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Drug Treatment

Ophthalmology. 2016 Aug 23. [Epub ahead of print]

Ranibizumab Treatment for Pigment Epithelial Detachment Secondary to Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of the HARBOR Study.

Sarraf D, London NJ, Khurana RN, Dugel PU, Gune S, Hill L, Tuomi L.

PURPOSE: To analyze the effect of baseline presence and height of pigment epithelial detachments (PEDs) on visual and anatomic outcomes at 24 months in patients with neovascular age-related macular degeneration (AMD) treated with ranibizumab.

DESIGN: Post hoc analysis of HARBOR, a 24-month, phase III, randomized, multicenter, double-masked, active treatment-controlled study (clinicaltrials.gov identifier, NCT00891735).

PARTICIPANTS: One thousand ninety-seven patients with neovascular AMD.

METHODS: Intravitreal ranibizumab 0.5 mg or 2.0 mg monthly or pro re nata (PRN) after 3 monthly loading doses.

MAIN OUTCOME MEASURES: We evaluated the effect of presence and height of baseline PED on several outcomes at 24 months, including best-corrected visual acuity (BCVA), change in PED height, resolution of PED, and number of injections in the PRN arms. Development of macular atrophy at month 24 by presence or absence of PED was evaluated.

RESULTS: Five hundred ninety-eight (54.5%) patients showed PED at baseline. In the ranibizumab 0.5-mg PRN group, mean numbers of injections were similar for patients with PED present or absent at baseline (14.0 vs. 12.5). Mean BCVA gains from baseline to 24 months were seen in all treatment groups and were comparable in patients with or without PED at baseline treated with ranibizumab 0.5 mg monthly (PED present at baseline, +9.0 letters; PED absent at baseline, +11.3 letters), 0.5 mg PRN (present, +8.4; absent, +7.9), 2.0 mg monthly (present, +7.1; absent, +11.1), or 2.0 mg PRN (present, +7.2; absent, +8.8). When analyzed by baseline PED height, mean BCVA gains were demonstrated and comparable in all treatment groups at 24 months except for patients treated with ranibizumab 2.0 mg monthly in the extra-large group (PEDs ≥352 μm; mean BCVA change, -0.8 letters). At 24 months, 53.2% (0.5 mg monthly), 44.5% (0.5 mg PRN), 70.4% (2.0 mg monthly), and 57.3% (2.0 mg PRN) of patients showed complete resolution of PED.

CONCLUSIONS: Ranibizumab 0.5 mg given monthly or PRN effectively treated PEDs in patients with neovascular AMD, and significant vision gains resulted regardless of PED status and height at baseline. In this analysis, there was no additional vision benefit with a higher dose of ranibizumab (2.0 mg).

PMID: 27566855

Drugs Aging. 2016 Aug 26. [Epub ahead of print]

Clinical Applications of Dexamethasone for Aged Eyes.

Abadia B, Calvo P, Ferreras A, Bartol F, Verdes G, Pablo L.

ABSTRACT: The risk of severe eye problems has been found to increase significantly with age, particularly between the fifth and sixth decades of life. Cataracts, dry eye, neovascular age-related macular degeneration, diabetic retinopathy and retinal vein occlusion (RVO) are very common and very different age-related ocular diseases that reduce the patient's quality of life. The rationale for using corticosteroids to treat anterior and posterior ocular segment diseases is driven by inflammation. Dexamethasone, one of the most powerful corticosteroids available, is widely used for topical or intravitreal administration. Topical dexamethasone has proven efficacy for the management of postoperative inflammation in the anterior segment after cataract surgery and symptom relief in dry-eye disease. A new sustained-release 700 µg dexamethasone intravitreal implant (DEX) was recently approved for the treatment of macular edema following RVO, diabetic macular edema, or non-infectious uveitis, and its use is increasing, especially when other therapeutic agents have failed. The most common side effects are increased intraocular pressure and cataract formation. The potency of DEX, alone or in combination with other agents, makes DEX a promising option for treating several retinal diseases.

PMID: 27566619

Eye (Lond). 2016 Aug 26. [Epub ahead of print]

Aflibercept in diabetic macular edema: evaluating efficacy as a primary and secondary therapeutic option.

Ashraf M, Souka A, Adelman R, Forster SH.

ABSTRACT: The recent results of Protocol T have illustrated the efficacy of aflibercept in the treatment of diabetic macular edema. It also demonstrated that in patients with poor vision (<6/12), aflibercept offers anatomical and visual advantages over ranibizumab and bevacizumab in the first 12 months of treament. At 2 years, the difference between the three drugs decreased with patients with a better baseline VA (69-78) showing a statistically insignificant advantage for ranibizumab compared with aflibercept.These results were achieved using a pro-re nata (PRN) protocol, which was not previously studied in large phase 3 trials, VIVID and VISTA, that chose to compare the 2.0 mg dose in a monthly and bimonthly regimen. In this review article, we analyzed earlier studies such as DAVINCI and VIVID and VISTA to determine which treatment strategy offers the best results; monthly, bimonthly, or PRN. We also studied the different doses for aflibercept used in DAVINCI to determine which is more effective the 0.5 mg dose or the 2.0 mg dose. In addition, we analyzed the recent data from protocol T with regards to visual and anatomic outcomes to try to determine whether these results concur with previous studies. Finally, we discuss the role of aflibercept as a potential alternative to any diabetic macular edema regimen regardless what the primary drug used is.Eye advance online publication, 26 August 2016; doi:10.1038/eye.2016.174.

PMID: 27564719

Ophthalmology. 2016 Aug 20. [Epub ahead of print]

Treatment Patterns and Visual Outcomes during the Maintenance Phase of Treat-and-Extend Therapy for Age-Related Macular Degeneration.

Essex RW, Nguyen V, Walton R, Arnold JJ, McAllister IL, Guymer RH, Morlet N, Young S, Barthelmes D, Gillies MC; Fight Retinal Blindness Study Group.

PURPOSE: To present the treatment patterns, disease activity, and visual outcomes of eyes in the maintenance phase of a treat-and-extend regimen for neovascular age-related macular degeneration

(nAMD). To compare the maintenance phase behavior of eyes with a shorter induction phase (≤3 injections) with those requiring a longer induction phase (>3 injections).

DESIGN: Database observational study.

PARTICIPANTS: Eyes with nAMD receiving anti-vascular endothelial growth factor (VEGF) treatment using a treat-and-extend protocol. Persistently active eyes were excluded, as were eyes with <12 months follow-up during the maintenance phase.

METHODS: Clinical information from a large prospective international voluntary registry of nAMD was analyzed. The maintenance phase was defined as starting at the first clinician-reported grading of lesion inactivity.

MAIN OUTCOME MEASURES: For analyses by eye: treatment interval at first reactivation; time to first reactivation; and visual acuity change during the study period. For analyses by visit: choroidal neovascular membrane activity graded by the treating physician; time since previous injection; and visual acuity loss since previous injection (>0 letters and ≥15 letters).

RESULTS: The mean change in visual acuity during the maintenance phase was +1.0 letters at 12 months -0.6 letters at 24 months and -1.5 at 36 months. Median treatment interval increased from 35 days at study entry to 63 days at 12 months and was 60 days at 36 months. 38.5% of eyes remained inactive at all observed visits during the maintenance phase (minimum 1 year follow-up, mean 945 days). The most common treatment interval at first reactivation was 8 weeks. Treatment intervals beyond 12 weeks seemed to be associated with increased risk of disease reactivation, with risk of reactivation reaching 37.4% at treatment intervals of ≥20 weeks. Eyes with a longer induction phase had worse visual outcomes in the maintenance phase, and earlier and more-frequent disease reactivation, although they received injections less frequently.

CONCLUSIONS: The detailed behavior of eyes in the maintenance phase of treat-and-extend management for nAMD is presented. Visual acuity was well maintained during the study period. The most common interval at which reactivation first occurred was 8 weeks. Longer duration of induction phase was associated with worse visual acuity outcomes and earlier disease reactivation, perhaps because of undertreatment.

PMID: 27554034

Wien Klin Wochenschr. 2016 Aug 22. [Epub ahead of print]

Short-term effect of aflibercept on visual acuity and central macular thickness in patients not responding to ranibizumab and bevacizumab.

Maksys S, Richter-Müksch S, Weingessel B, Vécsei-Marlovits PV.

PURPOSE: To analyze the clinical outcome of treatment with aflibercept in patients not responding to ranibizumab and bevacizumab.

METHODS: Retrospective review of 32 eyes from 30 consecutive patients with choroidal neovascularization (CNV) who showed no response to treatment with ranibizumab or bevacizumab and were switched to aflibercept. Visual acuity, central macular thickness (CMT) and presence or absence of intraretinal or subretinal fluid were analyzed before switching to aflibercept, after each of three uploading dose injections of aflibercept and 6, 8 and 10 weeks after the third aflibercept injection. All eyes had previous ranibizumab injections and the mean number of previous injections was 14.75 (± 7.38). Mean duration of previous anti-vascular endothelial growth factor (VEGF) treatment was 38 months (± 27.35 months).

RESULTS: Mean visual acuity before switching to aflibercept was 0.40 ± 0.30 logMAR. After the third injection visual acuity was 0.3 ± 0.3 logMAR and 10 weeks after the third injection it was 0.50 ± 0.20 logMAR. No significant differences were seen during treatment and follow-up. The mean CMT was 394 ±

118 µm at baseline, at follow-up (first, second and third, group week 6, group week 8 and group week 10) it was 317 ± 108 µm, 301 ± 99 µm, 292 ± 83 µm, 270 ± 78 µm, 340 ± 146 µm and 377 ± 92 µm, respectively. Significant reductions in CMT were seen between the first and third follow-up injections and at group week 8. Of the patients 59.4 % were complete non-responders to aflibercept.

CONCLUSION: Aflibercept results in improvement in CMT in non-responders to ranibizumab and bevacizumab as long as therapy is given continuously and can therefore be an alternative therapy.

PMID: 27550436

Retin Cases Brief Rep. 2016 Aug 23. [Epub ahead of print]

ACUTE MACULAR NEURORETINOPATHY AFTER RANIBIZUMAB INJECTION IN A DIABETIC PATIENT.

Wheatley HM, Sarraf D.

PURPOSE: To report a case of acute macular neuroretinopathy occurring after intravitreal ranibizumab injection for diabetic macular edema.

METHODS: Observational clinical case report.

RESULTS: The patient received an intravitreal ranibizumab (0.3 mg) injection for diabetic macular edema. Three days later, he had a decline in vision associated with a central and paracentral scotoma. Optical coherence tomography (OCT) demonstrated bandlike hyperreflectivity of the outer nuclear and plexiform layers corresponding to the patient's scotoma, consistent with the diagnosis of acute macular neuroretinopathy. There was spontaneous resolution of the abnormalities observed in optical coherence tomography, but only partial resolution of the scotoma was observed 4 months after presentation.

CONCLUSION: Diabetic retinopathy may be associated with acute macular neuroretinopathy. The temporal relationship between ranibizumab injection and the onset of acute macular neuroretinopathy in this case report raises the possibility of a causal relationship.

PMID: 27556909

Ophthalmic Surg Lasers Imaging Retina. 2016 Aug 1;47(8):752-62.

Assistive Device for Efficient Intravitreal Injections.

Ullrich F, Michels S, Lehmann D, Pieters RS, Becker M, Nelson BJ.

ABSTRACT: Intravitreal therapy is the most common treatment for many chronic ophthalmic diseases, such as age-related macular degeneration. Due to the increasing worldwide demand for intravitreal injections, there exists a need to render this medical procedure more time- and cost-efficient while increasing patient safety. The authors propose a medical assistive device that injects medication intravitreally. Compared to the manual intravitreal injection procedure, an automated device has the potential to increase safety for patients, decrease procedure times, allow for integrated data storage and documentation, and reduce costs for medical staff and expensive operating rooms. This work demonstrates the development of an assistive injection system that is coarsely positioned over the patient's head by the human operator, followed by automatic fine positioning and intravitreal injection through the pars plana. Several safety features, such as continuous eye tracking and iris recognition, have been implemented. The functioning system is demonstrated through ex vivo experiments with porcine eyes. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:752-762.].

PMID: 27548453

Acta Ophthalmol. 2016 Aug 22. [Epub ahead of print]

Effect of intravitreal ranibizumab injection on aqueous humour cytokine levels in patients with diabetic macular oedema.

Shiraya T, Kato S, Araki F, Ueta T.

PMID: 27545866

Other Treatment and Diagnosis

J Med Signals Sens. 2016 Jul-Sep;6(3):166-71.

Three-dimensional Segmentation of Retinal Cysts from Spectral-domain Optical Coherence Tomography Images by the Use of Three-dimensional Curvelet Based K-SVD.

Esmaeili M, Dehnavi AM, Rabbani H, Hajizadeh F.

ABSTRACT: This paper presents a new three-dimensional curvelet transform based dictionary learning for automatic segmentation of intraretinal cysts, most relevant prognostic biomarker in neovascular age-related macular degeneration, from 3D spectral-domain optical coherence tomography (SD-OCT) images. In particular, we focus on the Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) system, and show the applicability of our algorithm in the segmentation of these features. For this purpose, we use recursive Gaussian filter and approximate the corrupted pixels from its surrounding, then in order to enhance the cystoid dark space regions and future noise suppression we introduce a new scheme in dictionary learning and take curvelet transform of filtered image then denoise and modify each noisy coefficients matrix in each scale with predefined initial 3D sparse dictionary. Dark pixels between retinal pigment epithelium and nerve fiber layer that were extracted with graph theory are considered as cystoid spaces. The average dice coefficient for the segmentation of cystoid regions in whole 3D volume and within central 3 mm diameter on the MICCAI 2015 OPTIMA Cyst Segmentation Challenge dataset were found to be 0.65 and 0.77, respectively.

PMID: 27563573

Retina. 2016 Aug 23. [Epub ahead of print]

DISCORDANCE BETWEEN BLUE-LIGHT AUTOFLUORESCENCE AND NEAR-INFRARED AUTOFLUORESCENCE IN AGE-RELATED MACULAR DEGENERATION.

Heiferman MJ, Fawzi AA.

PURPOSE: To identify the origin and significance of discordance between blue-light autofluorescence (BL-AF; 488 nm) and near-infrared autofluorescence (NI-AF; 787 nm) in patients with age-related macular degeneration (AMD).

METHODS: A total of 86 eyes of 59 patients with a diagnosis of AMD were included in this cross-sectional study conducted between March 9, 2015 and May 1, 2015. A masked observer examined the BL-AF, NI-AF, and spectral-domain optical coherence tomography images. Areas with discordance of autofluorescence patterns between NI-AF and BL-AF images were correlated with structural findings at the corresponding location in optical coherence tomography scans.

RESULTS: Seventy-nine eyes had discordance between BL-AF and NI-AF. The most common optical coherence tomography finding accounting for these discrepancies was pigment migration accounting for 35 lesions in 21 eyes. The most clinically relevant finding was geographic atrophy missed on BL-AF in 7 eyes.

CONCLUSION: Our findings indicate that variations in the distribution of lipofuscin, melanin and melanolipofuscin account for the majority of discordance between BL-AF and NI-AF. Given our finding of missed geographic atrophy lesions on BL-AF in 24% of eyes with geographic atrophy (7/29 eyes), clinicians should consider multimodal imaging, including NI-AF and optical coherence tomography, especially in clinical trials of geographic atrophy.

PMID: 27557087

Ophthalmic Surg Lasers Imaging Retina. 2016 Aug 1;47(8):778-81.

Diagnosis and Follow-Up of Nonexudative Choroidal Neovascularization With Multiple Optical Coherence Tomography Angiography Devices: A Case Report.

Lane M, Ferrara D, Louzada RN, Fujimoto JG, Seddon JM.

ABSTRACT: Nonexudative choroidal neovascularization (CNV) is a new phenomenon that has only recently been described in the literature with the advent of optical coherence tomography angiography (OCTA) imaging. The authors present a 1-year longitudinal follow-up of a nonexudative CNV lesion secondary to age-related macular degeneration. This report describes the appearance of the lesion on two commercially available spectral-domain OCTA devices and one prototype swept-source OCTA device. Management of these cases is still debatable. Watchful waiting with regular follow-up using serial OCTA to monitor disease progression has been valuable in this case. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:778-781.].

PMID: 27548457

Retina. 2016 Aug 22. [Epub ahead of print]

GEOGRAPHIC ATROPHY: Semantic Considerations and Literature Review.

Schmitz-Valckenberg S, Sadda S, Staurenghi G, Chew EY, Fleckenstein M, Holz FG; CAM (Classification of Atrophy Meeting)-Group.

PURPOSE: There is a lack of agreement regarding the types of lesions and clinical conditions that should be included in the term "geographic atrophy." Varied and conflicting views prevail throughout the literature and are currently used by retinal experts and other health care professionals.

METHODS: We reviewed the nominal definition of the term "geographic atrophy" and conducted a search of the ophthalmologic literature focusing on preceding terminologies and the first citations of the term "geographic atrophy" secondary to age-related macular degeneration.

RESULTS: According to the nominal definition, the term "geography" stands for a detailed description of the surface features of a specific region, indicating its relative position. However, it does not necessarily imply that the borders of the region must be sharply demarcated or related to any anatomical structures. The term "geographical areas of atrophy" was initially cited in the 1960s in the ophthalmologic literature in the context of uveitic eye disease and shortly thereafter also for the description of variants of "senile macular degeneration." However, no direct explanation could be found in the literature as to why the terms "geographical" and "geographic" were chosen. Presumably the terms were used as the atrophic regions resembled the map of a continent or well-defined country borders on thematic geographical maps. With the evolution of the terminology, the commonly used adjunct "of the retinal pigment epithelium" was frequently omitted and solely the term "geographic atrophy" prevailed for the nonexudative late-stage of age-related macular degeneration itself. Along with the quantification of atrophic areas, based on different imaging modalities and the use of both manual and semiautomated approaches, various and inconsistent definitions for the minimal lesion diameter or size of atrophic lesions have also emerged.

CONCLUSION: Reconsideration of the application of the term "geographic atrophy" in the context of age-

related macular degeneration seems to be prudent given ongoing advances in multimodal retinal imaging technology with identification of various phenotypic characteristics, and the observation of atrophy development in eyes under antiangiogenic therapy.

PMID: 27552292

Ophthalmic Surg Lasers Imaging Retina. 2016 Aug 1;47(8):708-15.

Hyperacuity Exam Screens for Choroidal Neovascularization in Age-Related Macular Degeneration on a Mobile Device.

Chen JS, Adelman RA.

BACKGROUND AND OBJECTIVE: Timely treatment of age-related macular degeneration (AMD) is integral in improving outcomes. To catch choroidal neovascularization as soon as possible, patients should monitor vision at home. The objective of this study is to explore the Hyperacuity App (HAC) as a screen for progression of disease in AMD.

PATIENTS AND METHODS: A cross-sectional, single-center study was performed with 33 subjects. Consent was obtained and patient information was protected in accordance with the protocol approved by the Yale Human Research Protection Program. A masked retinal subspecialist then graded the spectral-domain optical coherence tomography (SD-OCT) taken the same day to determine which patients required treatment. Further data about the patient were obtained through chart review.

RESULTS: The HAC was shown to have 92.3% sensitivity and 61.5% specificity in distinguishing between patients who required treatment and those who did not require treatment.

CONCLUSION: The HAC is a potential screen for choroidal neovascularization in AMD.

PMID: 27548447

Invest Ophthalmol Vis Sci. 2016 Aug 1;57(10):4315-20.

Association of Hyperreflective Foci Present in Early Forms of Age-Related Macular Degeneration With Known Age-Related Macular Degeneration Risk Polymorphisms.

Altay L, Scholz P, Schick T, Felsch M, Hoyng CB, den Hollander AI, Langmann T, Fauser S.

PURPOSE: We evaluated the association of hyperreflective foci (HF) observed in early and intermediate age-related macular degeneration (AMD) with known AMD risk alleles.

METHODS: In this pilot case-control study, HF were defined as lesions with reflectivity equal or higher than the retinal pigment epithelium band in spectral domain optical coherence tomography (SDOCT). Hyperreflective foci in the outer nuclear layer and photoreceptor complex were evaluated in 518 individuals with early and intermediate AMD. Definite presence of HF was defined as at least 10 HF in all SDOCT scans. Genotyping was performed for 22 single nucleotide polymorphisms (SNPs). Associations between AMD severity stages, HF, and SNPs were determined by logistic regression analyses.

RESULTS: Hyperreflective foci (n ≥ 10) were significantly associated with AMD severity and the association was strongest with intermediate AMD (odds ratio [OR], 8.45; P = 1.092*10-8). Independently, HF showed associations with ARMS2 rs104909/HtRA1 rs11200638 (OR, 1.64; P = 0.017), CFH rs1061170 (OR, 1.70; P = 0.011), and APOE4/TOMM40 rs2075650 (OR, 2.26; P = 0.005) variants. Within the group of intermediate AMD, associations were similar (ARMS2 rs104909/HtRA1 rs11200638 OR, 1.79, P = 0.010; CFH rs1061170 OR, 1.77, P = 0.013; APOE4/TOMM40 rs2075650 OR, 1.98; P = 0.034) and showed additional trending associations with VEGFA rs943080 variant (OR, 0.59; P = 0.024). After Bonferroni-correction for 22 SNPs, none of the associations was statistically significant (P ≤ 0.0023).

CONCLUSIONS: The presence of HF is related to AMD severity. Despite limited power of this pilot study,

our results suggest an association of HF with polymorphisms in ARMS2/HTRA1, CFH, APOE4/TOMM40, and VEGFA genes which could be triggered by modification of the extracellular matrix, altered complement system or lipid metabolism.

PMID: 27552409

Epidemiology

Acta Ophthalmol. 2016 Aug 22. [Epub ahead of print]

Reduced occurrence of severe visual impairment after introduction of anti-Vascular Endothelial Growth Factor in wet age-related macular degeneration - a population- and register-based study from northern Sweden.

Granstam E, Westborg I, Barkander A, Börjesson M, Lindahl S, Meszaros E, Wojciechowska-Zajac A, Wagner P, Albrecht S, Karlsson N, Bjärnhall G, Lövestam-Adrian M.

PURPOSE: To study the occurrence of severe visual impairment (SVI) and treatment outcome at 12 months in patients treated for wet age-related macular degeneration (AMD) by use of data from the Swedish Macula Register (SMR) and referrals to the regional low vision clinics in five northern counties.

METHODS: Referrals to low vision clinics during 2005, 2009 and 2013 and treatment outcome at 12 months from the SMR database from 2008 until 2013 in patients >65 years of age in five northern counties were included in the survey.

RESULTS: The rate of referral due to AMD was significantly reduced during the time period (-48%; $p < 0.001$). At 12 months, a significant slight mean improvement in logMAR visual acuity (VA) was observed (-0.01, SD 0.37; $p < 0.001$) after a mean of 5.0 ± 2.3 anti-vascular endothelial growth factor (VEGF)-injections were administered. Age and low baseline VA was associated with less favourable visual outcome ($p < 0.001$).

CONCLUSION: Referral rate to low vision clinic is a valuable tool for estimating occurrence of SVI and fell between the years 2005 until 2013. Data from the SMR showed improvement in visual acuity on the whole, but also identified patients at high risk for developing SVI during anti-VEGF-treatment.

PMID: 27545047

Pathogenesis

Prog Retin Eye Res. 2016 Aug 23. [Epub ahead of print]

Autophagy in the eye: Development, degeneration, and aging.

Boya P, Esteban-Martínez L, Serrano-Puebla A, Gómez-Sintes R, Villarejo-Zori B.

ABSTRACT: Autophagy is a catabolic pathway that promotes the degradation and recycling of cellular components. Proteins, lipids, and even whole organelles are engulfed in autophagosomes and delivered to the lysosome for elimination. In response to stress, autophagy mediates the degradation of cell components, which are recycled to generate the nutrients and building blocks required to sustain cellular homeostasis. Moreover, it plays an important role in cellular quality control, particularly in neurons, in which the total burden of altered proteins and damaged organelles cannot be reduced by redistribution to daughter cells through cell division. Research has only begun to examine the role of autophagy in the visual

system. The retina, a light-sensitive tissue, detects and transmits electrical impulses through the optic nerve to the visual cortex in the brain. Both the retina and the eye are exposed to a variety of environmental insults and stressors, including genetic mutations and age-associated alterations that impair their function. Here, we review the main studies that have sought to explain autophagy's importance in visual function. We describe the role of autophagy in retinal development and cell differentiation, and discuss the implications of autophagy dysregulation both in physiological aging and in important diseases such as age-associated macular degeneration and glaucoma. We also address the putative role of autophagy in promoting photoreceptor survival and discuss how selective autophagy could provide alternative means of protecting retinal cells. The findings reviewed here underscore the important role of autophagy in maintaining proper retinal function and highlight novel therapeutic approaches for blindness and other diseases of the eye.

PMID: 27566190

Exp Eye Res. 2016 Aug 23. [Epub ahead of print]

AMD-like retinopathy associated with intravenous iron.

Song D, Kanu LN, Li Y, Kelly KL, Bhuyan RK, Aleman T, Morgan JI, Dunaief JL.

ABSTRACT: Iron accumulation in the retina is associated with the development of age-related macular degeneration (AMD). IV iron is a common method to treat iron deficiency anemia in adults, and its retinal manifestations have not hitherto been identified. To assess whether IV iron formulations can be retina-toxic, we generated a mouse model for iron-induced retinal damage. Male C57BL/6J mice were randomized into groups receiving IV iron-sucrose (+Fe) or 30% sucrose (-Fe). Iron levels in neurosensory retina (NSR), retinal pigment epithelium (RPE), and choroid were assessed using immunofluorescence, quantitative PCR, and the Perls' iron stain. Iron levels were most increased in the RPE and choroid while levels in the NSR did not differ significantly in +Fe mice compared to controls. Eyes from +Fe mice shared histological features with AMD, including Bruch's membrane (BrM) thickening with complement C3 deposition, as well as RPE hypertrophy and vacuolization. This focal degeneration correlated with areas with high choroidal iron levels. Ultrastructural analysis provided further detail of the RPE/photoreceptor outer segment vacuolization and Bruch's membrane thickening. Findings were correlated with a clinical case of a 43-year-old patient who developed numerous retinal drusen, the hallmark of AMD, within 11 months of IV iron therapy. Our results suggest that IV iron therapy may have the potential to induce or exacerbate a form of retinal degeneration. This retinal degeneration shares features with AMD, indicating the need for further study of AMD risk in patients receiving IV iron treatment.

PMID: 27565570

J Ophthalmol. 2016;2016:2913612. Epub 2016 Aug 1.

Cellular and Molecular Pathology of Age-Related Macular Degeneration: Potential Role for Proteoglycans.

Al Gwairi O, Thach L, Zheng W, Osman N, Little PJ.

ABSTRACT: Age-related macular degeneration (AMD) is a retinal disease evident after the age of 50 that damages the macula in the centre of retina. It leads to a loss of central vision with retained peripheral vision but eventual blindness occurs in many cases. The initiation site of AMD development is Bruch's membrane (BM) where multiple changes occur including the deposition of plasma derived lipids, accumulation of extracellular debris, changes in cell morphology, and viability and the formation of drusen. AMD manifests as early and late stage; the latter involves cell proliferation and neovascularization in wet AMD. Current therapies target the later hyperproliferative and invasive wet stage whilst none target early developmental stages of AMD. In the lipid deposition disease atherosclerosis modified proteoglycans bind and retain apolipoproteins in the artery wall. Chemically modified trapped lipids are immunogenic and can initiate a chronic inflammatory process manifesting as atherosclerotic plaques and subsequent artery blockages,

heart attacks, or strokes. As plasma derived lipoprotein deposits are found in BM in early AMD, it is possible that they arise by a similar process within the macula. In this review we consider aspects of the pathological processes underlying AMD with a focus on the potential role of modifications to secreted proteoglycans being a cause and therefore a target for the treatment of early AMD.

PMID: 27563459

Clin Exp Optom. 2016 Aug 25. [Epub ahead of print]

Bilateral choroidal neovascularisation associated with adult-onset foveomacular vitelliform dystrophy.

Au CP, Pandya VB, Mitchell P.

PMID: 27558081

Cell Death Discov. 2016 Jul 4;2:16054. eCollection 2016.

Retinal pigment epithelial cell necroptosis in response to sodium iodate.

Hanus J, Anderson C, Sarraf D, Ma J, Wang S.

ABSTRACT: Age-related macular degeneration (AMD) is a degenerative disease of the retina and the leading cause of blindness in the elderly in developed countries. The late stage of dry AMD, or geographic atrophy (GA), is characterized by extensive retinal pigment epithelium (RPE) degeneration. The underlying molecular mechanism for RPE cell death in GA remains unclear. Our previous study has established that RPE cells die predominantly from necroptosis in response to oxidative stress in vitro. Here, we extend our study and aim to characterize the nature of RPE cell death in response to sodium iodate (NaIO3) in vitro and in a NaIO3-induced retina degeneration mouse model. We found that NaIO3 induces RPE necroptosis in vitro by using a combination of molecular hallmarks. By using TUNEL assays, active caspase-3 and HMGB1 immunostaining, we confirmed that photoreceptor cells die mainly from apoptosis and RPE cells die mainly from necroptosis in response to NaIO3 in vivo. RPE necroptosis in this model is also supported by use of the RIPK1 inhibitor, Necrostatin-1. Furthermore, using novel RIPK3-GFP transgenic mouse lines, we detected RIPK3 aggregation, a hallmark of necroptosis, in the RPE cells in vivo after NaIO3 injection. Our findings suggest the necessity of re-evaluating RPE cell death mechanism in AMD models and have the potential to influence therapeutic development for dry AMD, especially GA.

PMID: 27551542

Front Neurol. 2016 Aug 8;7:127. eCollection 2016.

Amyloidosis in Retinal Neurodegenerative Diseases.

Masuzzo A, Dinet V, Cavanagh C, Mascarelli F, Krantic S.

ABSTRACT: As a part of the central nervous system, the retina may reflect both physiological processes and abnormalities related to pathologies that affect the brain. Amyloidosis due to the accumulation of amyloid-beta (Aβ) was initially regarded as a specific and exclusive characteristic of neurodegenerative alterations seen in the brain of Alzheimer's disease (AD) patients. More recently, it was discovered that amyloidosis-related alterations, similar to those seen in the brain of Alzheimer's patients, also occur in the retina. Remarkably, these alterations were identified not only in primary retinal pathologies, such as age-related macular degeneration (AMD) and glaucoma, but also in the retinas of Alzheimer's patients. In this review, we first briefly discuss the biogenesis of Aβ, a peptide involved in amyloidosis. We then discuss some pathological aspects (synaptic dysfunction, mitochondrial failure, glial activation, and vascular

abnormalities) related to the neurotoxic effects of Aβ. We finally highlight common features shared by AD, AMD, and glaucoma in the context of Aβ amyloidosis and further discuss why the retina, due to the transparency of the eye, can be considered as a "window" to the brain.

PMID: 27551275

Retin Cases Brief Rep. 2016 Aug 19. [Epub ahead of print]

RETINAL VEIN OCCLUSION IN A PATIENT WITH MATERNALLY INHERITED DIABETES AND DEAFNESS.

Sanfilippo CJ, Prasad P, Sarraf D.

PURPOSE: To report a case of maternally inherited diabetes and deafness complicated by branch retinal vein occlusion and cystoid macular edema.

METHODS: Retrospective case report. Multimodal imaging including spectral domain optical coherence tomography, en face optical coherence tomography, and fundus autofluorescence was preformed, and the findings are presented.

FINDINGS: A 58-year-old female with a history of diabetes mellitus, hearing loss, and a previous diagnosis of age-related macular degeneration presented with decreased vision in the right eye. Clinical examination and multimodal imaging demonstrated a right inferior branch retinal vein occlusion complicated by cystoid macular edema and bilateral maculopathy suspicious for maternally inherited diabetes and deafness. Genetic testing confirmed an A3243G mitochondrial mutation.

CONCLUSION: Multimodal retinal imaging is a key to guide diagnosis of rare genetic diseases such as maternally inherited diabetes and deafness. We report the unusual presentation of maternally inherited diabetes and deafness complicated by branch retinal vein occlusion and cystoid macular edema.

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Stem Cells

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Directing Differentiation of Pluripotent Stem Cells Toward Retinal Pigment Epithelium Lineage.

Choudhary P, Booth H, Gutteridge A, Surmacz B, Louca I, Steer J, Kerby J, Whiting PJ.

ABSTRACT: Development of efficient and reproducible conditions for directed differentiation of pluripotent stem cells into specific cell types is important not only to understand early human development but also to enable more practical applications, such as in vitro disease modeling, drug discovery, and cell therapies. The differentiation of stem cells to retinal pigment epithelium (RPE) in particular holds promise as a source of cells for therapeutic replacement in age-related macular degeneration. Here we show development of an efficient method for deriving homogeneous RPE populations in a period of 45 days using an adherent, monolayer system and defined xeno-free media and matrices. The method utilizes sequential inhibition and activation of the Activin and bone morphogenetic protein signaling pathways and can be applied to both human embryonic stem cells and induced pluripotent stem cells as the starting population. In addition, we use whole genome transcript analysis to characterize cells at different stages of differentiation that provides further understanding of the developmental dynamics and fate specification of RPE. We show that with the described method, RPE develop through stages consistent with their formation during embryonic development. This characterization- together with the absence of steps involving embryoid bodies, three-dimensional culture, or manual dissections, which are common features of other protocols-makes this

process very attractive for use in research as well as for clinical applications.

SIGNIFICANCE: This report describes a novel method of directed differentiation to generate retinal pigment epithelium (RPE) cells from pluripotent stem cells. The employed method is based on adherent monolayer culture using xeno-free conditions and manipulation of the Activin and bone morphogenetic protein signaling pathway using small molecules and recombinant proteins. Whole genome microarray analysis was performed to characterize the differentiation process and understand the developmental path of RPE generation in vitro. This method can be applied for generation of RPE for research as well as for clinical applications.

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Laminin modification subretinal bio-scaffold remodels retinal pigment epithelium-driven microenvironment in vitro and in vivo.

Peng CH, Chuang JH, Wang ML, Jhan YY, Chien KH, Chung YC, Hung KH, Chang CC, Lee CK, Tseng WL, Hwang DK, Hsu CH, Lin TC, Chiou SH, Chen SJ.

ABSTRACT: Advanced age-related macular degeneration (AMD) may lead to geographic atrophy or fibrovascular scar at macular, dysfunctional retinal microenvironment, and cause profound visual loss. Recent clinical trials have implied the potential application of pluripotent cell-differentiated retinal pigment epithelial cells (dRPEs) and membranous scaffolds implantation in repairing the degenerated retina in AMD. However, the efficacy of implanted membrane in immobilization and supporting the viability and functions of dRPEs, as well as maintaining the retinal microenvironment is still unclear. Herein we generated a biomimetic scaffold mimicking subretinal Bruch's basement from plasma modified polydimethylsiloxane (PDMS) sheet with laminin coating (PDMS-PmL), and investigated its potential functions to provide a subretinal environment for dRPE-monolayer grown on it. Firstly, compared to non-modified PDMS, PDMS-PmL enhanced the attachment, proliferation, polarization, and maturation of dRPEs. Second, PDMS-PmL increased the polarized tight junction, PEDF secretion, melanosome pigment deposit, and phagocytotic-ability of dRPEs. Third, PDMS-PmL was able to carry a dRPEs/photoreceptor-precursors multilayer retina tissue. Finally, the in vivo subretinal implantation of PDMS-PmL in porcine eyes showed well-biocompatibility up to 2-year follow-up. Notably, multifocal ERGs at 2-year follow-up revealed well preservation of macular function in PDMS-PmL, but not PDMS, transplanted porcine eyes. Trophic PEDF secretion of macular retina in PDMS-PmL group was also maintained to preserve retinal microenvironment in PDMS-PmL eyes at 2 year. Taken together, these data indicated that PDMS-PmL is able to sustain the physiological morphology and functions of polarized RPE monolayer, suggesting its potential of rescuing macular degeneration in vivo.

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Diet, Lifestyle, and Low Vision

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Vision impairment and major eye diseases reduce vision-specific emotional well-being in a Chinese population.

Fenwick EK, Ong PG, Man RE, Sabanayagam C, Cheng CY, Wong TY, Lamoureux EL.

AIMS: To assess the relationship between vision impairment (VI) and major eye diseases, with vision-specific emotional well-being in a Chinese population.

METHODS: In this population-based cross-sectional study, 3353 Chinese participants aged 40-80 years answered the emotional well-being scale of the Impact of Vision Impairment questionnaire, validated using Rasch analysis. Participants underwent visual acuity testing and collection of sociodemographic and medical data from standardised questionnaires. The relationships between presenting bilateral VI, presence of major eye diseases (cataract, undercorrected refractive error, glaucoma, age-related macular degeneration and diabetic retinopathy) and emotional well-being were assessed using linear regression models. Stratified analyses for age, gender, education and immigration status were conducted to determine if change in β coefficients differed within each stratum.

RESULTS: Approximately half of patients (n=1805) had normal vision, and 43% (n=1534) and 3.4% (n=114) had moderate and severe bilateral VI, respectively. Vision-specific emotional well-being systematically worsened as severity of bilateral VI increased (p<0.001). Compared with no VI and no eye diseases, respectively, severe bilateral VI (23%; β -1.84; 95% CI -2.23 to -1.43) and glaucoma (β -1.88; 95% CI -3.00 to -0.76) were associated with a clinically meaningful reduction in emotional well-being. The reduction in vision-related emotional well-being was substantially and significantly greater in men compared with women (p<0.05).

CONCLUSIONS: Severe VI and glaucoma are associated with substantial decrements in vision-specific emotional well-being, highlighting the importance of preventing progression of vision loss. Evidence-based interventions to improve vision-related coping skills and emotional management for patients with severe VI and glaucoma are warranted.

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Health Econ Rev. 2015 Dec;6(1):37. Epub 2016 Aug 26.

Financial burden and quality of life of informal caregivers of patients with wet age-related macular degeneration.

Weyer-Wendl H, Walter P.

PURPOSE: The purpose of this research is to quantify the cost burden, care times and the impact on the quality of life (QoL) of informal caring relatives caring for patients with wet age-related macular degeneration (wet AMD). Moreover we investigated the impact of care times on the QoL.

METHODS: Through a specifically designed questionnaire, 150 caring relatives were interviewed retrospectively on all accrued financial costs, caring times incurred and the current QoL, assessed by a Visual Analogue Scale for happiness (VAS).

RESULTS: The caring time incurred was on average 6.4 ± 8.5 (mean +/- SD) hours per week. The QoL was on average rated at 6.7 ± 1.9 on a ten point scale. Financial strain was incurred by the direct non-medical costs of on average € 405 ± 1104 and the direct medical costs of on average € 134 ± 340 per year. Indirect costs were stated by two caregivers as amounting to € 2400 and € 6000 net income loss per year respectively. Caregivers of privately insured patients with wet AMD carried a financial cost burden which was up to six times higher than caregivers of patients who were on state insurance while showing the same visual acuity.

CONCLUSION: The evaluation shows that caregivers of privately insured patients with wet AMD have higher costs than caregivers of patients with state insurance coverage. This burden seems to be a factor to be considered independently since it does not appear to have any relation to patients AMD acuity.

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Educating smokers about the risk of blindness - insights to improve tobacco product health warning labels.

Kennedy RD, Hammond D, Spafford MM, Douglas O, Brûlé J, Fong GT, Schultz AS.

BACKGROUND: Health warning labels (HWL) on tobacco products help educate smokers about the health effects from smoking; however, there is a need to improve HWL content including images and text to increase effectiveness. In Canada, a HWL was created that communicates smoking's causal association with "blindness" from age-related macular degeneration (AMD). This study surveyed Canadian optometrists about their opinions regarding the image and text used in the "blindness" HWL.

METHODS: An online survey was sent to all 4528 registered Canadian optometrists. Respondents were asked if the HWL conveyed important and believable information, and if the picture was appropriate. Optometrists were invited to make open-ended comments about the label which were analyzed using a qualitative analysis framework suitable for health policy evaluation. Frequency distributions were calculated for closed-ended questions.

RESULTS: The survey was completed by 850 respondents (19 %). Most respondents (90 %) reported the message was believable/somewhat believable; while 35 % felt the picture was "too graphic". Some respondents reported in their open-ended comments that they were concerned the HWL was internally inconsistent because it reports there is "no effective treatment in most cases" for AMD but the image depicts someone undergoing surgery. There was concern that this may discourage patients from seeking needed treatment.

CONCLUSION: The majority of Canadian optometrist respondents were in agreement that the new, "RISK OF BLINDNESS" pictorial HWL includes important, believable information. Some optometrists had concerns that the HWL included a confusing message or a message that may discourage some patients from pursuing treatment for AMD. Future development of blindness-related HWL should seek practitioner input.

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