

Issue 326

Wednesday 3 May, 2017

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

If you have not already subscribed, please email Rob Cummins at research@mdfoundation.com.au with 'Subscribe to MD Research News' in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your 'unsubscribe' request or by clicking on the link at the bottom of the email linking you to this page.

Drug treatment

JAMA Ophthalmol. 2017 Apr 27. [Epub ahead of print]

Change in Diabetic Retinopathy Through 2 Years: Secondary Analysis of a Randomized Clinical Trial Comparing Aflibercept, Bevacizumab, and Ranibizumab.

Bressler SB, Liu D, Glassman AR, Blodi BA, Castellarin AA, Jampol LM, Kaufman PL, Melia M, Singh H, Wells JA; Diabetic Retinopathy Clinical Research Network.

IMPORTANCE: Anti-vascular endothelial growth factor (anti-VEGF) therapy for diabetic macular edema (DME) favorably affects diabetic retinopathy (DR) improvement and worsening. It is unknown whether these effects differ across anti-VEGF agents.

OBJECTIVE: To compare changes in DR severity during aflibercept, bevacizumab, or ranibizumab treatment for DME.

DESIGN, SETTING, AND PARTICIPANTS: Preplanned secondary analysis of data from a comparative effectiveness trial for center-involved DME was conducted in 650 participants receiving aflibercept, bevacizumab, or ranibizumab. Retinopathy improvement and worsening were determined during 2 years of treatment. Participants were randomized in 2012 through 2013, and the trial concluded on September 23, 2015.

INTERVENTIONS: Random assignment to aflibercept, 2.0 mg; bevacizumab, 1.25 mg; ranibizumab, 0.3 mg, up to every 4 weeks through 2 years following a retreatment protocol.

MAIN OUTCOMES AND MEASURES: Percentages with retinopathy improvement at 1 and 2 years and cumulative probabilities for retinopathy worsening through 2-year without adjustment for multiple outcomes.

RESULTS: A total of 650 participants (495 [76.2%] nonproliferative DR [NPDR], 155 proliferative DR [PDR]) were analyzed; 302 (46.5%) were women and mean (SD) age was 61 (10) years; 425 (65.4%) were white. At 1 year, among 423 NPDR eyes, 44 of 141 (31.2%) treated with aflibercept, 29 of 131 (22.1%) with bevacizumab, and 57 of 151 (37.7%) with ranibizumab had improvement of DR severity (adjusted difference: 11.7%; 95% CI, 2.9% to 20.6%; $P = .004$ for aflibercept vs bevacizumab; 8.9%; 95% CI, 1.7% to 16.1%; $P = .01$ for ranibizumab vs bevacizumab; and 2.9%; 95% CI, -5.7% to 11.4%; $P = .51$ for aflibercept vs ranibizumab). At 2 years, 33 eyes (24.8%) in the aflibercept group, 25 eyes (22.1%) in the bevacizumab group, and 40 eyes (31.0%) in the ranibizumab group had DR improvement; no treatment group differences were identified. For 93 eyes with PDR at baseline, 1-year improvement rates were 75.9% for aflibercept, 31.4% for bevacizumab, and 55.2% for ranibizumab (adjusted difference: 50.4%; 95% CI, 26.8% to 74.0%; $P < .001$ for aflibercept vs bevacizumab; 20.4%; 95% CI, -3.1% to 44.0%; $P = .09$ for ranibizumab vs bevacizumab; and 30.0%; 95% CI, 4.4% to 55.6%; $P = .02$ for aflibercept vs ranibizumab). These rates and treatment group differences appeared to be maintained at 2 years. Despite the reduced numbers of injections in the second year, 66 (59.5%) of NPDR and 28 (70.0%) of PDR eyes that manifested improvement at 1 year maintained improvement at 2 years. Two-year cumulative rates for retinopathy worsening ranged from 7.1% to 10.2% and 17.2% to 26.4% among anti-VEGF groups for NPDR and PDR

eyes, respectively. No statistically significant treatment differences were noted.

CONCLUSIONS AND RELEVANCE: At 1 and 2 years, eyes with NPDR receiving anti-VEGF treatment for DME may experience improvement in DR severity. Less improvement was demonstrated with bevacizumab at 1 year than with aflibercept or ranibizumab. Aflibercept was associated with more improvement at 1 and 2 years in the smaller subgroup of participants with PDR at baseline. All 3 anti-VEGF treatments were associated with low rates of DR worsening. These data provide additional outcomes that might be considered when choosing an anti-VEGF agent to treat DME.

PMID: 28448655

Jpn J Ophthalmol. 2017 Apr 26. [Epub ahead of print]

The relationship between vascular endothelial dysfunction and treatment frequency in neovascular age-related macular degeneration.

Ueda-Consolvo T, Hayashi A, Ozaki M, Nakamura T, Yagou T, Abe S.

PURPOSE: To assess the correlation between endothelial dysfunction and frequency of antivasculat endothelial growth factor (anti-VEGF) treatment for neovascular age-related macular degeneration (nAMD).

METHODS: We examined 64 consecutive patients with nAMD who were evaluated for endothelial function by use of peripheral arterial tonometry (EndoPAT 2000; Itamar Medical, Caesarea, Israel) at Toyama University Hospital from January 2015. We tallied the number of anti-VEGF treatments between January 2014 and December 2015 and determined the correlation between the number of anti-VEGF injections and endothelial function expressed as the reactive hyperemia index (RHI). Multiple regression analysis was also performed to identify the independent predictors of a larger number of injections.

RESULTS: The mean number of anti-VEGF injections was 8.2 ± 3.3 . The mean lnRHI was 0.47 ± 0.17 . The lnRHI correlated with the number of anti-VEGF injections ($r = -0.56$; $P = 0.030$). The multiple regression analysis revealed that endothelial function, neovascular subtypes, and treatment regimens were associated with the number of injections.

CONCLUSIONS: Endothelial dysfunction may affect the efficacy of anti-VEGF therapy. Neovascular subtypes may also predict a larger number of injections.

PMID: 28447271

J Ocul Pharmacol Ther. 2017 Apr 26. [Epub ahead of print]

Effect of Epiretinal Membranes on Antivasculat Endothelial Growth Factor Treatment for Neovascular Age-Related Macular Degeneration.

Cho HJ, Kim JM, Kim HS, Lee DW, Kim CG, Kim JW.

PURPOSE: To evaluate the effect of epiretinal membranes (ERMs), detected with spectral-domain optical coherence tomography (SD-OCT), on the outcome of antivasculat endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (nAMD).

METHODS: A total of 434 eyes with treatment-naive nAMD were retrospectively included and analyzed. All patients were administered an initial series of 3 monthly loading injections of ranibizumab or aflibercept, followed by further injections as required. The visual and anatomical outcomes were compared between the eyes with ERMs and those without. Features of ERMs at baseline assessed with SD-OCT were evaluated and correlated with visual outcomes.

RESULTS: Sixty-eight eyes (15.7%) with nAMD presented ERMs at baseline. The mean best-corrected visual acuity (BCVA) of these eyes, expressed as the logarithm of the minimum angle of resolution,

improved from 0.75 ± 0.48 (Snellen equivalent: 20/112) to 0.59 ± 0.44 (20/77) after 12 months of treatment ($P = 0.021$). Central foveal thickness also decreased from $381 \pm 191 \mu\text{m}$ to $294 \pm 167 \mu\text{m}$ ($P < 0.001$). Compared to the eyes without ERMs (366 eyes), the eyes with ERMs had a significantly thicker central fovea after treatment ($P = 0.020$). However, the intergroup differences in BCVA improvement were not significant. No significant association was found between visual outcome after treatment and ERM features on OCT at baseline.

CONCLUSIONS: In eyes with nAMD, ERMs were infrequent. Central foveal thickness was significantly greater after anti-VEGF treatment in eyes with nAMD and ERMs. However, the presence of ERMs in eyes with nAMD did not affect visual outcome.

PMID: 28445077

Curr Eye Res. 2017 Apr 25;1-5. [Epub ahead of print]

Comparison of Conbercept with Ranibizumab for the Treatment of Macular Edema Secondary to Branch Retinal Vein Occlusion.

Li F, Sun M, Guo J, Ma A, Zhao B.

PURPOSE: To confirm the therapeutic efficacy of conbercept for the treatment of macular edema (ME) secondary to branch retinal vein occlusion (BRVO).

METHODS: In this prospective, randomized, and comparative study, patients were randomized and divided into conbercept ($n = 18$) and ranibizumab ($n = 17$) groups. After an initial intravitreal injection of either conbercept or ranibizumab, a pro re nata (PRN) strategy was adopted based on loss of visual acuity (VA) or increase in central macular thickness (CMT).

RESULTS: All patients were followed for ≥ 6 months. Baseline best-corrected visual acuities (BCVAs) were 0.67 ± 0.37 and 0.511 ± 0.23 logMAR in the conbercept and ranibizumab groups, respectively ($p = 0.087$, t-test). Baseline CMTs were 512.5 ± 115.22 and $491.23 \pm 114.72 \mu\text{m}$ in the conbercept and ranibizumab groups, respectively ($p = 0.993$, t-test). Significant improvements in BCVA and reduction of CMT were observed in both groups at each follow-up visit and compared to baseline values ($p < 0.05$, t-test). No significant differences in improvement of BCVA ($p > 0.05$, t-test) or reduction of CMT ($p > 0.05$, t-test) were noted in either group. Mean numbers of injections were 2.28 ± 0.96 and 2.65 ± 1.17 for the conbercept and ranibizumab groups, respectively ($p = 0.478$, t-test), with no statistically significant differences between the two groups.

CONCLUSION: Intravitreal injection of conbercept is shown to be safe and effective for the treatment of ME secondary to BRVO, based on 6-month follow-up data.

PMID: 28441077

Asia Pac J Ophthalmol (Phila). 2017 Apr 10. [Epub ahead of print]

Intravitreal Aflibercept for Patients With Diabetic Macular Edema Refractory to Bevacizumab or Ranibizumab: Analysis of Response to Aflibercept.

Chen YY, Chang PY, Wang JK.

PURPOSE: To investigate the short-term efficacy and safety of intravitreal aflibercept in a case series of patients with diabetic macular edema (DME) refractory to ranibizumab or bevacizumab.

DESIGN: A retrospective chart review.

METHODS: From September 2013 to March 2016, we identified patients with DME who developed resistance to bevacizumab or ranibizumab. Three monthly intravitreal aflibercept injections were

administered in refractory cases. Nonresponse to aflibercept was defined as a paradoxical increase in central foveal thickness (CFT) and gain in best-corrected visual acuity (BCVA) of less than 1 line at 1 month after treatment compared with before aflibercept administration.

RESULTS: Out of a total of 72 eyes in 72 refractory patients, 42 eyes (58.3%) responded to aflibercept injections. The BCVA and CFT were 0.65 ± 0.32 logMAR and 438.5 ± 80.1 μ m, respectively, before aflibercept treatment and significantly improved to 0.31 ± 0.17 logMAR ($P = 0.0008$) and 297.9 ± 19.1 μ m ($P = 0.0004$), respectively, 1 month after 3 aflibercept injections in responders. No differences in baseline characteristics, including age, sex, glycosylated hemoglobin, serum creatinine, total cholesterol, lens status, grades of diabetic retinopathy, and CFT/BCVA before aflibercept management ($P > 0.05$), were observed between responders and nonresponders. There were 17 vitrectomized eyes in 30 nonresponders (56.7%), a significantly higher rate than among the 42 responders (0%; $P = 0.00001$).

CONCLUSIONS: Three monthly intravitreal aflibercept injections had benefit in nearly two thirds of cases with DME resistant to bevacizumab or ranibizumab over short-term follow-up. Vitrectomized eyes responded poorly to aflibercept treatment.

PMID: 28436640

Ophthalmol Ther. 2017 Apr 27. [Epub ahead of print]

A Systematic Review of the Treat and Extend Treatment Regimen with Anti-VEGF Agents for Neovascular Age-Related Macular Degeneration.

Gemenetzi M, Patel PJ.

Abstract: Despite significant progress in retaining vision for neovascular age-related macular degeneration patients in the era of treatment with intravitreal anti-VEGF agents, there is no universally accepted treatment regimen that defines the frequency of treatment needed to achieve the optimal visual outcomes while simultaneously balancing the burden of long-term, frequent and high-cost treatment. Treat and extend has recently and consistently been used by retina specialists to minimise the financial and psychological costs of the need for frequent treatment with anti-VEGF injections. This is a systematic review that presents evidence from clinical trials and the real world on the utilisation of treat and extend with anti-VEGF intravitreal injections in neovascular age-related macular degeneration, and discusses the experience gained thus far from the utilisation of such regimens to preserve vision when treating patients over the long-term.

PMID: 28451952

BMC Ophthalmol. 2017 Apr 27;17(1):58.

24-month clinical outcomes of a treat-and-extend regimen with ranibizumab for wet age-related macular degeneration in a real life setting.

Vardarinos A, Gupta N, Janjua R, Iron A, Empeslidis T, Tsaousis KT.

BACKGROUND: To evaluate the clinical effectiveness and analyze the outcomes of a treat-and-extend (T&E) treatment regimen with ranibizumab for wet age-related macular degeneration (ARMD) in real life clinical settings over the first 2 years (24 months) of treatment.

METHODS: Retrospective analysis of visual acuity, spectral domain optical coherence tomography (SD-OCT) parameters and treatment burden data of 56 eyes of 54 unselected treatment naive patients diagnosed with exudative ARMD. Monthly injections were offered until no signs of disease activity such as intra-retinal (IRF) or sub-retinal fluid (SRF) were evident on SD-OCT, followed by a gradual extension of the treatment interval by 2 weeks until a maximum of 12 weeks.

RESULTS: The study met its main objective, demonstrating a mean best-corrected visual acuity gain of 8.3 letters (mean 68.8 ± 11) at month 12 and 5.2 letters (mean 65.7 ± 12.3) at 24 months compared to baseline (mean 60.5 ± 8.9). Anatomical improvement was also documented with a mean reduction of central retinal thickness by $139.7 \mu\text{m}$ at 24 months (244.9 ± 48.3) compared to baseline (384.6 ± 154.9). Forty-seven eyes (83.9% N = 56) gained vision or preserved baseline vision with 23 eyes (41.1%) gaining 10 letters or more at month 12. Out of the 46 eyes that completed 24 months of treatment and monitoring, 27 (58.7% N = 46) kept a BCVA above baseline with 18 of those (39% N = 46) maintaining a 10-letter gain throughout the 24 months. Six eyes (13% N = 46) lost more than 10 letters by month 24. The mean number of injections was 12.1 ± 2.8 over the 24-month period. Twenty-seven eyes (55.1% N = 56) achieved a treatment interval of 10 weeks or more at month 12, while the respective number at month 24 was 20 eyes (43.4% N = 46) in addition though to four more patients (8.7% N = 46) who were not receiving injections at month 24 since they were placed on a Monitor & Extend regime.

CONCLUSIONS: This is the first UK real-life study of a T&E treatment protocol with ranibizumab for exudative ARMD in a 24-month period and suggests that such a regimen is clinically effective and can achieve favourable outcomes with a significant reduction of the treatment burden compared to monthly PRN.

PMID: 28449645

Eye (Lond). 2017 Apr 28. [Epub ahead of print]

Influence of baseline diabetic retinopathy status on initial anatomical response of intravitreal ranibizumab therapy for diabetic macular oedema.

Nicholson L, Patrao NV, Ramu J, Vazquez-Alfageme C, Muwas M, Rajendram R, Hykin PG, Sivaprasad S.

Purpose: Intraocular vascular endothelial growth factor (VEGF) levels increases with the severity of diabetic retinopathy. Response of diabetic macular oedema (DMO) to ranibizumab is driven by VEGF suppression. We hypothesised that the initial reduction of central macular thickness by ranibizumab should be maximum in severe diabetic retinopathy until the levels of VEGF decreases to the levels observed in eyes with mild retinopathy. **Methods** Consecutive patients with centre-involving DMO (central subfield thickness (CSFT) $>300 \mu\text{m}$) who had three consecutive monthly ranibizumab injections followed by as needed therapy were included. Retinopathy status was graded as mild non-proliferative diabetic retinopathy (NPDR) (G1), moderate to severe NPDR with no prior panretinal photocoagulation (G2), and treated PDR (G3). **Results** Two hundred and thirty-nine eyes from 204 patients with a mean age of 64.9 years were included. The distribution was 31.4 G1, 32.2 G2, and 36.4% G3. Mean baseline CSFT for all eyes was $458.5 \pm 110.8 \mu\text{m}$. Baseline CSFT for G1, G2, and G3, respectively, were 437.6 ± 90.9 , 472.3 ± 109.8 , and $464.7 \pm 124.9 \mu\text{m}$ ($P=0.2155$). Mean change in CSFT after three consecutive injections was $128.5 \pm 116.6 \mu\text{m}$. The mean changes were $95.8 \pm 101.4 \mu\text{m}$ for G1, $137.2 \pm 112.9 \mu\text{m}$ for G2, and $148.9 \pm 126.9 \mu\text{m}$ for G3. The changes in CSFT between groups adjusted for baseline CSFT were statistically significant ($P=0.0473$). At 6 and 12 months after a mean of 4.5 and 7.7 injections, the changes between groups were no longer significant, $P=0.4783$ and $P=0.8271$, respectively. **Conclusions** The initial anatomical response of DMO with intravitreal ranibizumab injections was maximum in eyes with treated PDR, suggesting that the higher the VEGF levels, the better the response with ranibizumab. Eye advance online publication, 28 April 2017; doi:10.1038/eye.2017.69.

PMID: 28452992

Clin Ophthalmol. 2017 Apr 6;11:621-629. eCollection 2017.

Testing the clinical value of multifocal electroretinography and microperimetry and the effects of intravitreal therapy with ranibizumab on macular function in the course of wet age-related macular degeneration: a 1-year prospective study.

Reinsberg M, Hilgers RD, Lüdeke I, Nassar K, Grisanti S, Grisanti S, Lüke J, Lüke M.

PURPOSE: To investigate the clinical value of multifocal electroretinography (mfERG) and microperimetry and the effects of intravitreal therapy with ranibizumab (Lucentis®) on macular function in the course of neovascular age-related macular degeneration (nAMD).

MATERIALS AND METHODS: We conducted a prospective single-arm interventional cohort study with 20 nAMD patients older than 50 years. Examinations were scheduled monthly for 1 year during intravitreal therapy with ranibizumab. The examinations included mfERG, microperimetry, spectral domain optical coherence tomography, and best-corrected visual acuity using ETDRS score.

RESULTS: During the 12-month observation period, a significant positive linear correlation between the logarithm of minimum angle of resolution (logMAR) and scotoma area ($r=0.28$, 95% confidence interval [CI] 0.21-0.35), between logMAR and fovea thickness in optical coherence tomography ($r=0.11$, 95% CI 0.04-0.2), and a significant negative correlation between logMAR and mfERG (-0.37 , 95% CI -0.43 to -0.31) were observed. A significant ranibizumab effect on logMAR was found ($P=0.0065$). From a total of 25 relapses, 14 were able to be predicted correctly by mfERG P1 decrease in the preceding month. However, there was no statistically significant relation between prediction and observed relapses (Fisher's exact test, $P=0.6726$).

CONCLUSION: Our results indicate a possible role of mfERG and microperimetry in the monitoring of macular function and prediction of recurrence during intravitreal pharmacotherapy in wet AMD.

PMID: 28435212 PMCID: PMC5388268

Clin Ophthalmol. 2017 Apr 5;11:619. eCollection 2017.

Erratum: Prolongation of injection interval after switching therapy from ranibizumab to aflibercept in Japanese patients with macular edema secondary to branch retinal vein occlusion [Corrigendum].

Abstract: [This corrects the article on p. 403 in vol. 11, PMID: 28260852].

PMID: 28435211 PMCID: PMC5388265

Other treatment & diagnosis

Eur J Pharm Biopharm. 2017 Apr 22. [Epub ahead of print]

Long-term release and stability of pharmaceutical proteins delivered from solid lipid implants.

Vollrath M, Engert J, Winter G.

Abstract: Solid lipid implants (SLIs) prepared by twin-screw (tsc) extrusion represent a promising technology platform for the sustained release of pharmaceutical proteins. In this work, we report on two aspects, long-term release and stability of released protein. First, SLIs were produced by tsc-extrusion containing the low melting triglyceride H12 and the high melting triglyceride Dynasan D118. Two different proteins available in a freeze-dried matrix containing hydroxypropyl- β -cyclodextrine (HP- β -CD) were incorporated into the lipid matrix: a monoclonal antibody (mAb) from the IgG1 class and the fab-fragment Ranibizumab (Lucentis®). SLIs, composed of 10% protein lyophilisate and both triglycerides, were extruded at 35°C and 40rpm. Sustained release of both proteins was observed in a sustained manner for approximately 120days. Protein load per implant was increased by three different approaches resulting in a protein load of 3.00mg per implant without affecting the release profiles. The incubation medium containing the released protein was collected, concentrated and analyzed including liquid chromatography (SE-HPLC, IEX, HIC), electrophoresis (SDS-PAGE, on-chip gel electrophoresis) and FT-IR spectroscopy. The mAb showed a monomer loss of up to 7% (SE-HPLC) and IEX analysis revealed the formation of 16% acidic

subspecies after 18 weeks. FT-IR spectra of mAb indicated the formation of random coil structures towards the end of the release study. Ranibizumab was mainly released in its monomeric form (> 95%), and approximately 5% hydrophobic subspecies were formed after 18 weeks of release. FT-IR analysis revealed no changes in secondary structure. The release and stability profiles of both proteins underline the potential of SLIs as a delivery system. SLIs provide a promising platform for applications where really long-term release is needed, for example for intraocular delivery of anti-vascular endothelial growth factor (VEGF) drugs for age related macular degeneration (AMD).

PMID: 28442372

Indian J Ophthalmol. 2017 Mar;65(3):191-197.

Circulating biomarkers in glaucoma, age-related macular degeneration, and diabetic retinopathy.

Nath M, Halder N, Velpandian T.

Abstract: Biomarkers to predict the altering physiological conditions over the period leading toward the ocular disorders are of major importance in therapeutics. Isolation and validation of the biomarkers specific to ocular diseases are a challenging task. Glaucoma is a neurodegenerative disease of the eye where the correlation of biomarkers in circulating fluid may be made specific for the eye. However, conditions such as wet age-related macular degeneration (AMD) and proliferative diabetic retinopathy (DR), circulating biomarkers might be having some degree of overlap with other conditions like cancer where a common factor such as angiogenesis is involved. Diabetes, a systemic disorder affecting the target organs such as eye, kidney, heart, and nervous system can be predicted using common circulating biomarkers. However, these markers need to be validated along with various stages of disease progression to enable the possibility of targeted pharmacological interventions apart from good glycemic control alone. This review compiles the attempts made to correlate such circulating biomarkers in the ocular conditions such as glaucoma, AMD, and DR in the search for a surrogate marker for diagnostic and prognostic value. To make biomarkers for the common convenience, genetic markers are excluded from this review.

PMID: 28440247

Invest Ophthalmol Vis Sci. 2017 Apr 1;58(4):2318-2328.

Automated Staging of Age-Related Macular Degeneration Using Optical Coherence Tomography.

Venhuizen FG, van Ginneken B, van Asten F, van Grinsven MJJP, Fauser S, Hoyng CB, Theelen T, Sánchez CI.

PURPOSE: To evaluate a machine learning algorithm that automatically grades age-related macular degeneration (AMD) severity stages from optical coherence tomography (OCT) scans.

METHODS: A total of 3265 OCT scans from 1016 patients with either no signs of AMD or with signs of early, intermediate, or advanced AMD were randomly selected from a large European multicenter database. A machine learning system was developed to automatically grade unseen OCT scans into different AMD severity stages without requiring retinal layer segmentation. The ability of the system to identify high-risk AMD stages and to assign the correct severity stage was determined by using receiver operator characteristic (ROC) analysis and Cohen's κ statistics (κ), respectively. The results were compared to those of two human observers. Reproducibility was assessed in an independent, publicly available data set of 384 OCT scans.

RESULTS: The system achieved an area under the ROC curve of 0.980 with a sensitivity of 98.2% at a specificity of 91.2%. This compares favorably with the performance of human observers who achieved sensitivities of 97.0% and 99.4% at specificities of 89.7% and 87.2%, respectively. A good level of agreement with the reference was obtained ($\kappa = 0.713$) and was in concordance with the human observers ($\kappa = 0.775$ and $\kappa = 0.755$, respectively).

CONCLUSIONS: A machine learning system capable of automatically grading OCT scans into AMD severity stages was developed and showed similar performance as human observers. The proposed automatic system allows for a quick and reliable grading of large quantities of OCT scans, which could increase the efficiency of large-scale AMD studies and pave the way for AMD screening using OCT.

PMID: 28437528

Clin Exp Optom. 2017 Apr 23. [Epub ahead of print]

A deeper look at torpedo maculopathy.

Hamm C, Shechtman D, Reynolds S.

BACKGROUND: Torpedo maculopathy is a rare, congenital maculopathy classically diagnosed funduscopically as a 'torpedo-shaped' lesion located temporal to the fovea. This case describes a torpedo maculopathy with non-classic optical coherence tomographic (OCT) findings and collaborative OCT angiographic (OCTA) findings.

CASE REPORT: A 60-year-old Caucasian woman presented with a history of longstanding distortion and paracentral scotoma of the right eye. She had a positive family history of age-related macular degeneration. Visual acuity was 6/6 in each eye. Dilated fundus examination revealed a torpedo-shaped lesion in the right eye with a hypo-pigmented head pointing toward the fovea and a hyper-pigmented tail end. OCT imaging of the macula of the right eye revealed a subretinal cleft space with underlying thinning of the retinal pigment epithelium, increased choroidal reflectivity, as well as retinal pigment epithelial and choroidal excavation. OCTA choriocapillaris segmentation showed a hypo-reflective area associated with the lesion, adjacent to hyper-reflectivity. The patient was diagnosed with torpedo maculopathy of the right eye.

CONCLUSIONS: OCT and OCTA imaging have been instrumental in developing a deeper understanding of many maculopathies, allowing for accurate diagnosis of macular conditions. Although the aetiology remains unclear, these imaging devices may provide further insight into the lesion in torpedo maculopathy.

PMID: 28436087

Pathogenesis

J Ocul Pharmacol Ther. 2017 Apr 25. [Epub ahead of print]

A Novel Neuroprotective Small Molecule for Glial Cell Derived Neurotrophic Factor Induction and Photoreceptor Rescue.

Baranov P, Lin H, McCabe K, Gale D, Cai S, Lieppman B, Morrow D, Lei P, Liao J, Young M.

PURPOSE: Degenerative diseases of the retina, such as retinitis pigmentosa and age-related macular degeneration, are characterized by the irreversible loss of photoreceptors. Several growth factors, including glial cell derived neurotrophic factor (GDNF), have been shown to rescue retinal neurons. An alternative strategy to direct GDNF administration is its induction in host retina by small molecules. Here we studied the ability of a novel small molecule GSK812 to induce GDNF in vitro/in vivo and rescue photoreceptors.

METHODS: GDNF induction in vitro was assessed in human ARPE-19, human retinal progenitor cells (RPCs) and mouse pluripotent cell-derived eyecups. For time course pharmacokinetic and GDNF induction studies in C57Bl/6 mice, GSK812 sustained release formulation was injected intravitreally. The same delivery approach was used in the rhodopsin knockout mice and Royal College of Surgeon (RCS) rats to assess long-term GDNF induction and photoreceptor rescue.

RESULTS: The suspension provided sustained GSK812 delivery with 28 µg of drug remaining in the eye 2 weeks after a single injection. GSK812 suspension injection in C57Bl/6 mice resulted in significant

upregulation of GDNF mRNA (>1.8-fold) and protein levels (>2.8-fold). Importantly, GSK812 treatment resulted in outer nuclear layer preservation in rho-/- mice with a 2-fold difference in photoreceptor number. In the RCS rat, the GSK812 injection provided long-term rescue of photoreceptors and outer segments, accompanied by function preservation as well.

CONCLUSIONS: GSK812 is a potent neuroprotectant that can induce GDNF in normal and diseased retina. This induction results in photoreceptor rescue in 2 models of retinal degeneration.

PMID: 28441076

Mol Med Rep. 2017 Apr 20. [Epub ahead of print]

Different distributions of M1 and M2 macrophages in a mouse model of laser-induced choroidal neovascularization.

Zhou Y, Yoshida S, Kubo Y, Yoshimura T, Kobayashi Y, Nakama T, Yamaguchi M, Ishikawa K, Oshima Y, Ishibashi T.

Abstract: Choroidal neovascularization (CNV) is a serious complication of age-related macular degeneration. The aim of the present study was to investigate the expression and distribution of M1 and M2 macrophages in a laser-induced CNV adult mouse model. The mRNA expression levels of M1, M2 and pan macrophage markers, and macrophage-associated angiogenic cytokines, were determined by reverse transcription-quantitative polymerase chain reaction. Immunofluorescence studies were performed to determine the location of the macrophages. The expression levels of M1 macrophage markers increased to a greater extent compared with M2 markers in the retinal pigment epithelium (RPE)-choroid complexes following laser photocoagulation. By contrast, the expression levels of M2 macrophage markers increased primarily in the retinas. Immunofluorescence studies revealed that the increased number of cluster of differentiation (CD)206-positive cells were located primarily in the retina, whereas the CD80-positive cells were located around the site of CNVs in the RPE-choroid. In addition, the M1-associated cytokines increased to a greater extent in the RPE-choroid complexes, whereas the M2-associated cytokines were highly expressed in the retinas. These findings indicate that M1 and M2 macrophage numbers increased following CNV; however, the locations were different in this mouse model of laser-induced CNV. The results of the present study suggest that M1 macrophages have a more direct role in inhibiting the development of CNV.

PMID: 28440413

Mol Neurodegener. 2017 Apr 24;12(1):31.

Microglia-derived IL-1 β promotes chemokine expression by Müller cells and RPE in focal retinal degeneration.

Natoli R, Fernando N, Madigan M, Chu-Tan JA, Valter K, Provis J, Rutar M.

BACKGROUND: Chemokine signalling is required for the homing of leukocytes during retinal inflammation, and is associated with pathogenesis of diseases such as age-related macular degeneration (AMD). Here, we explore the role of interleukin-1 β (IL-1 β) in modulating AMD-associated chemokines Ccl2, Cxcl1, and Cxcl10 during photo-oxidative retinal damage, and the effect on both the accumulation of outer-retinal macrophages, and death of photoreceptors.

METHODS: Inhibition of retinal IL-1 β expression was performed using either siRNA or antibody neutralisation, which was intravitreally injected in SD rats prior to photo-oxidative damage. Changes in the expression and localisation of IL-1 β , Ccl2, Cxcl1 and Cxcl10 genes were assessed using qPCR and in situ hybridisation, while the recruitment of retinal macrophages was detected using immunohistochemistry for IBA1. Levels of photoreceptor cell death were determined using TUNEL.

RESULTS: Photo-oxidative damage elevated the expression of IL-1 β and inflammasome-related genes, and IL-1 β protein was detected in microglia infiltrating the outer retina. This was associated with increased expression of Ccl2, Cxcl1, and Cxcl10. Intravitreal IL-1 β inhibitors suppressed chemokine expression following damage and reduced macrophage accumulation and photoreceptor death. Moreover, in Müller and RPE cell cultures, and in vivo, Ccl2, Cxcl1 and Cxcl10 were variously upregulated when stimulated with IL-1 β , with increased macrophage accumulation detected in vivo.

CONCLUSIONS: IL-1 β is produced by retinal microglia and macrophages and promotes chemokine expression by Müller cells and RPE in retinal degeneration. Targeting IL-1 β may prove efficacious in broadly suppressing chemokine-mediated inflammation in retinal dystrophies such as AMD.

PMID: 28438165 PMCID: PMC5404662

Mol Vis. 2017 Apr 10;23:210-218. eCollection 2017.

Complement C5a receptor knockout has diminished light-induced microglia/macrophage retinal migration.

Song D, Sulewski ME Jr, Wang C, Song J, Bhuyan R, Sterling J, Clark E, Song WC, Dunaief JL.

PURPOSE: The complement system is involved in the pathogenesis of age-related macular degeneration (AMD). Because activated microglia are also associated with AMD, we studied the relationship between complement anaphylatoxin receptors and microglial recruitment.

METHODS: We assessed the effect of anaphylatoxin C3a receptor (C3aR) and C5a receptor (C5aR) knockout (KO) on light damage-induced migration of microglia/macrophages into the mouse outer retina via immunofluorescence and real-time quantitative PCR.

RESULTS: We found that the mRNA levels of C3, C5, C3aR, C5aR, and two activators of the complement alternative pathway, Cfb and Cfd, were all upregulated after light exposure. Retinal Iba1-positive microglia/macrophages express receptors for C3a and C5a. Light damage increased the number of retinal Iba1-positive cells and the mRNA levels of Iba1. Compared with the wild-type (WT) mice, these increases were attenuated in the C5aR KO mice but not in the C3aR KO mice.

CONCLUSIONS: C5aR but not C3aR promoted the recruitment of microglia/macrophages. These divergent properties of complement anaphylatoxins in the light damage model provide a rationale for testing the differential effects of these receptors in additional retinal and neurodegeneration models.

PMID: 28442885 PMCID: PMC5389337

J Lipid Res. 2017 Apr 25. [Epub ahead of print]

An In-silico model of retinal cholesterol dynamics (RCD Model): Insights into the pathophysiology of dry age-related macular degeneration.

Zekavat SM, Lu J, Maugeais C, Mazer NA.

Abstract: We developed an in-silico mathematical model of retinal cholesterol (Ch) dynamics (RCD) to quantify the physiological rate of Ch turnover in the rod outer segment (ROS), the lipoprotein transport mechanisms by which Ch enters and leaves the outer retina, and the rates of drusen growth and macrophage-mediated clearance in dry Age-Related Macular Degeneration (AMD). Based on existing experimental data and mechanistic hypotheses, we estimate the Ch turnover rate in the ROS to be 1-6 pg/mm²/min, dependent on the rate of Ch recycling in the outer retina, and find comparable rates for LDL receptor-mediated endocytosis of Ch by the retinal pigment epithelium (RPE), ABCA1-mediated Ch transport from the RPE to outer retina, ABCA1-mediated Ch efflux from the RPE to choroid, and the secretion of 70 nm ApoB-Ch particles from the RPE. The drusen growth rate is predicted to increase from

0.7 to 4.2 $\mu\text{m}/\text{year}$ in proportion to the flux of ApoB-Ch particles. The rapid regression of drusen may be explained by macrophage-mediated clearance if the macrophage density reaches ca. 3500 cells/ mm^2 . The RCD model quantifies retinal Ch dynamics and suggests that retinal Ch turnover and recycling, ApoB-Ch particle efflux, and macrophage-mediated clearance may explain the dynamics of drusen growth and regression.

PMID: 28442497

Int J Mol Sci. 2017 Apr 28;18(5).

A Review: Proteomics in Retinal Artery Occlusion, Retinal Vein Occlusion, Diabetic Retinopathy and Acquired Macular Disorders.

Cehofski LJ, Honoré B, Vorum H.

Abstract: Retinal artery occlusion (RAO), retinal vein occlusion (RVO), diabetic retinopathy (DR) and age-related macular degeneration (AMD) are frequent ocular diseases with potentially sight-threatening outcomes. In the present review we discuss major findings of proteomic studies of RAO, RVO, DR and AMD, including an overview of ocular proteome changes associated with anti-vascular endothelial growth factor (VEGF) treatments. Despite the severe outcomes of RAO, the proteome of the disease remains largely unstudied. There is also limited knowledge about the proteome of RVO, but proteomic studies suggest that RVO is associated with remodeling of the extracellular matrix and adhesion processes. Proteomic studies of DR have resulted in the identification of potential therapeutic targets such as carbonic anhydrase-I. Proliferative diabetic retinopathy is the most intensively studied stage of DR. Proteomic studies have established VEGF, pigment epithelium-derived factor (PEDF) and complement components as key factors associated with AMD. The aim of this review is to highlight the major milestones in proteomics in RAO, RVO, DR and AMD. Through large-scale protein analyses, proteomics is bringing new important insights into these complex pathological conditions.

PMID: 28452939

Sci Rep. 2017 Apr 28;7(1):1263.

Decreased Circulating Levels of Dickkopf-1 in Patients with Exudative Age-related Macular Degeneration.

Qiu F, Liu Z, Zhou Y, He J, Gong S, Bai X, Zeng Y, Liu Z, Ma JX.

Abstract: Aberrant activation of the Wnt/ β -catenin signaling pathway plays a pathogenic role in retinal inflammation and neovascularization. Here, we investigated whether circulating levels of Dickkopf-1 (DKK-1), a specific inhibitor of this pathway, are altered in patients with exudative age-related macular degeneration (AMD). Plasma was obtained from 128 patients with exudative AMD, 46 patients with atrophic AMD and 111 healthy controls. DKK-1 levels in plasma were measured using ELISA, and data analyzed with one-way ANOVA, logistic regression analysis and receiver-operating characteristic analysis (ROC). We found that DKK-1 levels were decreased in exudative AMD patients, compared with healthy controls ($P < 0.001$) and atrophic AMD patients ($P < 0.001$). The decrease was more prominent in patients with classic choroidal neovascularization (CNV) than those with occult CNV ($P < 0.001$). The odds ratio (OR) of exudative AMD was 11.71 (95% CI; 5.24-6.13) for lowest versus upper quartile of DKK-1 levels. For discriminating exudative AMD patients, the optimum diagnostic cutoff of DKK-1 was 583.1 pg/mL with the area under curve (AUC) 0.76 (95% CI, 0.70-0.82; $P < 0.001$), sensitivity 78.1% and specificity 63.1%. These findings suggested that decreased circulating DKK-1 levels are associated with the development and severity of exudative AMD, and have potential to become a biomarker for exudative AMD.

PMID: 28455497

ACS Chem Neurosci. 2017 Apr 27. [Epub ahead of print]

Artemisinin protects retinal neuronal cells against oxidative stress and restores rat retinal physiological function from light exposed-damage.

Yan F, Wang HT, Gao Y, Xu JP, Zheng W.

Abstract: Oxidative stress plays a key role in the pathogenesis of age-related macular degeneration (AMD), a leading cause of severe visual loss and blindness in the aging population which lacks any effective treatments currently. In this study, artemisinin, a well-known anti-malarial drug was found to suppress hydrogen peroxide (H₂O₂)-induced cell death in retinal neuronal RGC-5 cells. Artemisinin, in the therapeutically relevant dosage, concentration-dependently attenuated the accumulation of intracellular reactive oxygen species (ROS), increased mitochondrial membrane potential and decreased cell apoptosis in RGC-5 cells induced by H₂O₂. Western blot analysis showed that artemisinin upregulated the phosphorylation of p38 and extracellular signal-regulated kinases1/2 (ERK1/2) and reversed the inhibitory effect of H₂O₂ on the phosphorylation of these two kinases. Moreover, protective effect of artemisinin was blocked by the p38 kinase inhibitor PD160316 or ERK1/2 kinase pathway inhibitor PD98059, respectively. In contrast, c-Jun N-terminal kinase inhibitor and rapamycin had no effect in the protective effect of artemisinin. Taken together, these results demonstrated that artemisinin promoted the survival of RGC-5 cells from H₂O₂ toxicity via the activation of the p38 and ERK1/2 pathways. Interestingly, intravitreal injection of artemisinin, concentration-dependently reversed light exposed-damage (a dry AMD animal model) of rat retinal physiological function detected by flash electroretinogram. These results indicate that artemisinin can protect retinal neuronal functions from H₂O₂-induced damage in vitro and in vivo and suggest the potential application of artemisinin as a new drug in the treatment of retinal disorders like AMD.

PMID: 28447781

Biomed Res Int. 2017;2017:5343010.Epub 2017 Mar 20.

Ferulic Acid Suppresses Amyloid β Production in the Human Lens Epithelial Cell Stimulated with Hydrogen Peroxide.

Nagai N, Kotani S, Mano Y, Ueno A, Ito Y, Kitaba T, Takata T, Fujii N.

Abstract: It is well known that oxidative stresses induce the production of amyloid β (A β) in the brain, lens, and retina, leading to age-related diseases. In the present study, we investigated the effects of ferulic acid on the A β levels in H₂O₂-stimulated human lens epithelial (HLE) SRA 01/04 cells. Three types of A β peptides (A β 1-40, A β 1-42, and A β 1-43) were measured by ELISA, and the levels of mRNA for the expressed proteins related to A β production (APP, BACE1, and PS proteins) and degradation (ADAM10, NEP, and ECE1 proteins) were determined by quantitative real-time RT-PCR. H₂O₂ stimulation augmented gene expression of the proteins related to A β production, resulting in the production of three types of A β peptides. Treatment with 0.1 μ M ferulic acid attenuated the augmentations of gene expression and production of the proteins related to the secretion of three types of A β peptides in the H₂O₂-stimulated HLE cells. These results provided evidence of antioxidative functions of ferulic acid for lens epithelial cells.

PMID: 28409157 PMCID: PMC5376927

Angiogenesis. 2017 Apr 26. [Epub ahead of print]

Pathogenic role and therapeutic potential of pleiotrophin in mouse models of ocular vascular disease.

Wang W, LeBlanc ME, Chen X, Chen P1, Ji Y, Brewer M, Tian H, Spring SR, Webster KA, Li W.

Abstract: Angiogenic factors play an important role in the pathogenesis of diabetic retinopathy (DR),

neovascular age-related macular degeneration (nAMD) and retinopathy of prematurity (ROP). Pleiotrophin, a well-known angiogenic factor, was recently reported to be upregulated in the vitreous fluid of patients with proliferative DR (PDR). However, its pathogenic role and therapeutic potential in ocular vascular diseases have not been defined in vivo. Here using corneal pocket assays, we demonstrated that pleiotrophin induced angiogenesis in vivo. To investigate the pathological role of pleiotrophin we used neutralizing antibody to block its function in multiple in vivo models of ocular vascular diseases. In a mouse model of DR, intravitreal injection of pleiotrophin-neutralizing antibody alleviated diabetic retinal vascular leakage. In a mouse model of oxygen-induced retinopathy (OIR), which is a surrogate model of ROP and PDR, we demonstrated that intravitreal injection of anti-pleiotrophin antibody prevented OIR-induced pathological retinal neovascularization and aberrant vessel tufts. Finally, pleiotrophin-neutralizing antibody ameliorated laser-induced choroidal neovascularization, a mouse model of nAMD, suggesting that pleiotrophin is involved in choroidal vascular disease. These findings suggest that pleiotrophin plays an important role in the pathogenesis of DR with retinal vascular leakage, ROP with retinal neovascularization and nAMD with choroidal neovascularization. The results also support pleiotrophin as a promising target for anti-angiogenic therapy.

PMID: 28447229

Epidemiology

JAMA Ophthalmol. 2017 Apr 27. [Epub ahead of print]

Prevalence of Undiagnosed Age-Related Macular Degeneration in Primary Eye Care.

Neely DC, Bray KJ, Huisinigh CE, Clark ME, McGwin G Jr, Owsley C.

IMPORTANCE: Age-related macular degeneration (AMD) is the leading cause of irreversible vision impairment in older adults in the United States, yet little is known about whether AMD is appropriately diagnosed in primary eye care.

OBJECTIVES: To examine the prevalence of eyes with AMD in patients seen in primary eye care clinics who purportedly have normal macular health per their medical record and the association of AMD with patient and physician characteristics.

DESIGN, SETTING, AND PARTICIPANTS: In this cross-sectional study of primary eye care practices in Birmingham, Alabama, 644 persons 60 years or older with normal macular health per medical record based on their most recent dilated comprehensive eye examination by a primary eye care ophthalmologist or optometrist were enrolled from May 1, 2009, through December 31, 2011. Data analysis was performed from May 1, 2016, through December 20, 2016.

MAIN OUTCOMES AND MEASURES: Presence of AMD as defined by the Clinical Age-Related Maculopathy Staging system based on color fundus photography and a masked grader. Types of AMD-associated lesions were noted. Patient health and physician characteristics were collected.

RESULTS: The sample consisted of 1288 eyes from 644 participants (231 [35.9%] male and 413 [64.1%] female; mean [SD] age, 69.4 [6.1] years; 611 white [94.9%]) seen by 31 primary eye care ophthalmologists or optometrists. A total of 968 eyes (75.2%) had no AMD, in agreement with their medical record; 320 (24.8%) had AMD despite no diagnosis of AMD in the medical record. Among eyes with undiagnosed AMD, 32 (10.0%) had hyperpigmentation, 43 (13.4%) had hypopigmentation, 249 (77.8%) had small drusen, 250 (78.1%) had intermediate drusen, and 96 (30.0%) had large drusen. Undiagnosed AMD was associated with older patient age (odds ratio [OR], 1.06; 95% CI, 1.04-1.09; $P < .001$), male sex (age-adjusted OR, 1.39; 95% CI, 1.02-1.91; $P = .04$), and less than a high school education (age-adjusted OR, 2.40; 95% CI, 1.03-5.62; $P = .04$). Prevalence of undiagnosed AMD was not different for ophthalmologists and optometrists (age adjusted OR, 0.99; 95% CI, 0.71-1.36; $P = .94$).

CONCLUSIONS AND RELEVANCE: Approximately 25.0% of eyes deemed to be normal based on dilated eye examination by primary eye care physicians had macular characteristics that indicated AMD revealed

by fundus photography and trained raters. A total of 30.0% of eyes with undiagnosed AMD had AMD with large drusen that would have been treatable with nutritional supplements had it been diagnosed. Improved AMD detection strategies may be needed in primary eye care as more effective treatment strategies for early AMD become available in the coming years.

PMID: 28448669

Genetics

J Med Genet. 2017 Apr 26. [Epub ahead of print]

Frequent hypomorphic alleles account for a significant fraction of ABCA4 disease and distinguish it from age-related macular degeneration.

Zernant J, Lee W, Collison FT, Fishman GA, Sergeev YV, Schuerch K, Sparrow JR, Tsang SH, Allikmets R.

BACKGROUND: Variation in the ABCA4 gene is causal for, or associated with, a wide range of phenotypes from early onset Mendelian retinal dystrophies to late-onset complex disorders such as age-related macular degeneration (AMD). Despite substantial progress in determining the causal genetic variation, even complete sequencing of the entire open reading frame and splice sites of ABCA4 identifies biallelic mutations in only 60%-70% of cases; 20%-25% remain with one mutation and no mutations are found in 10%-15% of cases with clinically confirmed ABCA4 disease. This study was designed to identify missing causal variants specifically in monoallelic cases of ABCA4 disease.

METHODS: Direct sequencing and analysis were performed in a large familial ABCA4 disease cohort of predominately European descent (n=643). Patient phenotypes were assessed from clinical and retinal imaging data.

RESULTS: We determined that a hypomorphic ABCA4 variant c.5603A>T (p.Asn1868Ile), previously considered benign due to high minor allele frequency (MAF) (~7%) in the general population, accounts for 10% of the disease, >50% of the missing causal alleles in monoallelic cases, ~80% of late-onset cases and distinguishes ABCA4 disease from AMD. It results in a distinct clinical phenotype characterised by late-onset of symptoms (4th decade) and foveal sparing (85%). Intragenic modifying effects involving this variant and another, c.2588G>C (p.Gly863Ala) allele, were also identified.

CONCLUSIONS: These findings substantiate the causality of frequent missense variants and their phenotypic outcomes as a significant contribution to ABCA4 disease, particularly the late-onset phenotype, and its clinical variation. They also suggest a significant revision of diagnostic screening and assessment of ABCA4 variation in aetiology of retinal diseases.

PMID: 28446513

Stem cells

Am J Ophthalmol. 2017 Apr 20. [Epub ahead of print]

Experience With a Subretinal Cell-based Therapy in Patients With Geographic Atrophy Secondary to Age-related Macular Degeneration.

Ho AC, Chang TS, Samuel M, Williamson P, Willenbacher RF, Malone T.

PURPOSE: To evaluate the safety and tolerability of and clinical response to a single, subretinal dose of human umbilical tissue-derived cells (palucorcel [CNTO-2476]) in the eyes of adults aged ≥50 years with bilateral geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

DESIGN: Phase 1/2a, multicenter, open-label, dose-escalation, fellow-eye-controlled study.

METHODS: In the phase 1 portion, eyes were assigned to receive a single, subretinal dose of palucorcel (ranging from 6.0×10^4 to 5.6×10^5 viable cells). In the phase 2a portion, eyes were assigned to one of 2 palucorcel doses (6.0×10^4 or 3.0×10^5 cells) determined during the phase 1 portion. The intervention eye was the eye with worse baseline visual acuity.

RESULTS: A total of 35 eligible subjects underwent at least a partial surgical procedure. Palucorcel was administered in 33 eyes. Overall, 17.1% (6/35) of subjects experienced retinal detachments and 37.1% (13/35) experienced retinal perforations. No episodes of immune rejection or tumor formation were observed. At 1 year, ≥ 10 - and ≥ 15 -letter gains in BCVA were observed in 34.5% (10/29) and 24.1% (7/29) of eyes receiving palucorcel, respectively, and in 3.3% (1/30; for both) of fellow eyes.

CONCLUSIONS: The subretinal delivery procedure in this study was associated with a high rate of retinal perforations ($n = 13$) and retinal detachments ($n = 6$). When cells were sequestered in the subretinal space, palucorcel was well tolerated and may be associated with improvements in visual acuity. Larger randomized controlled studies are required to confirm these results. Future studies would require a modified surgical approach.

PMID: 28435054

Sci Transl Med. 2017 Apr 26;9(387).

What's old is new again: Autologous stem cell transplant for AMD.

Byrne LC.

Abstract: Transplanted RPE cells derived from induced pluripotent stem cells maintained vision and were well tolerated in a patient with age-related macular degeneration.

PMID: 28446683

Indian J Ophthalmol. 2017 Mar;65(3):177-183.

Pluripotent stem cells: A therapeutic source for age-related macular degeneration.

Parameswaran S, Krishnakumar S.

Abstract: Age-related macular degeneration (AMD) leads to progressive loss of central vision in the elderly. At a cellular level, there is aging of the retinal pigment epithelial (RPE) cells, and accumulation of lipofuscin that interferes with the proper functioning of RPE which eventually leads to apoptosis. Treatment depends on the stage of the disease. Wet AMD which has neovascularization is managed by local therapies such as laser photocoagulation and photodynamic therapy and is managed with injections of antivascular endothelial growth factor-based therapy. Unlike the wet AMD, an effective therapy does not exist for dry AMD and geographic atrophy. Cell replacement therapy has shown promise. This review discusses the opportunities in the various types of cell-based therapy, their limitations, and what is possible for India.

PMID: 28440245

Diet, lifestyle & low vision

Jpn J Ophthalmol. 2017 Apr 26. [Epub ahead of print]

Annual incidences of visual impairment during 10-year period in Mie prefecture, Japan.

Ikesugi K, Ichio T, Tsukitome H, Kondo M.

PURPOSE: To determine the annual incidence of visual impairment in a Japanese population during a 10-year period.

METHODS: We examined the physical disability certificates issued yearly between 2004 and 2013 in Mie prefecture, Japan. During this period 2468 visually impaired people were registered under the newly defined Act on Welfare of the Physically Disabled Persons' criteria. The age, sex distribution, and causes of visual impairment were determined from the certificates.

RESULTS: The major causes of visual impairment during the ten-year period were glaucoma (23.3%), diabetic retinopathy (17.3%), retinitis pigmentosa (12.2%), macular degeneration (9.0%), chorioretinal degeneration or high myopia (7.4%), optic atrophy (5.8%), stroke or brain tumor (5.4%) and cataracts (3.7%). The incidence of glaucoma was significantly higher throughout the period (2004-2013), and that of diabetic retinopathy was lower between 2007 and 2013. The incidence of retinitis pigmentosa did not change significantly during the 10-year period. The incidence of macular degeneration tended to increase between 2004 and 2007, but it decreased significantly between 2007 and 2013.

CONCLUSIONS: The results indicate that in Japan, the rates of the major causes of visual impairment altered in the most recent 10-year period reflecting the recent changes in the social background and advances in ocular and systemic treatment.

PMID: 28447270

Retina. 2017 Apr 27. [Epub ahead of print]

HEALTH CONDITIONS LINKED TO AGE-RELATED MACULAR DEGENERATION ASSOCIATED WITH DARK ADAPTATION.

Laíns I, Miller JB, Mukai R, Mach S, Vavvas D, Kim IK, Miller JW, Husain D.

PURPOSE: To determine the association between dark adaption (DA) and different health conditions linked with age-related macular degeneration (AMD).

METHODS: Cross-sectional study, including patients with AMD and a control group. Age-related macular degeneration was graded according to the Age-Related Eye Disease Study (AREDS) classification. We obtained data on medical history, medications, and lifestyle. Dark adaption was assessed with the extended protocol (20 minutes) of AdaptDx (MacuLogix). For analyses, the right eye or the eye with more advanced AMD was selected. Multivariate linear and logistic regressions were performed, accounting for age and AMD stage.

RESULTS: Seventy-eight subjects (75.6% AMD; 24.4% controls) were included. Multivariate assessments revealed that body mass index (BMI; $\beta = 0.30$, $P = 0.045$), taking AREDS vitamins ($\beta = 5.51$, $P < 0.001$), and family history of AMD ($\beta = 2.68$, $P = 0.039$) were significantly associated with worse rod intercept times. Abnormal DA (rod intercept time ≥ 6.5 minutes) was significantly associated with family history of AMD ($\beta = 1.84$, $P = 0.006$), taking AREDS supplements ($\beta = 1.67$, $P = 0.021$) and alcohol intake ($\beta = 0.07$, $P = 0.017$).

CONCLUSION:

Besides age and AMD stage, a higher body mass index, higher alcohol intake, and a family history of AMD seem to impair DA. In this cohort, the use of AREDS vitamins was also statistically linked with impaired DA, most likely because of an increased severity of disease in subjects taking them.

PMID: 28452839

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