disease Study 2 Home Monitoring of the Eye study, treatment data from the Wills Eye Hospital Treat & Extend study, and AMD progression data from the Age-Related Eye Disease Study 1 were used to simulate the long-term effects of telemonitoring patients with CNV in one eye or large drusen and/or pigment abnormalities in both eyes. Univariate and probabilistic sensitivity analysis and an alternative scenario using the Treat & Extend study control group outcomes were used to examine uncertainty in these data and assumptions.

INTERVENTIONS: Home telemonitoring of patients with AMD for early detection of CNV vs usual care.

MAIN OUTCOMES AND MEASURES: Incremental cost-effectiveness ratio, net present value of lifetime societal costs, and 10-year nominal government expenditures.

RESULT: Telemonitoring of patients with existing unilateral CNV or multiple bilateral risk factors for CNV (large drusen and retinal pigment abnormalities) incurs \$907 (95% CI, -\$6302 to \$2809) in net lifetime societal costs, costs \$1312 (95% CI, \$222-\$2848) per patient during 10 years from the federal government's perspective, and results in an incremental cost-effectiveness ratio of \$35 663 (95% CI, cost savings to \$235 613) per quality-adjusted life-year gained.

CONCLUSIONS AND RELEVANCE: Home telemonitoring of patients with AMD who are at risk for CNV was cost-effective compared with scheduled examinations alone. Monitoring patients with existing CNV in one eye is cost saving, but monitoring is generally not cost-effective among patients with low risk of CNV, including those with no or few risk factors. With Medicare coverage, monitoring incurs budgetary expenditures for the government but is cost-saving for patients at high risk of AMD. Monitoring could be cost saving to society if monitoring reduced the frequency of scheduled examinations or led to a reduction of one or more injections of ranibizumab.

PMID: 28358948

Comput Biol Med. 2017 Mar 16;84:89-97. [Epub ahead of print]

Diagnosis of retinal health in digital fundus images using continuous wavelet transform (CWT) and entropies.

Koh JE, Acharya UR, Hagiwara Y, Raghavendra U, Tan JH, Sree SV, Bhandary SV, Rao AK, Sivaprasad S, Chua KC, Laude A, Tong L.

Abstract: Vision is paramount to humans to lead an active personal and professional life. The prevalence of ocular diseases is rising, and diseases such as glaucoma, Diabetic Retinopathy (DR) and Age-related

Macular Degeneration (AMD) are the leading causes of blindness in developed countries. Identifying these diseases in mass screening programmes is time-consuming, labor-intensive and the diagnosis can be subjective. The use of an automated computer aided diagnosis system will reduce the time taken for analysis and will also reduce the inter-observer subjective variabilities in image interpretation. In this work, we propose one such system for the automatic classification of normal from abnormal (DR, AMD, glaucoma) images. We had a total of 404 normal and 1082 abnormal fundus images in our database. As the first step, 2D-Continuous Wavelet Transform (CWT) decomposition on the fundus images of two classes was performed. Subsequently, energy features and various entropies namely Yager, Renyi, Kapoor, Shannon, and Fuzzy were extracted from the decomposed images. Then, adaptive synthetic sampling approach was applied to balance the normal and abnormal datasets. Next, the extracted features were ranked according to the significances using Particle Swarm Optimization (PSO). Thereupon, the ranked and selected features were used to train the random forest classifier using stratified 10-fold cross validation. Overall, the proposed system presented a performance rate of 92.48%, and a sensitivity and specificity of 89.37% and 95.58% respectively using 15 features. This novel system shows promise in detecting abnormal fundus images, and hence, could be a valuable adjunct eye health screening tool that could be employed in polyclinics, and thereby reduce the workload of specialists at hospitals.

PMID: 28351716

Chemotherapy. 2017 Mar 29;62(3):199-204. [Epub ahead of print]

Central Macular Thickness Monitoring after a Taxane-Based Therapy in Visually Asymptomatic Patients.

Chelala E, Arej N, Antoun J, Kourie HR, Zaarour K, Haddad FG, Farhat F, El Karak F, Kattan J.

BACKGROUND: Taxanes are drugs used in various chemotherapeutical protocols to treat solid tumors. They have multiple systemic adverse effects, such as bone marrow suppression, alopecia, nausea, and vomiting, and may rarely cause ocular symptoms. In the past decade, a few reported cases have shown the occurrence of a cystoid macular edema with significant visual loss after the use of a taxane-based chemotherapy. The aim of this study was to compare the central macular thickness (CMT) before and after the initiation of a taxane-based therapy in visually asymptomatic patients and to elucidate the possible impact of these drugs on the vision of cancer patients.

METHODS: Patients with a confirmed diagnosis of a solid tumor were screened for any ophthalmic disease before inclusion and had a baseline macular spectral domain optical coherence tomography (OCT; RTVue-100; Optovue Inc., Fremont, CA, USA) before the initiation of a taxane-based chemotherapy according to different protocols, such as 4EC-4T, 3FEC/3T, or 4TC. OCT was repeated after 4 cycles (or 3 months) of treatment, and CMT was compared to baseline. Patients presenting diabetic retinopathy, age-related macular degeneration or any condition that causes macular edema confirmed by ophthalmic examination were excluded.

RESULTS: Fifty eyes of 25 patients were included; 92% of the subjects were female with a mean age of 48.52 years, 88% were diagnosed with breast cancer, 8% with esophageal cancer, and 4% with ovarian cancer. Docetaxel was the taxane administered to 92% of the patients. The received dose of docetaxel ranged between 110 and 160 mg. The other patients had paclitaxel in their protocols. No significant macular edema or drop in visual acuity were noted in any patient. Nevertheless, the mean CMT was found to be increased, particularly in the parafoveal and perifoveal areas (mean difference of +2.22 μm ; $p = 0.001$).

CONCLUSION: Taxane-based chemotherapy regimens seem to increase macular thickness, with a relative sparing of the fovea, in patients without significant macular edema. Further research is required to better explain the pathophysiology and possible impact of this phenomenon.

PMID: 28351058

Dev Ophthalmol. 2017;58:202-219. Epub 2017 Mar 28.

Macular Edema of Choroidal Origin.

Soubrane G.

Abstract: Macular edema is most often clinically defined as an accumulation of serous fluid within the neurosensory retina with increased thickness of the central retina. In exudative age-related macular degeneration the leakage of fluid from the choroidal new vessels may be the origin of macular edema. Their abnormal permeability and the inflammatory reaction are mechanisms involved in this accumulation of fluid, which occurs in all layers. Cystoid macular edema is more often associated with subepithelial occult choroidal neovascularization (CNV) than it is with pre-epithelial classic CNV. The simultaneous presence of choroidal new vessels and ME implies a number of cellular dysfunctions especially of Müller cells and subsequently metabolic alterations. The leakage from the choroidal new vessels, predominantly vascular endothelial growth factor (VEGF)-induced, may produce a large accumulation of fluid under the neurosensory retina. It is also likely that the key signaling steps occur prior to the upregulation of VEGF either initiated by, or facilitated by, cytokines, which act under normal basic conditions to counterbalance the integral VEGF effects and, in pathologic circumstances, may either counteract or serve to amplify the process.

PMID: 28351049

Dev Ophthalmol. 2017;58:178-190. Epub 2017 Mar 28.

Postsurgical Cystoid Macular Edema.

Zur D, Loewenstein A.

Abstract: Cystoid macular edema (CME) is a primary cause of reduced vision following both cataract and successful vitreoretinal surgery. The incidence of clinical CME following modern cataract surgery is 0.1-2.35%. Preexisting conditions such as diabetes mellitus and uveitis as well as intraoperative complications can raise the risk of postsurgical CME. The etiology of CME is not completely understood. Prolapsed or incarcerated vitreous and postoperative inflammatory processes have been proposed as causative agents. Pseudophakic CME is characterized by poor postoperative visual acuity. Fluorescein angiography shows the classical perifoveal petaloid staining pattern and late leakage of the optic disk. Optical coherence tomography is a useful diagnostic tool, which displays cystic spaces in the outer nuclear layer. The most important differential diagnoses include age-related macular degeneration and other causes of CME such as diabetic macular edema. Most cases of pseudophakic CME resolve spontaneously. The value of prophylactic treatment is doubtful. First-line treatment of postsurgical CME should include topical nonsteroidal anti-inflammatory drugs and corticosteroids. Oral carbonic anhydrase inhibitors can be considered complementary. In cases of resistant CME, periocular or intraocular corticosteroids present an option. Antiangiogenic agents, though experimental, should be considered for nonresponsive persistent CME. Surgical options should be reserved for special indications.

PMID: 28351047

Dev Ophthalmol. 2017;58:139-167. Epub 2017 Mar 28.

Retinal Vein Occlusions.

Jonas JB, Monés J, Glacet-Bernard A, Coscas G.

Abstract: Retinal vein occlusions (RVOs) have been defined as retinal vascular disorders characterized by dilatation of retinal veins with retinal and subretinal hemorrhages, macular edema, and a varying degree of retinal ischemia. Retinal angiography, either as fluorescein and indocyanine green (ICG) angiography or in

the form of optical coherence tomography (OCT)-based angiography, is essential for the diagnosis and assessment of the prognosis of RVOs. It allows the differentiation of diverse types of RVOs, such as perfused or nonperfused, as well as the detection of different modalities in the natural history of RVOs. OCT angiographic imaging in combination with dye angiography (fluorescein or ICG) is the most effective method to assess the amount and location of cystoid macular edema and the persistence, regression, and degree of ischemia. OCT can additionally display the presence and integrity of the outer limiting membrane and of the inner and outer segments of the photoreceptors as useful biomarkers for the prognosis and as a guide for the treatment of RVO. Due to the relatively often benign and self-limiting course of nonischemic RVOs, therapy may initially be delayed. If macular edema extends into the foveolar region and persists, intravitreal medical therapy including steroids (triamcinolone; fluocinolone or dexamethasone in slow-release devices) and/or anti-VEGF (vascular endothelial growth factor) drugs (bevacizumab, ranibizumab, aflibercept) may be intravitreally administered, avoiding the irreversibly destructive effect of laser coagulation, which previously was applied in a 'grid' pattern over the extrafoveal leaking area. The side effects of intraocularly applied steroids in relatively young patients including cataract formation and ocular hypertension have to be considered.

PMID: 28351046

JAMA Ophthalmol. 2017 Mar 30. [Epub ahead of print]

Determining the Value of Home Monitoring of Patients With Age-Related Macular Degeneration.

Pershing S, Stein JD.

PMID: 28358963

Pathogenesis

Inflamm Res. 2017 Mar 30. [Epub ahead of print]

Activation of liver X receptor α protects amyloid β 1-40 induced inflammatory and senescent responses in human retinal pigment epithelial cells.

Dai B, Lei C, Lin R, Tao L, Bin Y, Peng H, Lei B.

OBJECTIVE: To investigate whether activation of the liver X receptors (LXRs) inhibits amyloid β 1-40 ($A\beta$ 1-40) induced inflammatory and senescent responses in human retinal pigment epithelial (RPE) cells.

MATERIALS AND METHODS: Confluent cultures of human primary RPE and ARPE-19 cells pretreated with 5 μ M of TO901317 (TO90), a synthetic agonist of LXR, or vehicle were incubated with 1 μ M of $A\beta$ 1-40 or $A\beta$ 40-1. The optimum concentrations of $A\beta$ 1-40 and TO90 were determined by cell viability assay. Pro-inflammatory cytokines IL-6, IL-8, MCP-1 were detected by real-time polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA). Expression and localization of an aging protein p16INK4a (p16) were analyzed by western blotting and immunofluorescence. Expressions of LXRs and one of their target genes ATP-binding cassette transporter A1 (ABCA1) were examined by real-time PCR and western blotting. Phosphorylated transcription inhibition factor- κ B- α (p-I κ B- α) was assessed by western blotting.

RESULTS: A negative linear relationship between the $A\beta$ 1-40 concentration and the cell viability was evident, indicating $A\beta$ 1-40 decreased ARPE-19 cell viability in a dose-dependent manner. $A\beta$ 1-40 enhanced the expression of IL-6, IL-8, MCP-1 as well as p16 in both RPE cell lines at both mRNA and protein levels, whereas TO90 counteracted the detrimental effects. TO90 upregulated the expression of LXR α and its target gene ABCA1, but it did not affect the expression of LXR β . Meanwhile, TO90 inhibited the phosphorylation of I κ B- α mediated by $A\beta$ 1-40 stimulation.

CONCLUSION: Activation of the LXR α -ABCA1 axis may alleviate $A\beta$ 1-40 induced inflammatory and

senescent responses in RPE cells. The beneficial effect appears associated with the inhibition of the NF- κ B signaling pathway.

PMID: 28361293

Proc Natl Acad Sci U S A. 2017 Mar 27. [Epub ahead of print]

Complement modulation in the retinal pigment epithelium rescues photoreceptor degeneration in a mouse model of Stargardt disease.

Lenis TL, Sarfare S, Jiang Z, Lloyd MB, Bok D, Radu RA.

Abstract: Recessive Stargardt macular degeneration (STGD1) is caused by mutations in the gene for the ABCA4 transporter in photoreceptor outer segments. STGD1 patients and *Abca4*^{-/-} (STGD1) mice exhibit buildup of bisretinoid-containing lipofuscin pigments in the retinal pigment epithelium (RPE), increased oxidative stress, augmented complement activation and slow degeneration of photoreceptors. A reduction in complement negative regulatory proteins (CRPs), possibly owing to bisretinoid accumulation, may be responsible for the increased complement activation seen on the RPE of STGD1 mice. CRPs prevent attack on host cells by the complement system, and complement receptor 1-like protein y (CRRY) is an important CRP in mice. Here we attempted to rescue the phenotype in STGD1 mice by increasing expression of CRRY in the RPE using a gene therapy approach. We injected recombinant adeno-associated virus containing the CRRY coding sequence (AAV-CRRY) into the subretinal space of 4-wk-old *Abca4*^{-/-} mice. This resulted in sustained, several-fold increased expression of CRRY in the RPE, which significantly reduced the complement factors C3/C3b in the RPE. Unexpectedly, AAV-CRRY-treated STGD1 mice also showed reduced accumulation of bisretinoids compared with sham-injected STGD1 control mice. Furthermore, we observed slower photoreceptor degeneration and increased visual chromophore in 1-y-old AAV-CRRY-treated STGD1 mice. Rescue of the STGD1 phenotype by AAV-CRRY gene therapy suggests that complement attack on the RPE is an important etiologic factor in STGD1. Modulation of the complement system by locally increasing CRP expression using targeted gene therapy represents a potential treatment strategy for STGD1 and other retinopathies associated with complement dysregulation.

PMID: 28348233

Int J Mol Sci. 2017 Mar 29;18(4).

Inhibition or Stimulation of Autophagy Affects Early Formation of Lipofuscin-Like Autofluorescence in the Retinal Pigment Epithelium Cell.

Lei L, Tzekov R, Li H, McDowell JH, Gao G, Smith WC, Tang S, Kaushal S.

Abstract: The accumulation of lipofuscin in the retinal pigment epithelium (RPE) is dependent on the effectiveness of photoreceptor outer segment material degradation. This study explored the role of autophagy in the fate of RPE lipofuscin degradation. After seven days of feeding with either native or modified rod outer segments, ARPE-19 cells were treated with enhancers or inhibitors of autophagy and the autofluorescence was detected by fluorescence-activated cell sorting. Supplementation with different types of rod outer segments increased lipofuscin-like autofluorescence (LLAF) after the inhibition of autophagy, while the induction of autophagy (e.g., application of rapamycin) decreased LLAF. The effects of autophagy induction were further confirmed by Western blotting, which showed the conversion of LC3-I to LC3-II, and by immunofluorescence microscopy, which detected the lysosomal activity of the autophagy inducers. We also monitored LLAF after the application of several autophagy inhibitors by RNA-interference and confocal microscopy. The results showed that, in general, the inhibition of the autophagy-related proteins resulted in an increase in LLAF when cells were fed with rod outer segments, which further confirms the effect of autophagy in the fate of RPE lipofuscin degradation. These results emphasize the

complex role of autophagy in modulating RPE autofluorescence and confirm the possibility of the pharmacological clearance of RPE lipofuscin by small molecules.

PMID: 28353645

Ageing Res Rev. 2017 Mar 27;36:64-77. [Epub ahead of print]

DNA damage response and autophagy in the degeneration of retinal pigment epithelial cells- Implications for age-related macular degeneration (AMD).

Hyttinen JM, Błasiak J, Niittykoski M, Kinnunen K, Kauppinen A, Salminen A, Kaarniranta K.

Abstract: In this review we will discuss the links between autophagy, a mechanism involved in the maintenance of cellular homeostasis and controlling cellular waste management, and the DNA damage response (DDR), comprising various mechanisms preserving the integrity and stability of the genome. A reduced autophagy capacity in retinal pigment epithelium has been shown to be connected in the pathogenesis of age-related macular degeneration (AMD), an eye disease. This degenerative disease is a major and increasing cause of vision loss in the elderly in developed countries, primarily due to the profound accumulation of intra- and extracellular waste: lipofuscin and drusen. An abundance of reactive oxygen species is produced in the retina since this tissue has a high oxygen demand and contains mitochondria-rich cells. The retina is exposed to light and it also houses many photoactive molecules. These factors are clearly reflected in both the autophagy and DNA damage rates, and in both nuclear and mitochondrial genomes. It remains to be revealed whether DNA damage and DDR capacity have a more direct role in the development of AMD.

PMID: 28351686

Epidemiology

JAMA Ophthalmol. 2017 Mar 30. [Epub ahead of print]

Ethnic Differences in the Association Between Age-Related Macular Degeneration and Vision-Specific Functioning.

Fenwick EK, Man RE, Cheung CM, Sabanayagam C, Cheng CY, Neelam K, Chua J, Gan AT, Mitchell P, Wong TY, Lamoureux EL.

IMPORTANCE: Understanding the link between ethnicity and health is critical to making appropriate public policy decisions. Few population-level data are available about this connection, however, including the influence of ethnicity on the association between age-related macular degeneration (AMD) and vision-specific functioning (VSF).

OBJECTIVE: To identify the influence of ethnicity on VSF among Chinese, Malay, and Indian patients with AMD.

DESIGN, SETTING, AND PARTICIPANTS: This cross-sectional, population-based study relied on patients and their data from 3 population-based studies in 3 ethnic groups: Chinese, Malay and Indian. Of 10 033 Chinese, Malay, and Indian adults who participated in the study, 9962 (99.3%) who had gradable fundus images and Visual Function Index (VF-11) data available were included in the analyses for the present study. Unocular presenting distance visual acuity was measured using the logMAR chart. Separate multiple linear regression models examined the association between AMD and VSF in the 3 ethnic groups, adjusting for age, sex, presenting visual acuity in the better-seeing eye, educational level, income, smoking status, hypertension, diabetes, cardiovascular disease, total cholesterol level, and other eye conditions. Data were collected between January 20, 2004, and December 19, 2011; data analysis was conducted between November 12, 2015, and December 28, 2016.

EXPOSURES: Age-related macular degeneration according to fundus photographs graded using a modified Wisconsin Age-Related Maculopathy Grading System.

MAIN OUTCOMES AND MEASURES: Rasch analysis was used to convert VF-11 questionnaire scores to estimated interval measures of VSF.

RESULTS: Of the 9962 participants, the mean (SD) age was 58.8 (10.4) years; 4909 (49.3%) were male; 590 (5.9%) had early AMD (241 Chinese, 161 Malays, and 188 Indians) and 60 (0.6%) had late AMD (25 Chinese, 21 Malays, and 14 Indians). In the adjusted models, compared with no AMD, early AMD was associated with a small reduction in VSF (2.9%; $\beta = -0.12$; 95% CI, -0.23 to -0.00; $P = .046$) in the Chinese group but not in the Indian and Malay groups. Moreover, Chinese participants with late AMD had a clinically significant 19.1% loss of VSF ($\beta = -0.78$; 95% CI, -1.13 to -0.43, $P < .001$). In the Malay group, those with late AMD had a 13.5% drop in VSF ($\beta = -0.49$; 95% CI, -1.01 to 0.04; $P = .07$) compared with their counterparts without AMD. Similarly, late AMD was not associated with VSF in the Indian group.

CONCLUSIONS AND RELEVANCE: Early and late AMD negatively affected VSF in Chinese but not in Indian and Malay participants. This finding suggests that there is an independent ethnic influence in the association of the disease with VSF in multiethnic Asian populations, thus warranting ethnicity-based strategies to delay the onset or progression of AMD.

PMID: 28358956

JAMA Ophthalmol. 2017 Mar 30. [Epub ahead of print]

Ethnic Differences in Self-reported Visual Function Among Patients With Age-Related Macular Degeneration: Implications for Care.

Keay L.

PMID: 28358965

Genetics

Genome Med. 2017 Mar 27;9(1):29.

Genetic pleiotropy between age-related macular degeneration and 16 complex diseases and traits.

Grassmann F, Kiel C, Zimmermann ME, Gorski M, Grassmann V, Stark K; International AMD Genomics Consortium (IAMGDC), Heid IM, Weber BH.

BACKGROUND: Age-related macular degeneration (AMD) is a common condition of vision loss with disease development strongly influenced by environmental and genetic factors. Recently, 34 loci were associated with AMD at genome-wide significance. So far, little is known about a genetic overlap between AMD and other complex diseases or disease-relevant traits.

METHODS: For each of 60 complex diseases/traits with publicly available genome-wide significant association data, the lead genetic variant per independent locus was extracted and a genetic score was calculated for each disease/trait as the weighted sum of risk alleles. The association with AMD was estimated based on 16,144 AMD cases and 17,832 controls using logistic regression.

RESULTS: Of the respective disease/trait variance, the 60 genetic scores explained on average 4.8% (0.27 -20.69%) and 16 of them were found to be significantly associated with AMD (Q-values < 0.01 , p values from $< 1.0 \times 10^{-16}$ to 1.9×10^{-3}). Notably, an increased risk for AMD was associated with reduced risk for cardiovascular diseases, increased risk for autoimmune diseases, higher HDL and lower LDL levels in serum, lower bone-mineral density as well as an increased risk for skin cancer. By restricting the analysis to

1824 variants initially used to compute the 60 genetic scores, we identified 28 novel AMD risk variants (Q-values < 0.01 , p values from 1.1×10^{-7} to 3.0×10^{-4}), known to be involved in cardiovascular disorders, lipid metabolism, autoimmune diseases, anthropomorphic traits, ocular disorders, and neurological diseases. The latter variants represent 20 novel AMD-associated, pleiotropic loci. Genes in the novel loci reinforce previous findings strongly implicating the complement system in AMD pathogenesis.

CONCLUSIONS: We demonstrate a substantial overlap of the genetics of several complex diseases/traits with AMD and provide statistically significant evidence for an additional 20 loci associated with AMD. This highlights the possibility that so far unrelated pathologies may have disease pathways in common.

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Stem cells

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Retina tissue engineering by conjunctiva mesenchymal stem cells encapsulated in fibrin gel: Hypotheses on novel approach to retinal diseases treatment.

Soleimannejad M, Ebrahimi-Barough S, Nadri S, Riazi-Esfahani M, Soleimani M, Tavangar SM, Ai J.

BACKGROUND: Retinitis pigmentosa (RP) and age related macular degeneration (AMD) are two retinal diseases that progress by photoreceptor cells death. In retinal transplantation studies, stem and progenitor cells inject into the sub retinal space or vitreous and then these cells can be migrate to the site of retinal degeneration and locate in the host retina and reconstitute vision.

PRESENTATION OF THE HYPOTHESIS: Our hypothesis suggests that using human conjunctiva stem cells (as the source for increasing the number of human stem cells progenitor cells in retina dysfunction diseases) with fibrin gel and also assessing its relating in vitro (cellular and molecular processes) and in vivo (vision tests and pathology) could be a promising strategy for treatment of AMD and RP disorders.

TESTING THE HYPOTHESIS: In this idea, we describe a novel approach for retina tissue engineering with differentiation of conjunctiva mesenchymal stem cells (CJMSCs) into photoreceptor-like cells in fibrin gel with induction medium contain taurine. For assessment of differentiation, immunocytochemistry and real time PCR are used for the expression of Rhodopsin, RPE65, Nestin as differentiated photoreceptor cell markers in 2D and 3D culture. The results show that fibrin gel will offer a proper 3D scaffold for CJMSCs derived photoreceptor cell-like cells.

IMPLICATIONS OF THE HYPOTHESIS: Application of immune-privileged, readily available sources of adult stem cells like human conjunctiva stem cells with fibrin gel would be a promising strategy to increase the number of photoreceptor progenitor cells and promote involuntary angiogenesis needed in retina layer repair and regeneration.

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Diet, lifestyle & low vision

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Searching for Objects in Everyday Scenes: Measuring Performance in People With Dry Age-Related Macular Degeneration.

Taylor DJ, Smith ND, Crabb DP.

PURPOSE: Treatment success in clinical trials for AMD would ideally be aligned to measurable

performance in visual tasks rather than imperceptible changes on clinical charts. We test the hypothesis that patients with dry AMD perform worse than visually healthy peers on computer-based surrogates of "real-world" visual search tasks.

METHODS: A prospective case-control study was conducted in which patients with dry AMD performed a computer-based "real-world" visual search task. Participants searched for targets within images of everyday scenes while eye movements were recorded. Average search times across the images were recorded as a primary outcome measure. Comparisons were made against a 90% normative limit established in peers with healthy vision (controls). Eye movement parameters were examined as a secondary outcome measure.

RESULTS: Thirty-one patients and 33 controls with median (interquartile range) age of 75 (70-79) and 71 (66-75) years and logMAR binocular visual acuity 0.2 (0.18-0.31) and -0.06 (-0.12 to 0), respectively, were examined. Four, 18, and 9 patients were categorized as having early, intermediate, and late AMD, respectively. Nineteen (61%) patients exceeded the 90% normative limits for average search time; this was statistically significant (Fisher's exact test, $P < 0.0001$). On average, patients made smaller saccades than controls ($P < 0.001$).

CONCLUSIONS: People with dry AMD, certainly those with advanced disease, are likely to have measurable difficulties beyond those observed in visually healthy peers on "real-world" search tasks. Further work might establish this type of task as a useful outcome measure for clinical trials.

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Visual function quality of life measure changes upon conversion to neovascular age-related macular degeneration in second eyes.

Paulus YM, Jefferys JL, Hawkins BS, Scott AW.

PURPOSE: To determine changes in quality of life measures when choroidal neovascularization (CNV) developed in the second eye of patients with initially unilateral neovascular age-related macular degeneration (AMD).

METHODS: We analyzed responses to the 39-item National Eye Institute Visual Function Questionnaire (NEI-VFQ), 36-item Short Form Health Survey (SF-36), and Hospital Anxiety and Depression Scale (HADS) at baseline, and prior to and following second eye CNV diagnosis in 92 participants enrolled in two Submacular Surgery Trials. Paired t-tests for sample sizes over 30 and Wilcoxon signed-rank tests for sample sizes <30 were performed to compare scores.

RESULTS: CNV development resulted in statistically and clinically significant changes in responses to 20 of 39 NEI-VFQ items, indicating visual function decline during a mean interval of 25 months. Little difference was noted between baseline scores and prior to CNV diagnosis, which averaged 8.9 months duration. Subscales demonstrated a statistically significant decline in general vision, near activities, distance activities, social functioning, role difficulties, dependency, and driving. There were minimal changes in the HADS and SF-36 scales.

CONCLUSION: CNV development in the second eye had a dramatic effect on visual functioning based on patient responses to the NEI-VFQ questionnaire. Our investigation is believed to be the first study using data collected prospectively to demonstrate vision-related quality of life changes that resulted from development of CNV in AMD patients.

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