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MD Research News

Issue 267

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Drug treatment

Br J Ophthalmol. 2016 Feb 17. [Epub ahead of print]

Clinical correlation to differences in ranibizumab and aflibercept vascular endothelial growth factor suppression times.

Fauser S, Muether PS.

AIM: To determine clinical correlations to intraocular vascular endothelial growth factor A (VEGF-A) suppression times (VSTs) on the treatment of neovascular age-related macular degeneration (nAMD) with ranibizumab (Lucentis) or aflibercept (Eylea).

METHODS: Seven of 89 treatment-naïve nAMD eyes showed persistent choroidal neovascular membrane (CNV) activity throughout a spectral domain optical coherence tomography (SD-OCT)-driven pro re nata (PRN) regimen of intravitreal ranibizumab injections over 28±4 months. The treatment was switched to PRN aflibercept injections and patients were followed for another 15±2 months. A total of 160 aqueous humour specimens were collected before the intravitreal injections, and their VEGF-A concentrations were assayed by Luminex multiplex bead analysis (Luminex, Austin, Texas, USA). Intraocular VEGF-A concentrations were correlated to CNV activity shown by SD-OCT.

RESULTS: The mean duration of suppression of VEGF-A concentrations in aqueous humour below the lower limit of quantification of our assay was 34±5 (26-69) days for ranibizumab and 67±14 (49-89) days for aflibercept ($p<0.001$). The percentual reduction of central retinal volume (CRV) 6 weeks after injection was higher for aflibercept compared with ranibizumab ($p=0.009$). The time point of clinical re-activity occurred about 50% earlier than the respective VST for each ranibizumab and aflibercept.

CONCLUSIONS: The VST under aflibercept treatment exceeded that under ranibizumab treatment by a factor of 2. This difference correlated with differential clinical CRV reduction 6 weeks after the respective injection. For both medications, clinical activity was found at a time point as early as 50% of the individual VST.

PMID: 26888975 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Feb 17.[Epub ahead of print]

Individualized Ranibizumab Regimen Driven by Stabilization Criteria for Central Retinal Vein Occlusion: Twelve-Month Results of the CRYSTAL Study.

Larsen M, Waldstein SM, Boscia F, Gerding H, Monés J, Tadayoni R, Priglinger S, Wenzel A, Barnes E, Pilz S, Stubbings W, Pearce I; CRYSTAL Study Group.

PURPOSE: To assess the 12-month efficacy and safety profile of an individualized regimen of ranibizumab

0.5 mg driven by stabilization criteria in patients with macular edema secondary to central retinal vein occlusion (CRVO).

DESIGN: A 24-month, prospective, open-label, single-arm, multicenter study.

PARTICIPANTS: Three hundred fifty-seven patients.

METHODS: Patients were treated with monthly ranibizumab 0.5-mg injections (minimum of 3 injections) until stable visual acuity (VA) was maintained for 3 consecutive months. Thereafter, ranibizumab 0.5 mg was dosed as needed if monthly monitoring indicated a loss of VA resulting from disease activity.

MAIN OUTCOME MEASURES: Mean change from baseline at month 12 in best-corrected VA (BCVA; primary end point) and safety over 12 months. The efficacy of this regimen in subgroups categorized by baseline BCVA score, CRVO duration, or presence of macular ischemia (exploratory analysis).

RESULTS: At baseline, the mean BCVA was 53.0 letters and mean CRVO duration was 8.9 months (median, 2.4 months). Ranibizumab 0.5-mg treatment resulted in a statistically significant mean gain in BCVA from baseline at month 12 of 12.3 letters (standard deviation [SD], 16.72 letters; $P < 0.0001$). The mean number of ranibizumab injections up to month 12 was 8.1 (SD, 2.77). At month 12, mean BCVA gains were similar with or without macular ischemia at baseline (11.6 vs. 12.1 letters); the mean BCVA gain was higher with baseline CRVO duration of less than 3 months (13.4 letters) than with a longer duration (≥3 -<9 months, 11.1 letters; ≥9 months, 10.9 letters). Patients with lower baseline BCVA had larger mean BCVA gains at month 12 than those with higher baseline BCVA (≤39/40-59/≥60 and 18.0/12.7/8.9 letters, respectively), although the absolute BCVA at month 12 was higher with higher baseline BCVA. No new ocular or nonocular safety events were observed.

CONCLUSIONS: An individualized dosing regimen of ranibizumab 0.5 mg driven by stabilization criteria for up to 12 months resulted in significant BCVA gain in a broad population of patients with macular edema secondary to CRVO, including those with macular ischemia at baseline. The safety findings were consistent with those reported in previous ranibizumab studies in patients with CRVO.

PMID: 26896124 [PubMed - as supplied by publisher]

J Med Econ. 2016 Feb 16:1-20. [Epub ahead of print]

Cost-Effectiveness of Ranibizumab in the Treatment of Visual Impairment Due to Diabetic Macular Edema.

Haig J, Barbeau M, Ferreira A.

OBJECTIVE: Ranibizumab, an anti-vascular endothelial growth factor designed for ocular use, has been deemed cost-effective in multiple indications by several Health Technology Assessment bodies. This study assessed the cost-effectiveness of ranibizumab monotherapy or combination therapy (ranibizumab plus laser photocoagulation) compared with laser monotherapy for the treatment of visual impairment due to diabetic macular edema (DME).

METHODS: A Markov model was developed in which patients moved between health states defined by best-corrected visual acuity (BCVA) intervals and an absorbing 'death' state. The population of interest was patients with DME due to type 1 or type 2 diabetes mellitus. Baseline characteristics were based on those of participants in the RESTORE study. Main outputs were costs (in 2013 CA$) and health outcomes (in quality-adjusted life-years [QALYs]) and the incremental cost-effectiveness ratio (ICER) was calculated. This cost-utility analysis was conducted from healthcare system and societal perspectives in Quebec.

RESULTS: From a healthcare system perspective, the ICERs for ranibizumab monotherapy and combination therapy versus laser monotherapy were CA$24,494 and CA$36,414 per QALY gained, respectively. The incremental costs per year without legal blindness for ranibizumab monotherapy and combination therapy versus laser monotherapy were CA$15,822 and CA$20,616, respectively. Based on

the generally accepted Canadian ICER threshold of CA$50,000 per QALY gained, ranibizumab monotherapy and combination therapy were found to be cost-effective compared with laser monotherapy. From a societal perspective, ranibizumab monotherapy and combination therapy provided greater benefits at lower costs than laser monotherapy (ranibizumab therapy dominated laser therapy).

CONCLUSIONS: Ranibizumab monotherapy and combination therapy resulted in increased quality-adjusted survival and time without legal blindness, and lower costs from a societal perspective compared with laser monotherapy.

PMID: 26882365 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Feb 10. [Epub ahead of print]

A Crossover Design for Comparative Efficacy: A 36-Week Randomized Trial of Bevacizumab and Ranibizumab for Diabetic Macular Edema.

Wiley HE, Thompson DJ, Bailey C, Chew EY, Cukras CA, Jaffe GJ, Lee RW, Loken EK, Meyerle CB, Wong W, Ferris FL 3rd.

PURPOSE: To investigate the comparative efficacy of bevacizumab (Avastin) and ranibizumab (Lucentis; both Genentech, Inc, South San Francisco, CA) for diabetic macular edema (DME) using a crossover study design.

DESIGN: Randomized, double-masked, 36-week, 3-period crossover clinical trial.

PARTICIPANTS: Fifty-six subjects with DME involving the center of the macula in one or both eyes.

METHODS: Monthly intravitreous injections of bevacizumab (1.25 mg) or ranibizumab (0.3 mg).

MAIN OUTCOME MEASURES: Comparison of mean changes in visual acuity and central retinal thickness, tested using a linear mixed-effects model.

RESULTS: Based on the linear mixed-effects model, the 3-month estimated mean improvement in visual acuity was 5.3 letters for bevacizumab and 6.6 letters for ranibizumab (difference, 1.3 letters; P = 0.039). Estimated change in optical coherence tomography (OCT) central subfield mean thickness (CSMT) was -89 μm for bevacizumab and -137 μm for ranibizumab (difference, 48 μm; P < 0.001). Incorporating cumulative treatment benefit, the model yielded a predicted 36-week (9-month) average improvement in visual acuity of 7.1 letters (95% confidence interval [CI], 5.0-9.2) for bevacizumab and 8.4 letters (95% CI, 6.3-10.5) for ranibizumab, and a change in OCT CSMT of -128 μm (95% CI, -155 to -100) for bevacizumab and -176 μm (95% CI, -202 to -149) for ranibizumab. There was no significant treatment-by-period interaction (i.e., treatment difference was constant in all 3 periods), nor was there a significant differential carryover effect from one period to the next.

CONCLUSIONS: This trial demonstrated a statistically significant but small relative clinical benefit of ranibizumab compared with bevacizumab for treatment of DME, using a markedly reduced sample size relative to a full comparative efficacy study. The effects on visual acuity and central retinal thickness for the 2 drugs are consistent with those reported at 1 year for the concurrent parallel-group trial by the Diabetic Retinopathy Clinical Research Network testing bevacizumab, ranibizumab, and aflibercept for DME. The 3-period crossover design allowed for meaningful and efficient comparison, suggesting that this approach may be useful for future comparative efficacy studies of anti-vascular endothelial growth factor drugs for DME.

PMID: 26875003 [PubMed - as supplied by publisher]

Other treatment & diagnosis

PLoS One. 2016 Feb 19;11(2):e0149030.

Pseudodrusen in the Fellow Eye of Patients with Unilateral Neovascular Age-Related Macular Degeneration: A Meta-Analysis.

Zhou Q, Shaffer J, Ying GS.

IMPORTANCE: The fellow eye of patients with unilateral neovascular age-related degeneration (nAMD) is at increased risk of developing late AMD. Several cohort studies have evaluated the prevalence of pseudodrusen and the association between pseudodrusen and late AMD in the fellow eye of patients with unilateral nAMD. However, these studies have limited sample sizes and their results are inconsistent.

OBJECTIVE: To evaluate the prevalence rate of pseudodrusen, and the association between pseudodrusen and incidence of late AMD (nAMD and geographic atrophy (GA)) in the fellow eye of patients with unilateral nAMD.

DATA SOURCES: The PubMed, EMBASE, Web of Science, and Cochrane Library databases were searched up to July 2015, as well as other systematic reviews.

STUDY SELECTION: All cohort studies for pseudodrusen with late AMD in the fellow eye of patients with unilateral nAMD.

DATA EXTRACTION AND SYNTHESIS:

The numbers of patients with and without pseudodrusen at baseline and the numbers of incident nAMD and GA during follow up among patients with and without pseudodrusen were independently extracted by 2 authors. The results were pooled using random-effects meta-analysis. Heterogeneity was assessed using the I2 test.

MAIN OUTCOME MEASURES: Prevalence rate of pseudodrusen, risk ratios (RRs) and their 95% confidence intervals (95% CIs) for associations between pseudodrusen and the incidence of nAMD and GA in the fellow eye.

RESULTS: Five cohort studies (N = 677 patients) from 8 countries across 4 continents were included. The pooled prevalence rate of pseudodrusen in the fellow eye was 48.1% (95% CI: 36.7-59.5%, I2 = 87%). Pseudodrusen were associated with an increased risk of nAMD (RR = 1.54, 95% CI: 1.10-2.16, I2 = 42%), GA (RR = 4.70, 95% CI: 1.22-18.1, I2 = 64%), and late AMD (RR = 2.03, 95% CI: 1.35-3.06, I2 = 60%).

CONCLUSIONS: For patients with unilateral nAMD, pseudodrusen were present in about half of the fellow eyes. The presence of pseudodrusen was associated with a 1.5 times higher risk of developing nAMD, a 4.7 times higher risk of developing GA, and a 2 times higher risk of developing late AMD. Pseudodrusen should be considered in evaluating the risk of late AMD development; however, due to considerable heterogeneity across these studies, a larger study is needed to validate these findings.

PMID: 26895455 [PubMed - as supplied by publisher] Free full text

Ophthalmology. 2016 Feb 12. [Epub ahead of print]

Optical Coherence Tomography Angiography of Asymptomatic Neovascularization in Intermediate Age-Related Macular Degeneration.

Roisman L, Zhang Q, Wang RK, Gregori G, Zhang A, Chen CL, Durbin MK, An L, Stetson PF, Robbins G, Miller A, Zheng F, Rosenfeld PJ.

PURPOSE: To determine whether angiography with swept-source (SS) optical coherence tomography (OCT) identifies subclinical type 1 neovascularization in asymptomatic eyes with intermediate age-related

macular degeneration (iAMD).

DESIGN: Prospective, observational, consecutive case series.

PARTICIPANTS: Patients with asymptomatic iAMD in one eye and neovascular age-related macular degeneration (AMD) in their fellow eye.

METHODS: The patients underwent SS OCT angiography (OCTA), fluorescein angiography (FA), and indocyanine green angiography (ICGA), and the images from these 3 angiographic techniques were compared.

MAIN OUTCOME MEASURES: Identification of subclinical type 1 neovascularization with SS OCTA in asymptomatic eyes with iAMD.

RESULTS: Eleven consecutive patients with iAMD in one eye and neovascular AMD in their fellow eye were imaged with FA, ICGA, and SS OCTA between August 2014 and September 2015. Clinical examination of the 11 eyes revealed drusen and pigmentary abnormalities in the central macula and no evidence of macular fluid on routine OCT imaging. Ten of the 11 eyes had no evidence of leakage on FA and 1 eye had questionable fluorescein leakage. Indocyanine green angiography revealed the presence of central macular plaques in 3 of the 11 asymptomatic eyes with iAMD, and SS OCTA revealed unambiguous type 1 neovascularization corresponding to the plaques in all 3 eyes. Optical coherence tomography angiography did not identify neovascularization in the remaining 8 eyes.

CONCLUSIONS: Swept-source OCTA identified type 1 neovascularization corresponding to ICGA plaques in asymptomatic eyes with iAMD. The ability of OCTA to provide noninvasive, fast, detailed, depth-resolved identification of nonexudative neovascular lesions in eyes with iAMD suggests the need for a new classification system that distinguishes between neovascular and nonneovascular iAMD.

PMID: 26876696 [PubMed - as supplied by publisher]

Clin Exp Optom. 2016 Jan;99(1):56-60.

Self-recognition of recurrences among patients with exudative age-related macular degeneration.

Kim JH, Chang YS, Kim JW, Lee DW, Han JI, Kim CG.

PURPOSE: The aim was to investigate factors influencing a patient's self-recognition of the recurrence of exudative changes secondary to age-related macular degeneration (AMD).

METHODS: In this retrospective study, we reviewed medical records for patients with exudative AMD who were diagnosed with a recurrence of exudation. Various parameters were compared, including age, sex, diagnosis, spectacle use, visual acuity before and after the recurrence and the extent of the decrease in visual acuity. In addition, visual acuity and unaided vision before the recurrence were compared in patients who did not use eyeglasses.

RESULTS: Forty-eight eyes from 48 patients were included in the analysis. Twenty-seven patients (56.3 per cent) identified a decrease in visual acuity. These patients had better visual acuity before the recurrence ($p = 0.023$) and reported a greater decrease in visual acuity ($p = 0.005$) than patients who did not identify a visual change. Patients who wore spectacles were also more likely to notice the change in their visual acuity ($p = 0.027$). Visual acuity was significantly better than uncorrected vision ($p < 0.001$).

CONCLUSIONS: Patients who do not use eyeglasses or who have relatively poor vision tend not to promptly recognise visual deterioration caused by the recurrence of exudation. Prescribing eyeglasses may facilitate accurate self-recognition of the recurrence of exudation in cases where vision can be improved with correction.

PMID: 26875854 [PubMed - in process]

Ophthalmology. 2016 Feb 10. [Epub ahead of print]

Prevalence of Subretinal Drusenoid Deposits in Older Persons with and without Age-Related Macular Degeneration, by Multimodal Imaging.

Zarubina AV, Neely DC, Clark ME, Huisingh CE, Samuels BC, Zhang Y, McGwin G Jr, Owsley C, Curcio CA.

PURPOSE: To assess the prevalence of subretinal drusenoid deposits (SDD) in older adults with healthy maculas and early and intermediate age-related macular degeneration (AMD) using multimodal imaging.

DESIGN: Cross-sectional study.

PARTICIPANTS: A total of 651 subjects aged ≥60 years enrolled in the Alabama Study of Early Age-Related Macular Degeneration from primary care ophthalmology clinics.

METHODS: Subjects were imaged using spectral domain optical coherence tomography (SD OCT) of the macula and optic nerve head (ONH), infrared reflectance, fundus autofluorescence, and color fundus photographs (CFP). Eyes were assessed for AMD presence and severity using the Age-Related Eye Disease Study (AREDS) 9-step scale. Criteria for SDD presence were identification on ≥1 en face modality plus SD OCT or on ≥2 en face modalities if absent on SD OCT. Subretinal drusenoid deposits were considered present at the person level if present in 1 or both eyes.

MAIN OUTCOME MEASURES: Prevalence of SDD in participants with and without AMD.

RESULTS: Overall prevalence of SDD was 32% (197/611), with 62% (122/197) affected in both eyes. Persons with SDD were older than those without SDD (70.6 vs. 68.7 years, P = 0.0002). Prevalence of SDD was 23% in subjects without AMD and 52% in subjects with AMD (P < 0.0001). Among those with early and intermediate AMD, SDD prevalence was 49% and 79%, respectively. After age adjustment, those with SDD were 3.4 times more likely to have AMD than those without SDD (95% confidence interval, 2.3-4.9). By using CFP only for SDD detection per the AREDS protocol, prevalence of SDD was 2% (12/610). Of persons with SDD detected by SD OCT and confirmed by at least 1 en face modality, 47% (89/190) were detected exclusively on the ONH SD OCT volume.

CONCLUSIONS: Subretinal drusenoid deposits are present in approximately one quarter of older adults with healthy maculae and in more than half of persons with early to intermediate AMD, even by stringent criteria. The prevalence of SDD is strongly associated with AMD presence and severity and increases with age, and its retinal topography including peripapillary involvement resembles that of rod photoreceptors. Consensus on SDD detection methods is recommended to advance our knowledge of this lesion and its clinical and biologic significance.

PMID: 26875000 [PubMed - as supplied by publisher]

Photomed Laser Surg. 2016 Feb 18. [Epub ahead of print]

"Quantum Leap" in Photobiomodulation Therapy Ushers in a New Generation of Light-Based Treatments for Cancer and Other Complex Diseases: Perspective and Mini-Review.

Santana-Blank L, Rodríguez-Santana E, Santana-Rodríguez KE, Reyes H.

OBJECTIVE: Set within the context of the 2015 International Year of Light and Light-Based Technologies,and of a growing and aging world population with ever-rising healthcare needs, this perspective and mini-review focuses on photobiomodulation (PBM) therapy as an emerging, cost-effective, treatment option for cancer (i.e., solid tumors) and other complex diseases, particularly, of the eye (e.g., age-related macular degeneration, diabetic retinopathy, glaucoma, retinitis pigmentosa) and the central nervous system (e.g., Alzheimer's and Parkinson's disease).

BACKGROUND DATA: Over the last decades, primary and secondary mechanisms of PBM have been

revealed. These include oxygen-dependent and oxygen-independent structural and functional action pathways. Signal and target characteristics determine biological outcome, which is optimal (or even positive) only within a given set of parameters.

METHODS: This study was a perspective and nonsystematic literature mini-review.

RESULTS: Studies support what we describe as a paradigm shift or "quantum leap" in the understanding and use of light and its interaction with water and other relevant photo-cceptors to restore physiologic function.

CONCLUSIONS: Based on existing evidence, it is argued that PBM therapy can raise the standard of care and improve the quality of life of patients for a fraction of the cost of many current approaches. PBM therapy can, therefore,benefit large, vulnerable population groups, including the elderly and the poor, whilehaving a major impact on medical practice and public finances.

PMID: 26890728 [PubMed - as supplied by publisher]

Drug Deliv Transl Res. 2016 Feb 17. [Epub ahead of print]

Cytotoxicity considerations and electrically tunable release of dexamethasone from polypyrrole for the treatment of back-of-the-eye conditions.

Ramtin A, Seyfoddin A, Coutinho FP, Waterhouse GI, Rupenthal ID, Svirskis D.

Abstract: Age-related macular degeneration (AMD) and diabetic macular edema (DME) are common causes of blindness in people aged over 55 years. Current treatment involves frequent intravitreal administration of corticosteroids such as dexamethasone. The aim of this research was to formulate an electrically controlled delivery system for dexamethasone. Polypyrrole (PPy) was polymerized with dexamethasone sodium phosphate (Dex-P) through two approaches. Firstly, conventional films (CFs) of PPy were electropolymerized by applying a constant current density of 2 mA/cm2 for 4 min. Secondly, for the first time, we report drug-loaded ethanol-washed films (EWFs). EWFs were prepared in the same manner as CFs, except ethanol washing steps were introduced in the middle and at the end of PPy electropolymerization. The ethanol washing removed unbound PPy oligomers resulting in the formation of smooth surfaces with two distinct layers when viewed in cross-section. The EWFs showed superior electrochemical activity compared to CFs. Sustained release was observed from both CFs and EWFs with bursts of release triggered by electrical stimulation. The EWFs were initially more responsive to the electrical trigger, offering future opportunities to fine tune release. The cytotoxicity of aqueous extracts collected from both films was evaluated on human adult retinal pigment epithelium (ARPE-19) cells using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay with negligible toxicity observed. The results suggest PPy-Dex-P films are highly suitable for the development of electro-responsive implants for the treatment of AMD and DME.

PMID: 26887593 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2016 Feb 1;47(2):134-41.

Imaging of Melanin Disruption in Age-Related Macular Degeneration Using Multispectral Imaging.

Dugel PU, Zimmer CN.

BACKGROUND AND OBJECTIVE: To investigate whether multispectral imaging (MSI) is able to obtain a noninvasive view of melanin disruption associated with age-related macular degeneration (AMD), which could support early diagnosis and potential treatment strategies.

PATIENTS AND METHODS: A single retinal center, retrospective, observational, image analysis study of MSI images of 43 patients was done to determine the extent of melanin pigment exhibited in association

with AMD, based on the Age-Related Eye Disease Study classification and grading scale. Corresponding fundus photos were also graded for 12 of the eyes.

RESULTS: Fifty-one of 61 eyes (84%) of 43 patients with AMD were determined to have melanin disruption in their MSI images in at least the central and/or one of four inner ETDRS areas. There was a relationship between severity of disease and the degree of melanin disruption. The sensitivity of fundus photography for melanin pigment as compared to MSI was only 62.5%, with three false-negatives.

CONCLUSION: A direct, noninvasive, unobstructed view of melanin disruption associated with AMD can be observed using MSI.

PMID: 26878446 [PubMed - in process]

Zhonghua Yan Ke Za Zhi. 2015 Dec;51(12):885-7.

[The role of laser photocoagulation in the anti-vascular endothelial growth factor therapy era]. [Article in Chinese]

Wang F, Zhang P, Sun X.

Abstract: Anti-vascular endothelial growth factor (VEGF) therapy has recently become the first-line treatment for wet age related macular degeneration, macular edema secondary to diabetic retinopathy and retinal vein occlusion, retinopathy of prematurity and neovascular glaucoma. It is worth thinking about whether laser photocoagulation still has its therapeutic value in these diseases. The purpose of this article is to discuss the role of laser photocoagulation in the anti-VEGF therapy era. And the article also discussed the combined treatment strategy in order to avoid clinical errors and to provide a new insight for prevention and treatment of ocular neovascular disease in the future.

PMID: 26888269 [PubMed - in process]

Pathogenesis

J Biol Chem. 2016 Feb 18. [Epub ahead of print]

The B3 subunit of the cone cyclic nucleotide-gated channel regulates the light responses of cones and contributes to the channel structural flexibility.

Ding XQ, Thapa A, Ma H, Xu J, Elliott MH, Rodgers KK, Smith ML, Wang JS, Pittler SJ, Kefalov VJ.

Abstract: Cone photoreceptor cyclic nucleotide-gated (CNG) channels play a pivotal role in cone phototransduction, which is a process essential for daylight vision, color vision, and visual acuity. Mutations in the cone channel subunits CNGA3 and CNGB3 are associated with human cone diseases, including achromatopsia, cone dystrophies, and early-onset macular degeneration. Mutations in CNGB3 alone account for 50% of reported cases of achromatopsia. This work investigated the role of CNGB3 in cone light response and cone channel structural stability. As cones comprise only 2-3% of the total photoreceptor population in the wild-type mouse retina, we used Cngb3-/-/Nrl-/- mice with CNGB3 deficiency on a cone-dominant background in our study. We found that, in the absence of CNGB3, CNGA3 was able to travel to the outer segments, co-localize with cone opsin, and form tetrameric complexes. Electroretinogram analyses revealed reduced cone light response amplitude/sensitivity and slower response recovery in Cngb3-/-/Nrl-/- mice compared with Nrl-/- mice. Absence of CNGB3 expression altered the adaptation capacity of cones and severely compromised function in bright light. Biochemical analysis demonstrated that CNGA3 channels lacking CNGB3 were more resilient to proteolysis than CNGA3/CNGB3 channels, suggesting a hindered structural flexibility. Thus, CNGB3 regulates cone light response kinetics and the channel structural flexibility. This work advances our understanding of the biochemical and functional role of CNGB3 in cone photoreceptors.

PMID: 26893377 [PubMed - as supplied by publisher]

Oxid Med Cell Longev. 2016;2016:7420637. Epub 2015 Dec 28.

Relationship between Oxidative Stress, Circadian Rhythms, and AMD.

Fanjul-Moles ML, López-Riquelme GO.

Abstract: This work reviews concepts regarding oxidative stress and the mechanisms by which endogenous and exogenous factors produce reactive oxygen species (ROS). It also surveys the relationships between oxidative stress, circadian rhythms, and retinal damage in humans, particularly those related to light and photodamage. In the first section, the production of ROS by different cell organelles and biomolecules and the antioxidant mechanisms that antagonize this damage are reviewed. The second section includes a brief review of circadian clocks and their relationship with the cellular redox state. In the third part of this work, the relationship between retinal damage and ROS is described. The last part of this work focuses on retinal degenerative pathology, age-related macular degeneration, and the relationships between this pathology, ROS, and light. Finally, the possible interactions between the retinal pigment epithelium (RPE), circadian rhythms, and this pathology are discussed.

PMID: 26885250 [PubMed - in process] PMCID: PMC4738726

Immun Ageing. 2016 Feb 16;13:4. eCollection 2016.

Higher plasma levels of complement C3a, C4a and C5a increase the risk of subretinal fibrosis in neovascular age-related macular degeneration: Complement activation in AMD.

Lechner J, Chen M, Hogg RE, Toth L, Silvestri G, Chakravarthy U, Xu H.

BACKGROUND: The aim of this study was to investigate the plasma levels of complement C3a, C4a, and C5a in different types of neovascular age-related macular degeneration (nAMD) and whether the levels were related to patients' responsiveness to anti-VEGF therapy.

RESULTS: Ninety-six nAMD patients (including 61 with choroidal neovascularisation (CNV), 17 with retinal angiomatous proliferation (RAP), 14 with polypoidal choroidal vasculopathy (PCV) and 4 unclassified patients) and 43 controls were recruited to this case-control study. Subretinal fibrosis was observed in 45 nAMD patients and was absent in 51 nAMD patients. In addition, the responsiveness to anti-VEGF (Lucentis) therapy was also evaluated in nAMD patients. Forty-four patients were complete responders, 48 were partially responders, and only 4 patients did not respond to the therapy. The plasma levels of C3a, C4a and C5a were significantly higher in nAMD patients compared to controls. Further analysis of nAMD subgroups showed that the levels of C3a, C4a and C5a were significantly increased in patients with CNV but not RAP and PCV. Significantly increased levels of C3a, C4a and C5a were also observed in nAMD patients with subretinal fibrosis but not in those without subretinal fibrosis. Higher levels of C3a were observed in nAMD patients who responded partially to anti-VEGF therapy.

CONCLUSIONS: Our results suggest increased systemic complement activation in nAMD patients with CNV but not RAP and PCV. Our results also suggest that higher levels of systemic complement activation may increase the risk of subretinal fibrosis in nAMD patients.

PMID: 26884800 [PubMed] PMCID: PMC4754842

Biochim Biophys Acta. 2016 Feb 13. [Epub ahead of print]

Protective effects of retinoid x receptors on retina pigment epithelium cells.

Ayala-Peña V, Pilotti F, Volonté Y, Rotstein NP, Politi LE, German OL.

Abstract: Age-related macular degeneration (AMD) is among the main pathologies leading to blindness in adults and has currently no cure or effective treatment. Selective apoptosis of retina pigment epithelial

(RPE) cells results in the progressive loss of photoreceptor neurons, with the consequent gradual vision loss. Oxidative stress plays an important role in this process. We have previously determined that activation of RXRs protects rat photoreceptor neurons from oxidative stress- induced apoptosis. In this study we investigated whether RXR ligands prevented apoptosis in an RPE cell line, D407 cells, exposed to hydrogen peroxide (H2O2). H2O2 induced apoptosis of D407 cells, promoting p65NFκB nuclear translocation, increasing Bax mRNA expression, activating caspase-3 and altering cell morphology. We show, for the first time, that HX630, a RXR pan-agonist, protected D407 cells from H2O2-induced apoptosis, preventing p65NFκB nuclear translocation, increasing Bclxl and PPARγ mRNA levels and simultaneously decreasing Bax mRNA levels and caspase-3 activation. Pretreatment with a RXR antagonist blocked HX630 protection. LG100754, which binds RXRs but only activates heterodimers and is an antagonist of RXR homodimers, also had a protective effect. In addition, only agonists known to bind to RXR/PPARγ were protective. As a whole, our results suggest that RXR activation protects RPE cells from oxidative stress-induced apoptosis and this protection might involve signaling through a heterodimeric receptor, such as RXR/PPARγ. These data also imply that RXR agonists might provide potential pharmacological tools for treating retina degenerative diseases.

PMID: 26883505 [PubMed - as supplied by publisher]

Am J Pathol. 2016 Feb 12. [Epub ahead of print]

αB-Crystallin Regulates Subretinal Fibrosis by Modulation of Epithelial-Mesenchymal Transition.

Ishikawa K, Sreekumar PG, Spee C, Nazari H, Zhu D, Kannan R, Hinton DR.

Abstract: Subretinal fibrosis is an end stage of neovascular age-related macular degeneration, characterized by fibrous membrane formation after choroidal neovascularization. An initial step of the pathogenesis is an epithelial-mesenchymal transition (EMT) of retinal pigment epithelium cells. αB-crystallin plays multiple roles in age-related macular degeneration, including cytoprotection and angiogenesis. However, the role of αB-crystallin in subretinal EMT and fibrosis is unknown. Herein, we showed attenuation of subretinal fibrosis after regression of laser-induced choroidal neovascularization and a decrease in mesenchymal retinal pigment epithelium cells in αB-crystallin knockout mice compared with wild-type mice. αB-crystallin was prominently expressed in subretinal fibrotic lesions in mice. In vitro, overexpression of αB-crystallin induced EMT, whereas suppression of αB-crystallin induced a mesenchymal-epithelial transition. Transforming growth factor-β2-induced EMT was further enhanced by overexpression of αB-crystallin but was inhibited by suppression of αB-crystallin. Silencing of αB-crystallin inhibited multiple fibrotic processes, including cell proliferation, migration, and fibronectin production. Bone morphogenetic protein 4 up-regulated αB-crystallin, and its EMT induction was inhibited by knockdown of αB-crystallin. Furthermore, inhibition of αB-crystallin enhanced monotetraubiquitination of SMAD4, which can impair its nuclear localization. Overexpression of αB-crystallin enhanced nuclear translocation and accumulation of SMAD4 and SMAD5. Thus, αB-crystallin is an important regulator of EMT, acting as a molecular chaperone for SMAD4 and as its potential therapeutic target for preventing subretinal fibrosis development in neovascular age-related macular degeneration.

PMID: 26878210 [PubMed - as supplied by publisher]

Oxid Med Cell Longev. 2016;2016:3164734. Epub 2016 Jan 10.

The Role of the Reactive Oxygen Species and Oxidative Stress in the Pathomechanism of the Age-Related Ocular Diseases and Other Pathologies of the Anterior and Posterior Eye Segments in Adults.

Nita M, Grzybowski A.

Abstract: The reactive oxygen species (ROS) form under normal physiological conditions and may have

both beneficial and harmful role. We search the literature and current knowledge in the aspect of ROS participation in the pathogenesis of anterior and posterior eye segment diseases in adults. ROS take part in the pathogenesis of keratoconus, Fuchs endothelial corneal dystrophy, and granular corneal dystrophy type 2, stimulating apoptosis of corneal cells. ROS play a role in the pathogenesis of glaucoma stimulating apoptotic and inflammatory pathways on the level of the trabecular meshwork and promoting retinal ganglion cells apoptosis and glial dysfunction in the posterior eye segment. ROS play a role in the pathogenesis of Leber's hereditary optic neuropathy and traumatic optic neuropathy. ROS induce apoptosis of human lens epithelial cells. ROS promote apoptosis of vascular and neuronal cells and stimulate inflammation and pathological angiogenesis in the course of diabetic retinopathy. ROS are associated with the pathophysiological parainflammation and autophagy process in the course of the age-related macular degeneration.

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Oncotarget. 2016 Feb 11. [Epub ahead of print]

Improved cell metabolism prolongs photoreceptor survival upon retinal-pigmented epithelium loss in the sodium iodate induced model of geographic atrophy.

Zieger M, Punzo C.

Abstract: Age-related macular degeneration (AMD) is characterized by malfunction and loss of retinal-pigmented epithelium (RPE) cells. Because the RPE transfers nutrients from the choriocapillaris to photoreceptor (PR), PRs are affected as well. Geographic atrophy (GA) is an advanced form of AMD characterized by severe vision impairment due to RPE loss over large areas. Currently there is no treatment to delay the degeneration of nutrient deprived PRs once RPE cells die. Here we show that cell-autonomous activation of the key regulator of cell metabolism, the kinase mammalian target of rapamycin complex 1 (mTORC1), delays PR death in the sodium iodate induced model of RPE atrophy. Consistent with this finding loss of mTORC1 in cones accelerates cone death as cones fail to balance demand with supply. Interestingly, promoting rod survival does not promote cone survival in this model of RPE atrophy as both, rods and cones suffer from a sick and dying RPE. The findings suggest that activation of metabolic genes downstream of mTORC1 can serve as a strategy to prolong PR survival when RPE cells malfunction or die.

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Aging Cell. 2016 Feb 15. [Epub ahead of print]

Retinal pigment epithelial cell multinucleation in the aging eye - a mechanism to repair damage and maintain homoeostasis.

Chen M, Rajapakse D, Fraczek M, Luo C, Forrester JV, Xu H.

Abstract: Retinal pigment epithelial (RPE) cells are central to retinal health and homoeostasis. Dysfunction or death of RPE cells underlies many age-related retinal degenerative disorders particularly age-related macular degeneration. During aging RPE cells decline in number, suggesting an age-dependent cell loss. RPE cells are considered to be postmitotic, and how they repair damage during aging remains poorly defined. We show that RPE cells increase in size and become multinucleate during aging in C57BL/6J mice. Multinucleation appeared not to be due to cell fusion, but to incomplete cell division, that is failure of cytokinesis. Interestingly, the phagocytic activity of multinucleate RPE cells was not different from that of mononuclear RPE cells. Furthermore, exposure of RPE cells in vitro to photoreceptor outer segment (POS), particularly oxidized POS, dose-dependently promoted multinucleation and suppressed cell proliferation. Both failure of cytokinesis and suppression of proliferation required contact with POS. Exposure to POS also induced reactive oxygen species and DNA oxidation in RPE cells. We propose that

RPE cells have the potential to proliferate in vivo and to repair defects in the monolayer. We further propose that the conventionally accepted 'postmitotic' status of RPE cells is due to a modified form of contact inhibition mediated by POS and that RPE cells are released from this state when contact with POS is lost. This is seen in long-standing rhegmatogenous retinal detachment as overtly proliferating RPE cells (proliferative vitreoretinopathy) and more subtly as multinucleation during normal aging. Age-related oxidative stress may promote failure of cytokinesis and multinucleation in RPE cells.

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Oncotarget. 2016 Feb 14. [Epub ahead of print]

Hyperhomocysteinemia disrupts retinal pigment epithelial structure and function with features of age-related macular degeneration.

Ibrahim AS, Mander S, Hussein KA, Elsherbiny NM, Smith SB, Al-Shabrawey M, Tawfik A.

Abstract: The disruption of retinal pigment epithelial (RPE) function and the degeneration of photoreceptors are cardinal features of age related macular degeneration (AMD); however there are still gaps in our understanding of underlying biological processes. Excess homocysteine (Hcy) has been reported to be elevated in plasma of patients with AMD. This study aimed to evaluate the direct effect of hyperhomocysteinemia (HHcy) on structure and function of RPE. Initial studies in a mouse model of HHcy, in which cystathionine-β-synthase (cbs) was deficient, revealed abnormal RPE cell morphology with features similar to that of AMD upon optical coherence tomography (OCT), fluorescein angiography (FA), histological, and electron microscopic examinations. These features include atrophy, vacuolization, hypopigmentation, thickened basal laminar membrane, hyporeflective lucency, choroidal neovascularization (CNV), and disturbed RPE-photoreceptor relationship. Furthermore, intravitreal injection of Hcy per se in normal wild type (WT) mice resulted in diffuse hyper-fluorescence, albumin leakage, and CNV in the area of RPE. In vitro experiments on ARPE-19 showed that Hcy dose-dependently reduced tight junction protein expression, increased FITC dextran leakage, decreased transcellular electrical resistance, and impaired phagocytic activity. Collectively, our results demonstrated unreported effects of excess Hcy levels on RPE structure and function that lead to the development of AMD-like features.

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Epidemiology

Ophthalmology. 2016 Jan 28. [Epub ahead of print]

Incidence of Age-Related Macular Degeneration in a Multi-Ethnic United States Population: The Multi-Ethnic Study of Atherosclerosis.

Fisher DE, Klein BE, Wong TY, Rotter JI, Li X, Shrager S, Burke GL, Klein R, Cotch MF.

PURPOSE: To describe the incidence of age-related macular degeneration (AMD) and associated risk factors in 4 racial/ethnic groups (white, black, Hispanic, and Chinese) residing in the United States.

DESIGN: Prospective cohort study.

PARTICIPANTS: A total of 3811 participants, aged 46 to 86 years, from the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, with retinal data collected twice, on average, 8 years apart.

METHODS: Fundus images, taken using a digital camera through dark-adapted pupils using a standard protocol and the same equipment at both study visits, were graded centrally for early and late AMD on the basis of drusen size, type and area, increased retinal pigment, retinal pigment epithelial depigmentation, neovascular lesions, and geographic atrophy using the modified Wisconsin Age-Related Maculopathy Grading System. Demographic, clinical, and laboratory measures were included in multivariable regression

models to determine their impact on the variation in AMD incidence among racial/ethnic groups.

MAIN OUTCOME MEASURES: Incident early and late AMD.

RESULTS: The overall 8-year age- and sex-standardized incidence of early and late AMD were 4.1% and 2.3%, respectively, with incidence of early and late AMD highest in whites (5.3% and 4.1%, respectively), intermediate in Chinese (4.5% and 2.2%, respectively) and Hispanics (3.3% and 0.8%, respectively), and lowest in blacks (1.6% and 0.4%, respectively). By adjusting for age and sex, blacks had a 70% lower risk of developing early AMD than whites, and this decreased only slightly to a 67% lower risk after multivariable adjustment. By adjusting for age, sex, and race/ethnicity, hyperopia was associated with early AMD (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.04-2.20), as was astigmatism (OR, 1.47; 95% CI, 1.00-2.16), but not myopia (P = 0.29). Age, race/ethnicity, current smoking, hyperopia, and AMD-susceptibility genotypes Complement Factor H (CFH) RS1061170 and Age Related Maculopathy Susceptibility 2 (ARMS2) RS3793917 were independently associated with incident early AMD in multivariable models for the combined sample. However, the only statistically significant factor consistently associated with incident early AMD across the 4 racial/ethnic groups was increasing age. Risk factors for late AMD were not assessed because of its low incidence, particularly across racial/ethnic groups.

CONCLUSIONS: Variation in the incidence of early AMD exists among racial/ethnic groups in the United States and is not explained by the clinical, genetic, and environmental factors included in this study.

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Stem cells

J Ocul Pharmacol Ther. 2016 Feb 18. [Epub ahead of print]

Pluripotent Stem Cell-Based Therapies in Combination with Substrate for the Treatment of Age-Related Macular Degeneration.

Pennington BO, Clegg DO.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the western world, which severely decreases the quality of life in the patients and places an economic burden on their families and society. The disease is caused by the dysfunction of a specialized cell layer in the back of the eye called the retinal pigmented epithelium (RPE). Pluripotent stem cells can provide an unlimited source of RPE, and laboratories around the world are investigating their potential as therapies for AMD. To ensure the precise delivery of functional RPE to the diseased site, some groups are developing a therapy composed of mature RPE monolayers on a supportive scaffold for transplantation as an alternative to injecting a single-cell suspension. This review summarizes methods of generating RPE from pluripotent stem cells, compares biodegradable and biostable materials as scaffolds, and describes the specific combination of human embryonic stem cell-derived RPE on Parylene-C membranes, which is scheduled to begin clinical trials in the United Sates in 2016. Stem cell-derived RPE monolayers on scaffolds hold great promise for the treatment of AMD and other retinal diseases.

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Stem Cells Int. 2016;2016:8470263. Epub 2016 Jan 5.

iPSC-Derived Retinal Pigment Epithelium Allografts Do Not Elicit Detrimental Effects in Rats: A Follow-Up Study.

Westenskow PD, Bucher F, Bravo S, Kurihara T, Feitelberg D, Paris LP, Aguilar E, Lin JH, Friedlander M.

Abstract: Phototransduction is accomplished in the retina by photoreceptor neurons and retinal pigment epithelium (RPE) cells. Photoreceptors rely heavily on the RPE, and death or dysfunction of RPE is

characteristic of age-related macular degeneration (AMD), a very common neurodegenerative disease for which no cure exists. RPE replacement is a promising therapeutic intervention for AMD, and large numbers of RPE cells can be generated from pluripotent stem cells. However, questions persist regarding iPSC-derived RPE (iPS-RPE) viability, immunogenicity, and tumorigenesis potential. We showed previously that iPS-RPE prevent photoreceptor atrophy in dystrophic rats up until 24 weeks after implantation. In this follow-up study, we longitudinally monitored the same implanted iPS-RPE, in the same animals. We observed no gross abnormalities in the eyes, livers, spleens, brains, and blood in aging rats with iPSC-RPE grafts. iPS-RPE cells that integrated into the subretinal space outlived the photoreceptors and survived for as long as 2 1/2 years while nonintegrating RPE cells were ingested by host macrophages. Both populations could be distinguished using immunohistochemistry and electron microscopy. iPSC-RPE could be isolated from the grafts and maintained in culture; these cells also phagocytosed isolated photoreceptor outer segments. We conclude that iPS-RPE grafts remain viable and do not induce any obvious associated pathological changes.

PMID: 26880994 [PubMed] PMCID: PMC4736415

Diet, lifestyle & low vision

Clin Ophthalmol. 2016 Feb 3;10:257-67. eCollection 2016.

The emotional and physical impact of wet age-related macular degeneration: findings from the wAMD Patient and Caregiver Survey.

Varano M, Eter N, Winyard S, Wittrup-Jensen KU, Navarro R, Heraghty J.

OBJECTIVES: This was a cross-sectional survey to evaluate the physical and emotional impact of wet age-related macular degeneration (wAMD) on a global cohort of patients who were receiving (or had previously received) antivascular endothelial growth factor injections, and caregivers (paid and unpaid).

METHODS: The survey was performed in nine countries using an ophthalmologist-devised questionnaire.

RESULTS: A total of 910 patients and 890 caregivers completed the questionnaire. Most patients had been diagnosed and receiving antivascular endothelial growth factor injections for more than 1 year (74.7% and 63.8%, respectively), and many patients (82.1%) received support from a caregiver (usually a child/grandchild [47.3%] or partner [23.3%]). wAMD had a negative impact on most patients (71.6%); many rated fear (44.9%), sadness (39.9%), frustration (37.3%), and depression (34.0%) as common. It was linked to physical consequences, such as difficulty in reading (61.1%). Many effects were significantly greater in patients with a longer duration of disease or with wAMD in both eyes. Some caregivers (unpaid) also reported that caregiving had a negative impact on them (31.1%); many reported emotions such as sadness (34.9%) and depression (24.4%), but many also felt useful (48.4%). Overall, 27.2% of caregivers (unpaid) rated caregiving as inconvenient; this was linked to days of employment/personal obligations missed.

CONCLUSION: wAMD has a significant negative impact on the lives of patients, including vision-related depression, poor mobility, and limitations in day-to-day activities. The impact on nonprofessional caregivers may be underestimated in terms of emotional impact (such as depression) and loss of productivity.

PMID: 26893539 [PubMed]

Sci Rep. 2016 Feb 18;6:21018.

Protective effect of alpha-mangostin against oxidative stress induced-retinal cell death.

Fang Y, Su T, Qiu X, Mao P, Xu Y, Hu Z, Zhang Y, Zheng X, Xie P, Liu Q.

Abstract: It is known that oxidative stress plays a pivotal role in age-related macular degeneration (AMD) pathogenesis. Alpha-mangostin is the main xanthone purified from mangosteen known as anti-oxidative

properties. The aim of the study was to test the protective effect of alpha-mangostin against oxidative stress both in retina of light-damaged mice model and in hydrogen peroxide (H2O2)-stressed RPE cells. We observed that alpha-mangostin significantly inhibited light-induced degeneration of photoreceptors and 200 μM H2O2-induced apoptosis of RPE cells. 200 μM H2O2-induced generation of reactive oxygen species (ROS) and light-induced generation of malondialdehyde (MDA) were suppressed by alpha-mangostin. Alpha-mangostin stimulation resulted in an increase of superoxide dismutase (SOD) activity, glutathione peroxidase (GPX) activity and glutathione (GSH) content both in vivo and vitro. Furthermore, the mechanism of retinal protection against oxidative stress by alpha-mangostin involves accumulation and the nuclear translocation of the NF-E2-related factor (Nrf2) along with up-regulation the expression of heme oxygenas-1 (HO-1). Meanwhile, alpha-mangostin can activate the expression of PKC-δ and down-regulate the expression of mitogen-activated protein kinases (MAPKs), including ERK1/2, JNK, P38. The results suggest that alpha-mangostin could be a new approach to suspend the onset and development of AMD.

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