Macular Disease Foundation AUSTRALIA
Our focus is your vision

MD Research News

Issue 257

Friday 4 December, 2015

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

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.

Drug treatment

Ophthalmology. 2015 Nov 11. [Epub ahead of print]

First-Year Visual Acuity Outcomes in the United Kingdom of Providing Aflibercept According to the VIEW Study Protocol for Age-Related Macular Degeneration.

Talks JS, Lotery AJ, Ghanchi F, Sivaprasad S, Johnston RL, Patel N, McKibbin M, Bailey C, Mahmood S; United Kingdom Aflibercept Users Group.

Collaborators

PURPOSE: Aflibercept has the potential advantage of reducing capacity problems by allowing 2 monthly visits for patients with neovascular macular degeneration (nAMD) compared with monthly pro re nata regimens that are the most commonly used in the United Kingdom. This study aimed to report the visual outcomes achieved in routine clinical practice using the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW) protocol at 1 year and compare with trials data and other real-world reports.

DESIGN: Retrospective data analysis from an electronic medical record.

PARTICIPANTS: Consecutive series of treatment-naïve patients initiated on aflibercept for nAMD at least 1 year before data extraction.

METHODS: Data were anonymized and remotely extracted from 16 centers in the United Kingdom that use the same electronic medical record (EMR) system (Medisoft Ophthalmology; Medisoft Limited, Leeds, UK).

MAIN OUTCOME MEASURES: The minimum data set defined before first data entry and mandated by the EMR included age, gender, visual acuity, injection episodes, and complications.

RESULTS: The mean age was 80.0 years (median, 81.0 years) and 63.7% were women. During the first year of treatment with aflibercept, 1840 treatment-naïve eyes of 1682 patients received a median of 8 (mean, 7.0) injections at a median of 8 (mean, 7.3) visits. The mean baseline visual acuity was 53.7 letters, improving to 58.8 letters (+5.1-letter gain) at 1 year. In first-treated eyes, the respective figures were 52.7 letters at baseline and 58.2 letters at 1 year, a gain of +5.5 letters. The proportion achieving 70 letters or more increased from 16.4% at baseline to 33.7% at 1 year, and 92% avoided moderate visual loss at 1 year.

CONCLUSIONS: The visual acuity outcomes are comparable to randomized trials and better than many previous real-world data collections, with a mean +5.1-letter gain at 1 year compared with +8.4 letters in the integrated analysis of the VIEW 1 and VIEW 2 studies. Early visual gains were maintained through the year. Collection of outcomes beyond clinical trials can have limitations but better reflect the full pool of patients actually treated and are important to determine whether a particular treatment is performing as expected. Such data also have the potential to improve services by setting up a mechanism to compare sites.

PMID: 26578446 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2015 Nov 25:1-8. [Epub ahead of print]

Association of Baseline Visual Acuity and Retinal Thickness With 1-Year Efficacy of Aflibercept, Bevacizumab, and Ranibizumab for Diabetic Macular Edema.

Wells JA, Glassman AR, Jampol LM, Aiello LP, Antoszyk AN, Baker CW, Bressler NM, Browning DJ, Connor CG, Elman MJ, Ferris FL, Friedman SM, Melia M, Pieramici DJ, Sun JK, Beck RW; Diabetic Retinopathy Clinical Research Network.

IMPORTANCE: Comparisons of the relative effect of 3 anti-vascular endothelial growth factor agents to treat diabetic macular edema warrant further assessment.

OBJECTIVE: To provide additional outcomes from a randomized trial evaluating 3 anti-vascular endothelial growth factor agents for diabetic macular edema within subgroups based on baseline visual acuity (VA) and central subfield thickness (CST) as evaluated on optical coherence tomography.

DESIGN, SETTING, AND PARTICIPANTS: Post hoc exploratory analyses were conducted of randomized trial data on 660 adults with diabetic macular edema and decreased VA (Snellen equivalent, approximately 20/32 to 20/320). The original study was conducted between August 22, 2012, and August 28, 2013. Analysis was conducted from January 7 to June 2, 2015.

INTERVENTIONS: Repeated 0.05-mL intravitreous injections of 2.0 mg of aflibercept (224 eyes), 1.25 mg of bevacizumab (218 eyes), or 0.3 mg of ranibizumab (218 eyes) as needed per protocol.

MAIN OUTCOMES AND MEASURES: One-year VA and CST outcomes within prespecified subgroups based on both baseline VA and CST thresholds, defined as worse (20/50 or worse) or better (20/32 to 20/40) VA and thicker (≥400 μm) or thinner (250 to 399 μm) CST.

RESULTS: In the subgroup with worse baseline VA (n = 305), irrespective of baseline CST, aflibercept showed greater improvement than bevacizumab or ranibizumab for several VA outcomes. In the subgroup with better VA and thinner CST at baseline (61-73 eyes across 3 treatment groups), VA outcomes showed little difference between groups; mean change was +7.2, +8.4, and +7.6 letters in the aflibercept, bevacizumab, and ranibizumab groups, respectively. However, in the subgroup with better VA and thicker CST at baseline (31-43 eyes), there was a suggestion of worse VA outcomes in the bevacizumab group; mean change from baseline to 1 year was +9.5, +5.4, and +9.5 letters in the aflibercept, bevacizumab, and ranibizumab groups, respectively, and VA letter score was greater than 84 (approximately 20/20) in 21 of 33 (64%), 7 of 31 (23%), and 21 of 43 (49%) eyes, respectively. The adjusted differences and 95% CIs were 39% (17% to 60%) for aflibercept vs bevacizumab, 25% (5% to 46%) for ranibizumab vs bevacizumab, and 13% (-8% to 35%) for aflibercept vs ranibizumab.

CONCLUSIONS AND RELEVANCE: These post hoc secondary findings suggest that for eyes with better initial VA and thicker CST, some VA outcomes may be worse in the bevacizumab group than in the aflibercept and ranibizumab groups. Given the exploratory nature of these analyses and the small sample size within subgroups, caution is suggested when using the data to guide treatment considerations for patients.

PMID: 26605836 [PubMed - as supplied by publisher]

Curr Eye Res. 2015 Nov 18:1-5. [Epub ahead of print]

Evaluation of the New "SAVE" Protocol in Diabetic Macular Edema Over the Course of Anti-VEGF Treatment.

Reznicek L, Bolz M, Garip A, Kampik A, Kernt M, Mayer WJ.

BACKGROUND: To evaluate a recently established grading protocol for diabetic macular edema (DME) over the course of intravitreal anti-VEGF treatment with ranibizumab.

METHODS: Fluorescein angiography images and optical coherence tomography scans before treatment and after 3 monthly applied intravitreal ranibizumab injections were retrospectively graded for each included study eye according to the recently introduced "SAVE" grading protocol ("S"= subretinal fluid; "A"= "area of retinal thickening"; "V"="vitreo-retinal abnormalities"; "E"="etiology of leakage focal versus non-focal") and correlated with best-corrected visual acuity (BCVA) in letters (lett).

RESULTS: Five of the 39 included study eyes had subretinal fluid ("S") before treatment which resolved during treatment. BCVA of study eyes with an initial retinal thickening smaller than one disc diameter ("A") was non-significantly higher compared to patients with a retinal thickening greater than one disc diameter (34.0 ± 17.9 lett versus 25.3 ± 13.3 lett, p=0.236) but became significant during treatment (40.5 ± 10.0 lett versus 28.3 ± 13.1 lett, p=0.004). No difference in BCVA was observed between patients with or without vitreo-retinal abnormalities ("V") before and during therapy. BCVA in patients with focal leakage ("E") was significantly higher than in patients with non-focal leakage before (33.1 ± 12.3 lett versus 23.3 ± 13.3 lett, p=0.017) and during (38.9 ± 10.9 lett versus 26.3 ± 12.6 lett, p=0.002) therapy.

CONCLUSIONS: Applying the grading protocol "SAVE", focal leakage ("E") was the only retrospectively observed parameter which significantly correlated with a better BCVA before therapy and over the course of treatment in patients with fovea-involving DME.

PMID: 26580417 [PubMed - as supplied by publisher]

Retina. 2015 Nov 18. [Epub ahead of print]

RANIBIZUMAB FOR DIABETIC MACULAR EDEMA REFRACTORY TO MULTIPLE PRIOR TREATMENTS.

Ciulla TA, Hussain RM, Ciulla LM, Sink B, Harris A.

PURPOSE: Diabetic macular edema can be refractory to multiple treatment modalities. Although there have been anecdotal reports of ranibizumab showing efficacy when other modalities provided limited benefit, little has been published on treatment for refractory diabetic macular edema. This study sought to investigate this observation further.

METHODS: Retrospective chart review.

RESULTS: Thirty-three eyes of 22 patients with refractory diabetic macular edema were treated with 0.3 mg intravitreal ranibizumab. This group of eyes received an average of 5.1 prior treatments (macular laser, intravitreal bevacizumab, triamcinolone acetonide, or dexamethasone implant). The mean best corrected visual acuity before the initial ranibizumab injection was 20/110 and the mean central subfield thickness was 384 μm. After 7 visits over an average of 48 weeks, during which an average of 6 ranibizumab injections were administered, the mean visual acuity improved to 20/90 and the mean central subfield thickness improved to 335 μm. Both central subfield thickness and best corrected visual acuity improved with number of days of follow-up in a statistically significant fashion ($P < 0.01$). Similarly, both central subfield thickness and visual acuity improved with number of ranibizumab injections in a linear fashion, but this was not statistically significant.

CONCLUSION: Ranibizumab can improve diabetic macular edema refractory to prior treatments of laser photocoagulation, intravitreal triamcinolone acetonide, and bevacizumab.

PMID: 26583309 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2015 Nov 19:1-7. [Epub ahead of print]

Effect of Ranibizumab on the Decision to Drive and Vision Function Relevant to Driving in Patients With Diabetic Macular Edema: Report From RESTORE, RIDE, and RISE Trials.

Bressler NM, Varma R, Mitchell P, Suñer IJ, Dolan C, Ward J, Ferreira A, Ehrlich JS, Turpcu A.

Importance: The potential effect of treatments for diabetic macular edema (DME) on driving should be of value to patients and clinicians, such as ophthalmologists and other physicians, who treat patients with diabetes mellitus.

Objective: To determine the effect of ranibizumab on driving and patient-reported vision function relevant to driving among patients with DME.

Design, Setting, and Participants: This exploratory post hoc analysis was conducted between October 1, 2011, and July 25, 2015, based on deidentified data from phase 3, multicenter, randomized clinical trials (RIDE, RISE, and RESTORE trials). Individuals assigned randomly to monthly sham, 0.3-mg ranibizumab, or 0.5-mg ranibizumab in RIDE and RISE or to macular laser, macular laser plus 0.5-mg ranibizumab (3-monthly doses, then as needed), or 0.5-mg (3-monthly doses, then as needed) in RESTORE.

Main Outcomes and Measures: Driving items from the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25) at baseline through 24 months in RIDE/RISE (pooled) and through 12 months in RESTORE.

Results: A total of 71.2% of 753 patients in RIDE/RISE and 50.4% of 345 patients in RESTORE reported driving at baseline; at least 55% reported still driving at follow-up. Among those not driving at baseline in RIDE/RISE, at 12 months, 7.0% (95% CI, -5.0 to 19.0) more in the 0.3-mg group and 14.4% (95% CI, 1.1 to 27.7) more in the 0.5-mg group vs the sham group reported driving. Among those not driving at baseline in RESTORE, at 12 months, 4.2% (95% CI, -7.7 to 16.1) more in the laser plus 0.5-mg group and 0.9% (95% CI, -10.3 to 12.1) more in the 0.5-mg group vs the laser group reported driving. Although balanced at baseline across treatment groups for RESTORE and RIDE/RISE, the proportion of patients with best-corrected visual acuity typically required for an unrestricted license (20/40 or better in at least 1 eye) appeared greater at month 12 in the ranibizumab groups (77 of 80 [96.3%] for 0.5 mg + laser and 91 of 93 [97.8%] for 0.5 mg) vs laser (71 of 79 [89.9%]) in RESTORE, and at months 12 (112 of 123 [91.1%] and 136 of 137 [99.3%] in 0.3- and 0.5-mg groups, respectively) and 24 (113 of 123 [91.9%] and 135 of 137 [98.5%] in the 0.3- and 0.5-mg groups, respectively) vs sham (121 of 147 [82.3%] and 122 of 147 [83.0%]) in RIDE/RISE.

Conclusions and Relevance: These results suggest that 12 months after initiating ranibizumab for vision impairment from center-involved DME, patients not driving at initiation of treatment are more likely to report driving and have driving-eligible visual acuity of 20/40 or better in the better-seeing eye than those treated with sham or laser.

PMID: 26584450 [PubMed - as supplied by publisher]

J Med Chem. 2015 Nov 15. [Epub ahead of print]

Discovery of Oral VEGFR-2 Inhibitors with Prolonged Ocular Retention that are Efficacious in Models of Wet Age-Related Macular Degeneration.

Meredith EL, Mainolfi N, Poor S, Qiu Y, Miranda K, Powers J, Liu D, Ma F, Solovay C, Rao C, Johnson L, Ji N, Artman G, Hardegger L, Hanks S, Shen S, Woolfenden A, Fassbender E, Sivak J, Zhang Y, Long D, Cepeda R, Liu F, Hosagrahara VP, Lee W, Tarsa P, Anderson K, Elliott J, Jaffee B.

Abstract: The benefit of intravitreal anti-VEGF therapy in treating wet age-related macular degeneration (AMD) is well established. Identification of VEGFR-2 inhibitors with optimal ADME properties for an ocular indication provides opportunities for dosing routes beyond intravitreal injection. To identify such inhibitors, we employed a high-throughput in vivo screening strategy with rodent models of choroidal neovascularization and iterative compound design to identify VEGFR-2 inhibitors with potential to benefit wet AMD patients. These compounds demonstrate preferential ocular tissue distribution and efficacy after oral administration while minimizing systemic exposure.

PMID: 26568411 [PubMed - as supplied by publisher]

Expert Opin Drug Saf. 2015 Nov 15. [Epub ahead of print]

Safety of monoclonal antibodies and related therapeutic proteins for the treatment of neovascular macular degeneration: addressing outstanding issues.

Ziemssen F, Sobolewska B, Deissler H, Deissler H.

Introduction: The VEGF inhibitors most widely used to treat neovascular age-dependent macular degeneration (nAMD) are different proteins with structural features potentially relevant to adverse effects (AE). Two of these are also established in cancer therapy (with higher dosages and AEs). The importance of ocular AE and extraocular activities is still subject of controversy and ongoing research.

Areas covered: Potential risks of intraocular VEGF inhibition based on prospective studies, in vitro investigations, pharmacokinetics, and hints from anti-cancer treatment.

Expert opinion: nAMD is a frequently observed chronic clinical condition severely affecting the visual function of elderly persons. Intravitreal injection of VEGF-inactivating proteins is highly effective to prevent loss of vision. Anti-VEGF therapy is well tolerated and low rates of ocular and systemic AEs in smaller trials suggest a very high benefit/risk ratio. The proteins established in nAMD therapy show similar efficacies. In the controversy over the off-label use of bevacizumab purely on ground of much lower cost, the small, but potentially relevant differences between the available drugs are easily either dramatized (by pharmaceutical companies) or trivialised (by health insurances) and even political interference is involved. Facing the lack of a convincing body of evidence regarding safety, further long-term study results seem necessary.

PMID: 26568279 [PubMed - as supplied by publisher]

JAMA. 2015 Nov 24;314(20):2137-46.

Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial.

Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, Jampol LM, Inusah S, Aiello LP, Antoszyk AN, Baker CW, Berger BB, Bressler NM, Browning D, Elman MJ, Ferris FL 3rd, Friedman SM, Marcus DM, Melia M, Stockdale CR, Sun JK, Beck RW.

IMPORTANCE: Panretinal photocoagulation (PRP) is the standard treatment for reducing severe visual loss from proliferative diabetic retinopathy. However, PRP can damage the retina, resulting in peripheral vision loss or worsening diabetic macular edema (DME).

OBJECTIVE: To evaluate the noninferiority of intravitreous ranibizumab compared with PRP for visual acuity outcomes in patients with proliferative diabetic retinopathy.

DESIGN, SETTING, AND PARTICIPANTS: Randomized clinical trial conducted at 55 US sites among 305 adults with proliferative diabetic retinopathy enrolled between February and December 2012 (mean age, 52 years; 44% female; 52% white). Both eyes were enrolled for 89 participants (1 eye to each study group), with a total of 394 study eyes. The final 2-year visit was completed in January 2015.

INTERVENTIONS: Individual eyes were randomly assigned to receive PRP treatment, completed in 1 to 3 visits (n = 203 eyes), or ranibizumab, 0.5 mg, by intravitreous injection at baseline and as frequently as every 4 weeks based on a structured re-treatment protocol (n = 191 eyes). Eyes in both treatment groups could receive ranibizumab for DME.

MAIN OUTCOMES AND MEASURES: The primary outcome was mean visual acuity change at 2 years (5-letter noninferiority margin; intention-to-treat analysis). Secondary outcomes included visual acuity area under the curve, peripheral visual field loss, vitrectomy, DME development, and retinal neovascularization.

RESULTS: Mean visual acuity letter improvement at 2 years was +2.8 in the ranibizumab group vs +0.2 in the PRP group (difference, +2.2; 95% CI, -0.5 to +5.0; P < .001 for noninferiority). The mean treatment

group difference in visual acuity area under the curve over 2 years was +4.2 (95% CI, +3.0 to +5.4; P < .001). Mean peripheral visual field sensitivity loss was worse (-23 dB vs -422 dB; difference, 372 dB; 95% CI, 213-531 dB; P < .001), vitrectomy was more frequent (15% vs 4%; difference, 9%; 95% CI, 4%-15%; P < .001), and DME development was more frequent (28% vs 9%; difference, 19%; 95% CI, 10%-28%; P < .001) in the PRP group vs the ranibizumab group, respectively. Eyes without active or regressed neovascularization at 2 years were not significantly different (35% in the ranibizumab group vs 30% in the PRP group; difference, 3%; 95% CI, -7% to 12%; P = .58). One eye in the ranibizumab group developed endophthalmitis. No significant differences between groups in rates of major cardiovascular events were identified.

CONCLUSIONS AND RELEVANCE: Among eyes with proliferative diabetic retinopathy, treatment with ranibizumab resulted in visual acuity that was noninferior to (not worse than) PRP treatment at 2 years. Although longer-term follow-up is needed, ranibizumab may be a reasonable treatment alternative, at least through 2 years, for patients with proliferative diabetic retinopathy.

PMID: 26565927 [PubMed - in process]

Acta Ophthalmol. 2015 Nov 13. [Epub ahead of print]

Symmetry in early response to intravitreal ranibizumab in bilateral diabetic macular oedema.

Guillard M, Dupas B, El Sanharawi M, Erginay A, Tadayoni R, Massin P.

PURPOSE: To study the symmetry in response to bilateral diabetic macular oedema (DME) treated with bilateral intravitreal injections of ranibizumab (IVR).

METHODS: The charts of 36 eyes of 18 patients treated with a loading dose of three monthly IVR in both eyes were retrospectively reviewed. Favourable anatomical response was defined as a decrease by more than 10% in baseline central macular thickness (CMT), and favourable functional response was defined as an increase in visual acuity (VA) ≥5 letters. A symmetric response was defined as a similar anatomical and/or functional response in the first (FE) and second (SE) treated eyes.

RESULTS: The VA improved significantly after ranibizumab treatment in both eyes ($p < 0.01$). A statistically significant positive correlation was found for the functional response to ranibizumab between the FE and the SE ($R2 = 0.26$, $p = 0.03$). The mean CMT decreased significantly in both eyes ($p < 0.01$). A strong positive correlation was observed between the anatomical response to ranibizumab in the FE and the SE ($R2 = 0.37$, $p = 0.01$). Symmetric favourable anatomical and functional responses were observed in 13 patients (72%). In two additional patients, an asymmetric functional response was observed despite a decrease in retinal thickness in both eyes.

CONCLUSION: Symmetric anatomical and functional responses were observed in 72% of patients with DME after three initial IVR in each eye. This finding could be of clinical interest in the decision to treat the fellow eye, in a disease where a bilateral involvement is frequent.

PMID: 26564668 [PubMed - as supplied by publisher]

Pharmacoeconomics. 2015 Nov 12. [Epub ahead of print]

Cost-Effectiveness Models in Age-Related Macular Degeneration: Issues and Challenges.

Schmier JK, Hulme-Lowe CK.

Abstract: Age-related macular degeneration (AMD) is a common ophthalmic condition that can have few symptoms in its early stage but can progress to major visual impairment. While there are no treatments for early-stage AMD, there are multiple modalities of treatment for advanced disease. Given the increasing prevalence of the disease, there are dozens of analyses of cost effectiveness of AMD treatments, but

methods and approaches vary broadly. The goal of this review was to identify, characterize, and critique published models in AMD and provide guidance for their interpretation. After a literature review was performed to identify studies, and exclusion criteria applied to limit the review to studies comparing treatments for AMD, we compared methods across the 36 studies meeting the review criteria. To some extent, variation was related to targeting different audiences or acknowledging the most appropriate population for a given treatment. However, the review identified potential areas of uncertainty and difficulty in interpretation, particularly regarding duration of observation periods and the importance of visual acuity as an endpoint or a proxy for patient-reported utilities. We urge thoughtful consideration of these study characteristics when comparing results.

PMID: 26563248 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2015 Nov 12. [Epub ahead of print]

[Effectiveness of Intravitreal Aflibercept Injections in Patients who had Received 10 and More Ranibizumab Injections in Advance]. [Article in German]

Lenk J, Matthé E, Pillunat LE, Sandner D.

Background: Since 2007, the standard treatment for age related macular degeneration has been intravitreal injection of ranibizumab. However, despite continuous treatment, some patients fail to achieve remission or stabilisation of the disease. Since 2012, the recombinant fusion protein aflibercept has been available as an alternative treatment. In this study, we investigated whether patients who appear to be resistant to ranibizumab would benefit from treatment with aflibercept.

Methodology: This retrospective study covered 83 eyes of 81 patients, for whom treatment switch from ranibizumab to aflibercept was indicated. Inclusion criteria were an age ≥ 50 years and at least 10 ranibizumab injections before a switch to aflibercept. Patients with severely impaired visual acuity were excluded. Primary outcomes were improvement or loss of visual acuity (VA) and evaluation of central macular thickness (CMT) via SD-OCT. Secondary endpoints were percentage of eyes without activity of the choroidal neovascular membrane after aflibercept injections and loss or gain of letters on the visual chart. Statistical analysis was performed using SPSS.

Results: VA was 0.83 ± 0.34 logMAR before the first aflibercept injection, with a slight but not statistically significant improvement up to 0.79 ± 0.33 logMAR after the third aflibercept injection (p = 0.205). On the other hand, there was a clear reduction of CMT in OCT, from 451.4 ± 263.0 to 288.2 ± 128.2 µm (p = 0.0001). Overall, 73% of eyes exhibited better or stable VA and 27% of eyes lost VA. Interestingly, eyes with worse initial VA gained greater benefit from the switch to aflibercept (p = 0.001).

Conclusion: A switch to aflibercept may lead to stabilisation of choroidal neovascularisation and thus stabilise the visual acuity for patients who appear to be no longer responsive to treatment with ranibizumab.

PMID: 26562136 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2015 Nov 1;46(10):1021-7.

Intravitreal Aflibercept for Neovascular AMD: Short-Term Clinical Effects of Intravitreal Aflibercept Injection as a Predictor of Long-Term Results.

Liu EM, Shah G, Blinder KJ, Smith BT, Thomas MA.

BACKGROUND AND OBJECTIVE: To study the relationship between early response to intravitreal aflibercept injection (IAI) for neovascular age-related macular degeneration (nAMD) and long-term visual outcomes

PATIENTS AND METHODS: Seventeen patients with nAMD participated in this prospective clinical trial. All

patients received three initial monthly IAIs, followed by IAIs at 8-week intervals. Study visits were scheduled at 1 week, followed by every 2 weeks for the first 3 months and then every 4 weeks until the conclusion of the study at 48 weeks.

RESULTS: Eight eyes (47%) were dry on spectral-domain optical coherence tomography by week 2 (early responders), and the remaining nine eyes took an average of 7.5 weeks for fluid resolution (late responders). The mean change in best-corrected visual acuity (BCVA) at the final visit was +11.9 letters from baseline (P = .002). Average BCVA gain in early responders was +11.6 letters compared to +12.2 letters in late responders (P = .7).

CONCLUSIONS: Although there was not a statistically significant correlation between early response to IAI and better long-term outcomes, both early and late responders maintained excellent visual outcomes at 48 weeks.

PMID: 26599244 [PubMed - in process]

Clin Ophthalmol. 2015 Nov 3;9:2049-2056.

Foveal structure during the induction phase of anti-vascular endothelial growth factor therapy for occult choroidal neovascularization in age-related macular degeneration.

Kano M, Sekiryu T, Sugano Y, Oguchi Y, Ojima A, Itagaki K, Saito M.

PURPOSE: To evaluate the efficacy of monthly injections of aflibercept and ranibizumab on foveal structure after three months, for the treatment of occult choroidal neovascularization (CNV) in age-related macular degeneration (AMD).

METHODS: We retrospectively studied 103 eyes with treatment-naïve neovascular AMD with occult and no classic CNV. Seventy-four of 103 eyes were treated with ranibizumab (intravitreal ranibizumab injection [IVR] group); 29 eyes were treated with aflibercept (intravitreal aflibercept injection [IAI] group). The best-corrected visual acuity and the retinal and choroidal structure at the fovea were evaluated using optical coherence tomography.

RESULTS: The total foveal thickness, the height of serous retinal detachments, and subfoveal choroidal thickness were compared with baseline, and the incidence of retinal pigment epithelial elevation significantly decreased in the IAI group compared with the IVR group. In contrast, the thickness of the sensory retina at the fovea significantly decreased in the IVR group when compared with the IAI group. The logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity improved more significantly in the IVR group (-0.085±0.164) than in the IAI group (-0.020±0.125) at 3 months (P=0.017).

CONCLUSION: After intravitreal injection, aflibercept more rapidly reduced subretinal fluid and subfoveal choroidal thickness. In contrast, ranibizumab decreased the sensory retinal thickness compared with aflibercept. The responses of the retinal and choroidal tissue to these anti-VEGF agents may be different during the induction phase for eyes with occult CNV secondary to neovascular AMD.

PMID: 26604674 [PubMed - as supplied by publisher] PMCID: PMC4639548

Br J Ophthalmol. 2015 Nov 19. [Epub ahead of print]

Incidence and clinical features of post-injection endophthalmitis according to diagnosis.

Rayess N, Rahimy E, Shah CP, Wolfe JD, Chen E, DeCroos FC, Storey P, Garg SJ, Hsu J.

PURPOSE: To compare the incidence and clinical features of endophthalmitis after intravitreal antivascular endothelial growth factor (VEGF) therapy for diabetic eye disease, neovascular age-related macular degeneration (AMD) and retinal vein occlusion (RVO).

METHODS: Multicentre, retrospective, consecutive case-control study. All patients treated with intravitreal bevacizumab, ranibizumab or aflibercept for diabetic eye disease, neovascular AMD or RVO between 1 January 2009 and 30 September 2013 at three retina practices were included in this study. The total number of anti-VEGF injections administered for the three indications was calculated using billing records. Endophthalmitis cases were identified using both endophthalmitis log sheets and billing records. Patient charts were reviewed to confirm that endophthalmitis was directly related to anti-VEGF injection and to record clinical features and culture results.

RESULTS: During the study period, a total of 353 978 intravitreal anti-VEGF injections were performed. Presumed infectious endophthalmitis occurred in 119 of 296 017 injections performed for neovascular AMD (1/2487, 0.040%), 12 of 24 541 for diabetic eye disease (1/2045, 0.049%) and 4 of 32 418 for RVO (1/8104, 0.012%). $\chi 2$ analysis found endophthalmitis rates to be higher in diabetic eye disease compared with RVO (p=0.010) and higher in neovascular AMD compared with RVO (p=0.014), while diabetic eye disease and neovascular AMD (p=0.517) had similar rates. The average age of the overall neovascular AMD patient population (81.9 years) was significantly older than the diabetic eye disease (64.7 years, p<0.001) and RVO (73.4 years, p<0.001) populations.

CONCLUSIONS: Endophthalmitis rates appear to be lower in eyes with RVO compared with diabetic eye disease and neovascular AMD, possibly due to impaired immunity in diabetics and waning immunity in the generally older AMD population.

PMID: 26584579 [PubMed - as supplied by publisher]

PLoS One. 2015 Nov 16;10(11):e0143085. eCollection 2015.

The Chronic Care for Wet Age Related Macular Degeneration (CHARMED) Study: A Randomized Controlled Trial.

Markun S, Dishy A, Neuner-Jehle S, Rosemann T, Frei A.

BACKGROUND: In real life, outcomes in wet age related macular degeneration (W-AMD) continue to fall behind the results from randomized controlled trials. The aim of this trial was to assess if outcomes can be improved by an intervention in healthcare organization following recommendations of the Chronic Care Model (CCM).

METHODS: Multi-centered randomized controlled clinical trial. The multifaceted intervention consisted in reorganization of care (delivery by trained chronic care coaches, using reminder systems, performing structured follow-up, empowering patients in self-monitoring and giving decision-support). In the control usual care was continued. Main outcome measures were changes in ETDRS visual acuity, optical coherence tomography (OCT) macular retinal thickness and quality of life (NEI VFQ-25 questionnaire).

RESULTS: 169 consecutive patients in Swiss ophthalmology centers were included. Mean ETDRS baseline visual acuity of eyes with W-AMD was 57.8 (± 18.7). After 12 months, the between-group difference in mean change of ETDRS visual acuity was -4.8 (95%CI: -10.8 to +1.2, p = 0.15); difference in mean change of OCT was +14.0 (95% CI -39.6 to 67.6, p = 0.60); difference in mean change of NEI VFQ-25 composite score mean change was +2.1(95%CI: -1.3 to +5.5, p = 0.19).

CONCLUSIONS: The intervention aiming at improving chronic care was not associated with favorable outcomes within 12 months. Other approaches need to be tested to close the evidence-performance gap in W-AMD.

PMID: 26569501 [PubMed - in process] PMCID: PMC4646575

Eye Vis (Lond). 2015 May 27;2:9.

Outer retinal tubulation in diabetic macular edema following anti-VEGF treatment.

Al-Halafi AM.

BACKGROUND: To address the presence and features of outer retinal tubulation (ORT) found in diabetic macular edema (DME) treated with anti-vascular endothelial growth factor (anti-VEGF) and to differentiate between ORT and cystoid DME, which have different plans of management.

METHODS: This was a retrospective review of a total of 514 patients investigated with spectral domain optical coherence tomography (OCT) in patients with diabetic macular edema treated with anti-VEGF. ORT was seen in 12 eyes of 11 patients. The morphologic characteristics of ORT and its progress over time were examined using OCT data. The retinal images were obtained by horizontal and vertical scans to analyze the possible presence of ORT and to explore their morphologic features and location in the retinal layers.

RESULTS: ORT was seen in DME treated with anti-VEGF. ORT was shown as round or ovoid hyporeflective spaces with hyperreflective borders on the B-scans, measuring 30 to 120 μm high and 30 to 1775 μm wide. The tubules generally remained stable over time. In a retinal practice specializing in advanced diabetic retinopathy clinic, this ORT was seen in 12 eyes of 11 patients during a 12-month period. ORT presented either after receiving 0.05 mL open-label intravitreal injections of 0.5 mg ranibizumab or 1.25 mg bevacizumab.

CONCLUSION: ORT is found in DME treated with anti-VEGF that may show damage to the outer retina secondary to the severity and chronicity of the DME. ORT may be a result of underlying chronic and severe diabetic macular edema that may occur later possibly secondary to retinal layers rearrangement after several anti-VEGF injections. It is important to differentiate between ORT and cystoids DME. The presence of the ORT entity alone without the presence of DME does not require further anti-VEGF re-injections.

PMID: 26613090 [PubMed - as supplied by publisher] PMCID: PMC4660850 Free PMC Article

Br J Ophthalmol. 2015 Nov 9. [Epub ahead of print]

Current therapeutic development for atrophic age-related macular degeneration.

Hanus J, Zhao F, Wang S.

Abstract: Age-related macular degeneration (AMD), a degenerative disorder of the central retina, is the leading cause of irreversible blindness in the elderly. The underlying mechanism of the advanced form of dry AMD, also named geographic atrophy (GA) or atrophic AMD, remains unclear. Consequently, no cure is available for dry AMD or GA. The only prevention option currently available is the Age-Related Eye Disease Study (AREDS) formulation, which has been demonstrated to slow down the progression of dry AMD. This review summarises recent advances in therapy for dry AMD and GA. Building on the new understanding of the disease and recent technological breakthroughs, numerous ongoing clinical trials have the goal of meeting the need to cure AMD. Therapeutic agents are being developed to target the key features of the disease, including inhibiting the complement pathway and other inflammatory pathways, reducing oxidative stress and protecting retinal pigment epithelial (RPE) cells, inhibiting lipofuscin and visual cycle, regenerating RPE cells from stem cells and restoring choroidal blood flow. Some of these therapeutic options, especially the stem cell-based therapy, hold great promise, which brings great hope for this devastating blinding disease.

PMID: 26553922 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Clin Experiment Ophthalmol. 2015 Nov 19. [Epub ahead of print]

Classification of image artefacts in optical coherence tomography angiography of the choroid in macular diseases.

Chen FK, Viljoen RD, Bukowska DM.

BACKGROUND: To evaluate and classify image artefacts in optical coherence tomography (OCT) angiography (OCTA) of the choroid in a group of patients with macular diseases.

DESIGN: Retrospective observational study.

PARTICIPANTS: 5 patients with age-related macular degeneration, 3 with central serous retinopathy, 1 with polypoidal choroidal vasculopathy and 1 with multiple evanescent white dot syndrome.

METHODS: OCTA and OCT reflectivity (OCTR) maps were reviewed along with their fluorescein angiography and indocyanine green angiography. 60 OCTA images (20 outer retina, 20 Sattler and 20 Haller layers) were graded for image artefacts by 2 examiners independently.

MAIN OUTCOME MEASURES: OCTA artefacts and their correlation with OCTR maps, angiography and OCT B-scans.

RESULTS: Artefacts (frequency) were classified into (1) motion (70-100%), (2) fringe washout (100%), (3) decorrelation projection (0-20%), (4) masking and unmasking (50-65%), and (5) stromal decorrelation signal (100%). Motion artefact in OCTA is characterised by horizontal dark lines or bands not apparent on OCTR map. Fringe washout creates signal void within choroidal vessels due to fast blood flow. Decorrelation projection from retinal vasculature and choroidal new vessels above the Bruch's membrane are seen within the choroidal OCTA image. Masking and unmasking artefacts occur in regions of pigment epithelial detachment and atrophy. Decorrelation signals can also be seen in the choroidal stroma.

CONCLUSIONS: Our classification system of artefact in choroidal OCTA establishes a common terminology for clinical interpretation. This is important in enhancing our understanding of the principles of OCTA acquisition and it also serves as a bench mark for reading centres.

PMID: 26584465 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Nov 11. [Epub ahead of print]

Drusen Volume and Retinal Pigment Epithelium Abnormal Thinning Volume Predict 2-Year Progression of Age-Related Macular Degeneration.

Folgar FA, Yuan EL, Sevilla MB, Chiu SJ, Farsiu S, Chew EY, Toth CA; Age Related Eye Disease Study 2 Ancillary Spectral-Domain Optical Coherence Tomography Study Group.

PURPOSE: To analyze the value of novel measures of retinal pigment epithelium-drusen complex (RPEDC) volume to predict 2-year disease progression of intermediate age-related macular degeneration (AMD).

DESIGN: Prospective, observational study.

PARTICIPANTS: Three hundred forty-five AMD and 122 non-AMD participants enrolled in the Age Related Eye Disease Study 2 Ancillary Spectral-Domain (SD) Optical Coherence Tomography (OCT) study.

METHODS: High-density SD OCT macular volumes were obtained at yearly study visits. The RPEDC abnormal thickening (henceforth, OCT drusen) and RPEDC abnormal thinning (RAT) volumes were generated by semiautomated segmentation of total RPEDC within a 5-mm-diameter macular field.

MAIN OUTCOME MEASURES: Volume change and odds ratio (OR) with 95% confidence intervals (CI) for progression to advanced AMD with choroidal neovascularization (CNV) or central geographic atrophy (GA).

RESULTS: Complete volumes were obtained in 265 and 266 AMD eyes and in 115 and 97 control eyes at baseline and at year 2, respectively. In AMD eyes, mean (standard deviation) OCT drusen volume increased from 0.08 mm3 (0.16 mm3) to 0.10 mm3 (0.23 mm3; $P < 0.001$), and RAT volume increased from 8.3 × 10-4 mm3 (20.8 × 10-4 mm3) to 18.4 × 10-4 mm3 (46.6 × 10-4 mm3; $P < 0.001$). Greater

baseline OCT drusen volume was associated with 2-year progression to CNV (P = 0.002). Odds of developing CNV increased by 31% for every 0.1-mm3 increase in baseline OCT drusen volume (OR, 1.31; 95% CI, 1.06-1.63; P = 0.013). Greater baseline RAT volume was associated with significant 2-year increase in RAT volume (P < 0.001), noncentral GA (P < 0.001), and progression to central GA (P < 0.001). Odds of developing central GA increased by 32% for every 0.001-mm3 increase in baseline RAT volume (OR, 1.32; 95% CI, 1.14-1.53; P < 0.001). In non-AMD eyes, all volumes were significantly lower than AMD eyes and showed no significant 2-year change.

CONCLUSIONS: Macular OCT drusen and RAT volumes increased significantly in AMD eyes over 2 years. These quantitative SD OCT biomarkers predict 2-year AMD progression and may serve as useful biomarkers for future clinical trials.

PMID: 26578448 [PubMed - as supplied by publisher]

Optom Vis Sci. 2015 Nov 24. [Epub ahead of print]

Cost-Utility Analyses of Cataract Surgery in Advanced Age-Related Macular Degeneration.

Ma Y, Huang J, Zhu B, Sun Q, Miao Y, Zou H.

PURPOSE: To explore the cost-utility of cataract surgery in patients with advanced age-related macular degeneration (AMD).

METHODS: Patients who were diagnosed as having and treated for age-related cataract and with a history of advanced AMD at the Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University, were included in the study. All of the participants underwent successful phacoemulsification with foldable posterior chamber intraocular lens implantation under retrobulbar anesthesia. Best-corrected visual acuity (BCVA) and utility value elicited by time trade-off method from patients at 3-month postoperative time were compared with those before surgery. Quality-adjusted life years (QALYs) gained in a lifetime were calculated at a 3% annual discounted rate. Costs per QALY gained were calculated using the bootstrap method, and probabilities of being cost-effective were presented using a cost-effectiveness acceptability curve. Sensitivity analyses were performed to test the robustness of the results.

RESULTS: Mean logarithm of the minimum angle of resolution BCVA in the operated eye increased from 1.37 ± 0.5 (Snellen, 20/469) to 0.98 ± 0.25 (Snellen, 20/191) (p < 0.001); BCVA in the weighted average from both eyes (=75% better eye + 25% worse eye) was changed from 1.13 ± 0.22 (Snellen, 20/270) to 0.96 ± 0.17 (Snellen, 20/182) (p < 0.001). Utility values from both patients and doctors increased significantly after surgery (p < 0.001 and p = 0.007). Patients gained 1.17 QALYs by cataract surgery in their lifetime. The cost per QALY was 8835 Chinese yuan (CNY) (1400 U.S. dollars [USD]). It is cost-effective at the threshold of 115,062 CNY (18,235 USD) per QALY in China recommended by the World Health Organization. The cost per QALY varied from 7045 CNY (1116 USD) to 94,178 CNY (14,925 USD) in sensitivity analyses.

CONCLUSIONS: Visual acuity and quality of life assessed by utility value improved significantly after surgery. Cataract surgery was a cost-effective intervention for patients with coexistent AMD.

PMID: 26605501 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Oct 23;9:1999-2003.

Efficacy of vitrectomy and epiretinal membrane peeling in eyes with dry age-related macular degeneration.

Mason JO 3rd, Patel SA.

OBJECTIVE: To study the efficacy of epiretinal membrane (ERM) peeling in eyes with dry age-related

macular degeneration (AMD).

METHODS: We retrospectively analyzed patient charts on 17 eyes (16 patients) that underwent ERM peeling with a concurrent diagnosis of dry AMD.

RESULTS: Eyes with concurrent dry AMD and with a good preoperative best-corrected visual acuity (BCVA) (better than or equal to 20/50) had a statistically significant mean BCVA improvement at 6 months after ERM peeling. There was a statistical increase in mean BCVA from 20/95 to 20/56 in dry AMD eyes, and no eyes showed worsening in BCVA at 6 months or at most recent follow-up. Five/seventeen (29.4%) eyes had cataract formation or progression. There were no other complications, reoperations, or reoccurrences.

CONCLUSION: ERM peeling in eyes with dry AMD may show significant improvement, especially in eyes with good preoperative BCVA. The procedure is relatively safe with low complications and reoccurrences.

PMID: 26604669 [PubMed - as supplied by publisher] PMCID: PMC4629981

J Pharm Biomed Anal. 2015 Oct 20;117:560-567. [Epub ahead of print]

A novel fluorescence-based assay for measuring A2E removal from human retinal pigment epithelial cells to screen for age-related macular degeneration inhibitors.

Jin HL, Lee SC, Kwon YS, Choung SY, Jeong KW.

Abstract: Age-related macular degeneration (AMD) is a common retinal disease that leads to irreversible central vision loss in the elderly population. Recent studies have identified many factors related to the development of dry AMD, such as aging, cigarette smoking, genetic predispositions, and oxidative stress, eventually inducing the accumulation of lipofuscin, which is one of the most critical risk factors. One of the major lipofuscins in retinal pigment epithelial (RPE) cells is N-retinylidene-N-retinylethanolamine (also known as A2E), a pyridinium bis-retinoid. Currently there is a lack of effective therapy to prevent or restore vision loss caused by dry AMD. Recent studies have shown that 430nm blue light induces the oxidation of A2E and the activation of caspase-3 to subsequently cause the death of RPE cells, suggesting that removal of A2E from retinal pigment cells might be critical for preventing AMD. Here, we developed a fluorescence-labeled A2E analog (A2E-BDP) that functions similar to A2E in RPE cells, but is more sensitive to detection than A2E. A2E-BDP-based tracing of intracellular A2E will be helpful, not only for studying the accumulation and removal of A2E in human RPE cells but also for identifying possible inhibitors of AMD.

PMID: 26604166 [PubMed - as supplied by publisher]

Int Med Case Rep J. 2015 Oct 23;8:263-266.

En-face optical coherence tomography angiography of neovascularization elsewhere in hemicentral retinal vein occlusion.

Sogawa K, Nagaoka T, Ishibazawa A, Takahashi A, Tani T, Yoshida A.

PURPOSE: To evaluate how the growth of neovascularization elsewhere (NVE) was delineated in an eye with hemicentral retinal vein occlusion (CRVO) using optical coherence tomography (OCT) angiography.

PATIENTS AND METHODS: We examined a 64-year-old man diagnosed with hemi-CRVO. The area around the occluded vein was scanned using a spectral-domain OCT device (RTVue XR Avanti). Blood flow was detected using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. Color fundus photography, fluorescein angiography (FA), and OCT angiography examinations were performed at the first visit and at 3 and 6 months postpresentation.

RESULTS: At the first visit, FA revealed delayed retinal venous filling and extensive areas of capillary

nonperfusion. The patient underwent a trial of intravitreal ranibizumab injection (0.5 mg/0.05 mL) for the treatment of macular edema. At 3 months postpresentation, there was no NVE around the occluded vein in the en-face SSADA image, but at 6 months, NVE appeared on the occluded veins. The en-face SSADA image showed the NVE structure in the fibrovascular membrane on the occluded vein more clearly than FA images.

CONCLUSION: OCT angiography clearly visualized the sprouting of NVE in an eye with hemi-CRVO. New findings of the vascular structure of NVE in hemi-CRVO were revealed using the en-face SSADA algorithm.

PMID: 26604832 [PubMed - as supplied by publisher] PMCID: PMC4629966

Br J Ophthalmol. 2015 Nov 27. [Epub ahead of print]

Extramacular drusen are highly associated with age-related macular degeneration, but not with CFH and ARMS2 genotypes.

Ersoy L, Schick T, de Graft D, Felsch M, Hoyng CB, den Hollander AI, Kirchhof B, Fauser S, Liakopoulos S.

BACKGROUND: To evaluate the association of extramacular drusen (EMD) with age-related macular degeneration (AMD) and with complement factor H (CFH rs1061170) and age-related maculopathy susceptibility 2 (ARMS2 rs10490924) polymorphisms in individuals with and without AMD.

METHODS: In this case-control study, AMD staging was performed in 622 individuals. EMD were defined as ≥10 drusen (including ≥1 intermediate drusen) outside the Early Treatment of Diabetic Retinopathy Study Grid within field 2. Genotype associations for CFH and ARMS2 variants were assessed using logistic regression analysis.

RESULTS: EMD (n=213) showed a strong association with AMD (OR=3.85; p=1.66×10-13). AMD (n=316) was strongly associated with CFH (p=1.78×10-7) and ARMS2 genotypes (p=1.67×10-8). After adjustment for AMD, age and gender, EMD were neither associated with CFH (p=0.11) nor with ARMS2 (p=0.45) genotypes. In individuals without AMD, the groups with and without EMD showed no differences regarding both genetic variants.

CONCLUSIONS: The strong association between drusen within and outside of the macula suggests a common pathogenesis. However, EMD were not AMD-independently associated with CFH or ARMS2 genotypes. Our results indicate that patients without AMD but with EMD can serve as controls in studies evaluating AMD risk factors. Further studies are required to elucidate the aetiology and clinical relevance of EMD.

PMID: 26614632 [PubMed - as supplied by publisher]

Retina. 2015 Nov 18. [Epub ahead of print]

CORRELATION OF VISUAL ACUITY WITH FIBROTIC SCAR LOCATION IN TREATED NEOVASCULAR AGE-RELATED MACULAR DEGENERATION EYES.

Ryu CL, Al-Humaid S, Rampakakis E, Galic IJ, Chen JC.

PURPOSE: To determine whether the optical coherence tomography location of a subfoveal fibrovascular scar is correlated with visual outcome in eyes successfully treated with antivascular endothelial growth factor agents for neovascular age-related macular degeneration.

METHODS: Fifty-six eyes from 56 patients with a subfoveal disciform scar after antivascular endothelial growth factor treatment were included. The initial and final visual acuity, fluorescein angiography, and spectral domain optical coherence tomography scar characteristics were retrospectively reviewed.

RESULTS: Thirty-five of 56 eyes (62.5%) were classified as having entirely subretinal pigment epithelial

(sub-RPE) scars, and 21 eyes (37.5%) had subretinal component scars. Mean initial visual acuity was similar between sub-RPE and subretinal scars (20/100 vs. 20/125, P = 0.517); mean final visual acuity was better in the sub-RPE scar group (20/60 vs. 20/200, P = 0.001). Eyes with sub-RPE scar had better preservation of the external limiting membrane, ellipsoid layer, and retinal thickness (P < 0.001, P = 0.017, P = 0.004, respectively) than subretinal component scar eyes. There was no difference between the groups in scar thickness or scar area (P = 0.707, P = 0.186, respectively).

CONCLUSION: Sub-RPE location of subfoveal scarring in eyes treated for neovascular age-related macular degeneration is associated with better preservation of outer retinal structures and better vision, when compared with a subretinal scar.

PMID: 26583310 [PubMed - as supplied by publisher]

Optom Vis Sci. 2015 Nov 18. [Epub ahead of print]

Functional Visual Acuity in Age-Related Macular Degeneration.

Tomita Y, Nagai N, Suzuki M, Shinoda H, Uchida A, Mochimaru H, Izumi-Nagai K, Sasaki M, Tsubota K, Ozawa Y.

PURPOSE: We evaluated whether a functional visual acuity (FVA) system can detect subtle changes in central visual acuity that reflect pathological findings associated with age-related macular degeneration (AMD).

METHODS: Twenty-eight patients with unilateral AMD and logMAR monocular best corrected VA better than 0 in both eyes, as measured by conventional chart examination, were analyzed between November 2012 and April 2013. After measuring conventional VA, FVA, and contrast VA with best correction, routine eye examinations including spectral domain-optical coherence tomography were performed. Standard Schirmer test was performed, and corneal and lens densities were measured.

RESULTS: The FVA score ($p < 0.001$) and visual maintenance ratio ($p < 0.001$) measured by the FVA system, contrast VA ($p < 0. 01$), and conventional VA ($p < 0.01$) were significantly worse in the AMD-affected eyes than in the fellow eyes. No significant differences were observed in the anterior segment conditions. Forward stepwise regression analysis demonstrated that the length of interdigitation zone disruption, as visualized by optical coherence tomography imaging, correlated with the FVA score ($p < 0.01$) but not with any other parameters investigated.

CONCLUSIONS: The FVA system detects subtle changes in best corrected VA in AMD-affected eyes and reflects interdigitation zone disruption, an anatomical change in the retina recorded by optical coherence tomography. Further studies are required to understand the value of the FVA system in detecting subtle changes in AMD.

PMID: 26583795 [PubMed - as supplied by publisher]

Transl Vis Sci Technol. 2015 Oct 30;4(5):10. eCollection 2015.

Reengineering Human Bruch's Membrane Increases Rod Outer Segment Phagocytosis by Human Retinal Pigment Epithelium.

Moreira EF, Cai H, Tezel TH, Fields MA, Del Priore LV.

PURPOSE: We have shown previously that Bruch's membrane (BM) aging decreases retinal pigment epithelium (RPE) phagocytosis. Herein, we determine the effects of BM reengineering on RPE

phagocytosis.

METHODS: BM explants were dissected from young and old donor eyes. Some old BM explants were reengineered by cleaning with Triton X-100 and/or coating with extracellular matrix (ECM) ligands. ARPE-19 cell-derived ECM (ARPE-ECM) modified ("aged") by sodium nitrite was subjected to similar treatments. ARPE-19 cells were then cultured to confluence onto the different surfaces. Fluorescently-labeled bovine rod outer segments (ROS) were fed to cells with or without αVβ5 integrin antibody. Image acquisition and phagocytosis quantification was performed by fluorescence microscopy and ImageJ analysis.

RESULTS: Cleaning old donor-derived BM with detergent does not increase the uptake of ROS, but a combination of cleaning and coating with ECM ligands significantly increases RPE phagocytosis (54.9 ± 6.2 vs. 83.5 ± 6.5 arbitrary units; $P < 0.05$) to levels closer to young donor BM (123.6 ± 9.9 arbitrary units). Similar effects were observed on nitrite-modified ARPE-ECM subjected to the same treatments. Incubation of αVβ5 blocking antibody with ROS significantly decreased RPE phagocytosis.

CONCLUSIONS: The detrimental effects of aging BM on RPE phagocytosis can be reversed by reengineering the BM surface with detergent cleaning and recoating with ECM ligands.

TRANSLATION RELEVANCE: These results demonstrate that the therapeutic success of transplanted RPE cells may require, at least in part, reengineering of diseased BM to make it a more suitable environment for attachment, survival and proper functioning of the RPE.

PMID: 26557417 [PubMed] PMCID: PMC4633034

Proteomics Clin Appl. 2015 Nov 20. [Epub ahead of print]

Imaging mass spectrometry of the visual system: Advancing the molecular understanding of retina degenerations.

Bowrey HE, Anderson DM, Pallitto P, Gutierrez DB, Fan J, Crouch RK, Schey KL, Ablonczy Z.

Abstract: Visual sensation is fundamental for quality of life, and loss of vision to retinal degeneration is a debilitating condition. The eye is the only part of the central nervous system that can be non-invasively observed with optical imaging. In the clinics, various spectroscopic methods provide high spatial resolution images of the fundus and the developing degenerative lesions. However, the currently utilized tools are not specific enough to establish the molecular underpinnings of retinal diseases. In contrast, imaging mass spectrometry (IMS) is a powerful tool to identify molecularly specific disease indicators and classification markers. This technique is particularly well suited to the eye, where molecular information can be correlated with clinical data collected via non-invasive diagnostic imaging modalities. Recent studies during the last few recent years have uncovered a plethora of new spatially-defined molecular information on several vision-threatening diseases, including age-related macular degeneration (AMD), Stargardt disease, glaucoma, cataract, as well as lipid disorders. Even though mass spectrometry inside the eye cannot be performed non-invasively, by linking diagnostic and molecular information, these studies are the first step toward the development of smart ophthalmic diagnostic and surgical tools. Here we provide an overview of current approaches applying IMS technology to ocular pathology. This article is protected by copyright. All rights reserved.

PMID: 26586164 [PubMed - as supplied by publisher]

Phys Med Biol. 2015 Nov 18;60(24):9203-9213. [Epub ahead of print]

Kilovoltage radiosurgery with gold nanoparticles for neovascular age-related macular degeneration (AMD): a Monte Carlo evaluation.

Brivio D, Zygmanski P, Arnoldussen M, Hanlon J, Chell E, Sajo E, Makrigiorgos GM, Ngwa W.

Abstract: This work uses Monte Carlo radiation transport simulation to assess the potential benefits of gold nanoparticles (AuNP) in the treatment of neovascular age-related macular degeneration with stereotactic radiosurgery. Clinically, a 100 kVp x-ray beam of 4 mm diameter is aimed at the macula to deliver an ablative dose in a single fraction. In the transport model, AuNP accumulated at the bottom of the macula are targeted with a source representative of the clinical beam in order to provide enhanced dose to the diseased macular endothelial cells. It is observed that, because of the AuNP, the dose to the endothelial cells can be significantly enhanced, allowing for greater sparing of optic nerve, retina and other neighboring healthy tissue. For 20 nm diameter AuNP concentration of 32 mg g-1, which has been shown to be achievable in vivo, a dose enhancement ratio (DER) of 1.97 was found to be possible, which could potentially be increased through appropriate optimization of beam quality and/or AuNP targeting. A significant enhancement in dose is seen in the vicinity of the AuNP layer within 30 μm, peaked at the AuNP-tissue interface. Different angular tilting of the 4 mm beam results in a similar enhancement. The DER inside and in the penumbra of the 4 mm irradiation-field are almost the same while the actual delivered dose is more than one order of magnitude lower outside the field leading to normal tissue sparing. The prescribed dose to macular endothelial cells can be delivered using almost half of the radiation allowing reduction of dose to the neighboring organs such as retina/optic nerve by 49% when compared to a treatment without AuNP.

PMID: 26576672 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 Nov 19. [Epub ahead of print]

Müller glia activation by VEGF-antagonizing drugs: An in vitro study on rat primary retinal cultures.

Gaddini L, Varano M, Matteucci A, Mallozzi C, Villa M, Pricci F, Malchiodi-Albedi F.

Abstract: The effects of the anti-Vascular Endothelial Growth Factor (VEGF) drugs ranibizumab and aflibercept were studied in Müller glia in primary mixed cultures from rat neonatal retina. Treatment with both agents induced activation of Müller glia, demonstrated by increased levels of Glial Fibrillary Acidic Protein. In addition, phosphorylated Extracellular-Regulated Kinase 1/2 (ERK 1/2) showed enhanced immunoreactivity in activated Müller glia. Treatment with aflibercept induced an increase in K+ channel (Kir) 4.1 levels and both drugs upregulated Aquaporin 4 (AQP4) in activated Müller glia. The results show that VEGF-antagonizing drugs influence the homeostasis of Müller cells in primary retinal cultures, inducing an activated phenotype. Upregulation of Kir4.1 and AQP4 suggests that Müller glia activation following anti-VEGF drugs may not depict a detrimental gliotic reaction. Indeed, it could represent one of the mechanisms able to contribute to the therapeutic effects of these drugs, particularly in the presence of macular edema.

PMID: 26607807 [PubMed - as supplied by publisher]

Arterioscler Thromb Vasc Biol. 2015 Nov 24. [Epub ahead of print]

Myeloid-Derived Vascular Endothelial Growth Factor and Hypoxia-Inducible Factor Are Dispensable for Ocular Neovascularization.

Liyanage SE, Fantin A, Villacampa P, Lange CA, Denti L, Cristante E, Smith AJ, Ali RR, Luhmann UF, Bainbridge JW, Ruhrberg C.

OBJECTIVE: Ocular neovascularization (ONV) is a pathological feature of sight-threatening human diseases, such as diabetic retinopathy and age-related macular degeneration. Macrophage depletion in mouse models of ONV reduces the formation of pathological blood vessels, and myeloid cells are widely considered an important source of the vascular endothelial growth factor A (VEGF). However, the importance of VEGF or its upstream regulators hypoxia-inducible factor-1α and hypoxia-inducible factor-2α as myeloid-derived regulators of ONV remains to be determined.

APPROACH AND RESULTS: We used 2 mouse models of ONV, choroidal neovascularization and oxygen-

induced retinopathy, to show that Vegfa is highly expressed by several cell types, but not myeloid cells during ONV. Moreover, myeloid-specific VEGF ablation did not reduce total ocular VEGF during choroidal neovascularization or oxygen-induced retinopathy. In agreement, the conditional inactivation of Vegfa, Hif1a, or Hif2a in recruited and resident myeloid cells that accumulated at sites of neovascularization did not significantly reduce choroidal neovascularization or oxygen-induced retinopathy.

CONCLUSIONS: The finding that myeloid cells are not a significant local source of VEGF in these rodent models of ONV suggests that myeloid function in neovascular eye disease differs from wound healing and other neovascular pathologies.

PMID: 26603154 [PubMed - as supplied by publisher]

Restor Neurol Neurosci. 2015 Nov 17. [Epub ahead of print]

Hyper-vision of mirror symmetry in patients with macular degeneration reflects parafoveal cortical reorganization.

Clara C, Elisa D, Luisa P, Giovanni S, Luca B.

PURPOSE: This study aims at comparing participants with juvenile macular degeneration (MD) and normally sighted observers in their sensitivity to mirror and translational symmetry.

METHODS: We measured in 25 normal sighted and 9 MD participants sensitivity (d') to detect the symmetry of two dot patterns presented at the opposite sides of their central scotoma.

RESULTS: At a large dot patterns separation (13.3 deg), at which detection failed in normally sighted observers, MD patients had high sensitivity to mirror symmetry, whereas translational symmetry was undetected.

CONCLUSIONS: The mirror-translational dissociation is not predicted by the well-known phenomenon of shrinking the location of images surrounding the scotoma. Our results indicate higher capacity of MD with respect to normally sighted observers to organize mirror symmetric dot patterns far apart into a unique percept. Our results suggest that MD have acquired the capability to use information only present in mirror symmetry, i.e., the co-aligned position of the centre of low-frequency filters connecting symmetric dot pairs on opposite sides of the scotoma. This relevant functional change in vision of MD patients may find its explanation in a functionally acquired high-level cortical representation of visual input.

PMID: 26599474 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2015 Nov 1;46(10):1056-7.

Optical Coherence Tomography Angiography Imaging of Quiescent Choroidal Neovascularization in Age-Related Macular Degeneration.

Nehemy MB, Brocchi DN, Veloso CE.

Abstract: A 67-year-old asymptomatic man presented with bilateral drusen. Spectral-domain optical coherence tomography (OCT) showed no signs of choroidal neovascularization (CNV) and no intraretinal or subretinal fluid. OCT angiography (OCTA) revealed the presence of a type 1 CNV in the right eye. Management options were discussed with the patient, who opted for a clinical follow-up. This is the first description demonstrating the OCTA characteristics of a quiescent CNV secondary to age-related macular degeneration.

PMID: 26599251 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Nov 1;56(12):7388-97.

Cerebral Involvement in Stargardt's Disease: A VBM and TBSS Study.

Gaia O, Melillo P, Sirio C, D'Alterio FM, Prinster A, Testa F, Brunetti A, Simonelli F, Quarantelli M.

PURPOSE: To assess whether and to what extent macro- and/or microstructural modifications are present in the brain of patients with selective central visual loss due to a juvenile macular degeneration, Stargardt's disease (STGD), taking advantage of the complementary information provided by voxel-based morphometry (VBM) and diffusion tensor imaging (DTI).

METHODS: Eighteen patients with clinical and molecular diagnosis of STGD related to ABCA4 mutations and 23 normally sighted volunteers of comparable age and sex were enrolled. Structural T1-weighted (T1w) volumes, for brain tissue volume assessment by segmentation, and DTI, for the investigation of diffusivity parameters via a tract-based spatial statistics (TBSS) procedure, were acquired at 3 Tesla in all subjects. All patients underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA), biomicroscopy, ophthalmoscopy, electroretinography (ERG), microperimetry, and optical coherence tomography (OCT). Correlations between imaging data and clinical measures were tested.

RESULTS: Stargardt's disease patients showed a significant gray matter (GM) loss bilaterally in the occipital cortices, extending into the right precuneus, and in the fronto-orbital cortices. At TBSS, significant reductions in fractional anisotropy were detected throughout large regions in the supratentorial white matter (WM), more pronounced in the posterior areas. Gray matter volume correlated directly with mean visual sensitivity in the right middle frontal and left calcarine gyri, and inversely with retinal thickness in the left supramarginal gyrus.

CONCLUSIONS: In STGD, widespread microstructural WM alterations are present, suggestive of minor fiber loss coupled with GM loss, also in cortical regions not traditionally linked to visual pathways, at least partly related to the retinal damage.

PMID: 26574798 [PubMed - in process]

Nippon Ganka Gakkai Zasshi. 2015 Oct;119(10):671-7.

[Diagnostic Criteria for Atrophic Age-related Macular Degeneration]. [Article in Japanese]

Takahashi K, Shiraga F, Ishida S, Kamei M, Yanagi Y, Yoshimura N.

Abstract: Diagnostic criteria for dry age-related macular degeneration is described. Criteria include visual acuity, fundscopic findings, diagnostic image findings, exclusion criteria and classification of severity grades. Essential findings to make diagnosis as "geographic atrophy" are, 1) at least 250 μm in diameter, 2) round/oval/cluster-like or geographic in shape, 3) sharp delineation, 4) hypopigmentation or depigmentation in retinal pigment epithelium, 5) choroidal vessels are more visible than in surrounding area. Severity grades were classified as mild, medium and severe by relation of geographic atrophy to the fovea and attendant findings.

PMID: 26571627 [PubMed - in process]

Ophthalmic Res. 2015 Dec;55(1):45-52. Epub 2015 Nov 17.

Autologous Internal Limiting Membrane Fragment Transplantation for Large, Chronic, and Refractory Macular Holes.

De Novelli FJ, Preti RC, Ribeiro Monteiro ML, Pelayes DE, Junqueira Nóbrega M, Takahashi WY.

OBJECTIVE: To evaluate a technique of autologous internal limiting membrane (ILM) fragment transplantation for the treatment of large, chronic, and/or refractory macular holes (MH).

DESIGN: This was a 6-month prospective interventional case series.

METHOD: Ten eyes of 10 patients with MH underwent pars plana vitretomy (PPV) and ILM peeling followed by transplantation of an autologous ILM fragment to the MH. Six patients had primary MH with an internal diameter greater than 500 µm and a duration of more than 18 months, including 1 patient with nonproliferative diabetic retinopathy previously treated with panretinal photocoagulation. Four eyes with MH had previously been submitted to PPV (i.e. 1 for retinal detachment and 3 to attempt to close large MH). One of the latter also displayed juxtapapillary choroidal neovascularization due to age-related macular degeneration. The primary and secondary outcomes were MH closure and improvement of the best corrected visual acuity (BCVA), respectively.

RESULTS: Complete MH closure was achieved in all cases. A statistically significant improvement in the average BCVA was observed after 6 months of follow-up (p = 0.018; paired t test). The BCVA improved in 8 eyes (80%), and in 6 of those eyes it improved by ≥15 letters. In 1 patient, the BCVA remained unchanged after the surgery, but the visual field reportedly improved. One patient experienced a slight worsening (0.16 logMAR). Two cases developed atrophy of the retinal pigment epithelium despite MH closure and BCVA improvement.

CONCLUSION: Treatment with autologous ILM fragment transplantation seems to be an efficient alternative for large, chronic, and refractory MH.

PMID: 26569390 [PubMed - in process]

Top Curr Chem. 2016;370:113-34.

Inorganic Nanoparticles for Photodynamic Therapy.

Colombeau L, Acherar S, Baros F, Arnoux P, Gazzali AM, Zaghdoudi K, Toussaint M, Vanderesse R, Frochot C.

Abstract: Photodynamic therapy (PDT) is a well-established technique employed to treat aged macular degeneration and certain types of cancer, or to kill microbes by using a photoactivatable molecule (a photosensitizer, PS) combined with light of an appropriate wavelength and oxygen. Many PSs are used against cancer but none of them are highly specific. Moreover, most are hydrophobic, so are poorly soluble in aqueous media. To improve both the transportation of the compounds and the selectivity of the treatment, nanoparticles (NPs) have been designed. Thanks to their small size, these can accumulate in a tumor because of the well-known enhanced permeability effect. By changing the composition of the nanoparticles it is also possible to achieve other goals, such as (1) targeting receptors that are over-expressed on tumoral cells or neovessels, (2) making them able to absorb two photons (upconversion or biphoton), and (3) improving singlet oxygen generation by the surface plasmon resonance effect (gold nanoparticles). In this chapter we describe recent developments with inorganic NPs in the PDT domain. Pertinent examples selected from the literature are used to illustrate advances in the field. We do not consider either polymeric nanoparticles or quantum dots, as these are developed in other chapters.

PMID: 26589507 [PubMed - in process]

Pathogenesis

Mini Rev Med Chem. 2015 Nov 19. [Epub ahead of print]

The role oxidative stress in the pathogenesis of eye diseases: current status and a dual role of physical activity.

Kruk J, Kubasik-Kładna K, Aboul-Einein HY1.

Abstract: Extensive research during the past three decades has demonstrated the mechanisms by which

an imbalance in the redox status of prooxidant/antioxidant reactions in cells with advantage of prooxidant reactions (oxidative stress, OS) can cause peroxidation of nucleic acids, bases, lipids, proteins and carbohydrates, thus resulting in their damage. These actions result in stimulation of signal transduction pathways and activation of transcription factors that can lead to chronic inflammation and cause tissue dysfunction. The most important oxidants are reactive oxygen species (ROS) and reactive nitrogen species (RNS) generated by various metabolic pathways, physical, chemical and biological factors, and pathological conditions. The eye is one of the major target of the ROS/RNS attack due to exposition on several environmental factors like high pressure of oxygen, light exposure, ultraviolet rays, ionizing radiation, chemical pollutants, irritant, and pathogenic microbes, which are able to shift the redox status of a cell towards oxidizing conditions. There is increasing evidence indicating that persistent OS contributes to the development of many ocular diseases. Increases in the accumulation of hydrogen peroxide and markers of the oxidative damage to DNA, lipids, proteins observed in several eye diseases and usage of antioxidants in their treatment and prevention emphasize the involvement of OS pathways. This paper summarizes the present state of knowledge in the involvement of OS in the etiology of non-cancer ocular diseases (dry eye syndrome; corneal and conjunctive diseases; cataract; glaucoma; age-related macular degeneration; retinitis pigmentosa; diabetic retinopathy, autoimmune and inflammatory uveitis) and cancer ocular diseases (melanoma; retinoblastoma; lymphoma). The paper also discusses the potential applications of antioxidants in the prevention of eye diseases and shows a duality of physical exercise actions: protection against the ROS/RNS damage by regular-moderate physical activity and damaging effect through mediation of OS by endurance exercise without adaptable physical training.

PMID: 26586128 [PubMed - as supplied by publisher]

Cell Death Dis. 2015 Nov 12;6:e1972.

Protective effect of autophagy on human retinal pigment epithelial cells against lipofuscin fluorophore A2E: implications for age-related macular degeneration.

Zhang J, Bai Y, Huang L, Qi Y, Zhang Q, Li S, Wu Y, Li X.

Abstract: Age-related macular degeneration (AMD) is the leading cause of central vision loss in the elderly. Degeneration of retinal pigment epithelial (RPE) cells is a crucial causative factor responsible for the onset and progression of AMD. A2E, a major component of toxic lipofuscin implicated in AMD, is deposited in RPE cells with age. However, the mechanism whereby A2E may contribute to the pathogenesis of AMD remains unclear. We demonstrated that A2E was a danger signal of RPE cells, which induced autophagy and decreased cell viability in a concentration- and time-dependent manner. Within 15 min after the treatment of RPE with 25 μM A2E, the induction of autophagosome was detected by transmission electron microscopy. After continuous incubating RPE cells with A2E, intense punctate staining of LC3 and increased expression of LC3-II and Beclin-1 were identified. Meanwhile, the levels of intercellular adhesion molecule (ICAM), interleukin (IL)1β, IL2, IL-6, IL-8, IL-17A, IL-22, macrophage cationic peptide (MCP)-1, stromal cell-derived factor (SDF)-1, and vascular endothelial growth factor A (VEGFA) were elevated. The autophagic inhibitor 3-methyladenine (3-MA) and activator rapamycin were also used to verify the effect of autophagy on RPE cells against A2E. Our results revealed that 3-MA decreased the autophagosomes and LC3 puncta induced by A2E, increased inflammation-associated protein expression including ICAM, IL1β, IL2, IL-6, IL-8, IL-17A, IL-22, and SDF-1, and upregulated VEGFA expression. Whereas rapamycin augmented the A2E-mediated autophagy, attenuated protein expression of inflammation-associated and angiogenic factors, and blocked the Akt/mTOR pathway. Taken together, A2E induces autophagy in RPE cells at the early stage of incubation, and this autophagic response can be inhibited by 3-MA or augmented by rapamycin via the mTOR pathway. The enhancement of autophagy has a protective role in RPE cells against the adverse effects of A2E by reducing the secretion of inflammatory cytokines and VEGFA.

PMID: 26561782 [PubMed - in process]

Biomaterials. 2015 Oct 30;77:130-138. [Epub ahead of print]

Selective binding of C-6 OH sulfated hyaluronic acid to the angiogenic isoform of VEGF165.

Lim DK, Wylie RG, Langer R, Kohane DS.

Abstract: Vascular endothelial growth factor 165 (VEGF165) is an important extracellular protein involved in pathological angiogenesis in diseases such as cancer, wet age-related macular degeneration (wet-AMD) and retinitis pigmentosa. VEGF165 exists in two different isoforms: the angiogenic VEGF165a, and the anti-angiogenic VEGF165b. In some angiogenic diseases the proportion of VEGF165b may be equal to or higher than that of VEGF165a. Therefore, developing therapeutics that inhibit VEGF165a and not VEGF165b may result in greater anti-angiogenic activity and therapeutic benefit. To this end, we report the selective binding properties of sulfated hyaluronic acid (s-HA). Selective biopolymers offer several advantages over antibodies or aptamers including cost effective and simple synthesis, and the ability to make nanoparticles or hydrogels for drug delivery applications or VEGF165a sequestration. Limiting sulfation to the C-6 hydroxyl (C-6 OH) in the N-acetyl-glucosamine repeat unit of hyaluronic acid (HA) resulted in a polymer with strong affinity for VEGF165a but not VEGF165b. Increased sulfation beyond the C-6 OH (i.e. greater than 1 sulfate group per HA repeat unit) resulted in s-HA polymers that bound both VEGF165a and VEGF165b. The C-6 OH sulfated HA (Mw 150 kDa) showed strong binding properties to VEGF165a with a fast association rate constant (Ka; 2.8 × 106 M-1 s-1), slow dissociation rate constant (Kd; 2.8 × 10-3 s-1) and strong equilibrium binding constant (KD; ~1.0 nM)), which is comparable to the non-selective VEGF165 binding properties of the commercialized therapeutic anti-VEGF antibody (Avastin®). The C-6 OH sulfated HA also inhibited human umbilical vein endothelial cell (HUVEC) survival and proliferation and human dermal microvascular endothelial cell (HMVEC) tube formation. These results demonstrate that the semi-synthetic natural polymer, C-6 OH sulfated HA, may be a promising biomaterial for the treatment of angiogenesis-related disease.

PMID: 26588795 [PubMed - as supplied by publisher]

Saudi J Ophthalmol. 2015 Oct-Dec;29(4):287-291. Epub 2015 Jun 6.

Platelet derived growth factor inhibitors: A potential therapeutic approach for ocular neovascularization.

Sadiq MA, Hanout M, Sarwar S, Hassan M, Do DV, Nguyen QD, Sepah YJ.

Abstract: Retinochoroidal vascular diseases are the leading causes of blindness in the developed world. They include diabetic retinopathy (DR), retinal vein occlusion, retinopathy of prematurity, age-related macular degeneration (AMD), and pathological myopia, among many others. Several different therapies are currently under consideration for the aforementioned disorders. In the following section, agents targeting platelet-derived growth factor (PDGF) are discussed as a potential therapeutic option for retinochoroidal vascular diseases. PDGF plays an important role in the angiogenesis cascade that is activated in retinochoroidal vascular diseases. The mechanism of action, side effects, efficacy, and the potential synergistic role of these agents in combination with other treatment options is discussed. The future of treatment of retinochoroidal vascular diseases, particularly AMD, has become more exciting due to agents such as PDGF antagonists.

PMID: 26586980 [PubMed - as supplied by publisher] PMCID: PMC4625223

Arch Pharm Res. 2015 Nov 20. [Epub ahead of print]

Preventive effect of Vaccinium uliginosum L. extract and its fractions on age-related macular degeneration and its action mechanisms.

Yoon SM, Lee BL, Guo YR, Choung SY.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss and blindness among the elderly. Although the pathogenesis of this disease remains still obscure, several researchers have report that death of retinal pigmented epithelium (RPE) caused by excessive accumulation of A2E is crucial determinants of AMD. In this study, the preventive effect of Vaccinium uliginosum L. (V.U) extract and its fractions on AMD was investigated in blue light-irradiated human RPE cell (ARPE-19 cells). Blue light-induced RPE cell death was significantly inhibited by the treatment of V.U extract or its fraction. To identify the mechanism, FAB-MS analysis revealed that V.U inhibits the photooxidation of N-retinyl-N-retinylidene ethanolamine (A2E) induced by blue light in cell free system. Moreover, monitoring by quantitative HPLC also revealed that V.U extract and its fractions reduced intracellular accumulation of A2E, suggesting that V.U extract and its fractions inhibit not only blue light-induced photooxidation, but also intracellular accumulation of A2E, resulting in RPE cell survival after blue light exposure. A2E-laden cell exposed to blue light induced apoptosis by increasing the cleaved form of caspase-3, Bax/Bcl-2. Additionally, V.U inhibited by the treatment of V.U extract or quercetin-3-O-arabinofuranoside. These results suggest that V.U extract and its fractions have preventive effect on blue light-induced damage in RPE cells and AMD.

PMID: 26589689 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2015 Nov 18. [Epub ahead of print]

CHOROIDAL NEOVASCULARIZATION SECONDARY TO ALEXANDRITE LASER EXPOSURE.

Wang R, Wykoff CC, Christie L, Croft DE, Major JC Jr, Fish RH, Brown DM.

PURPOSE: To report macular photic trauma after accidental occupational exposure to a 750-nm Alexandrite laser and management of secondary choroidal neovascularization.

METHODS: Institutional review board-approved retrospective case report.

RESULTS: A 30-year-old woman presented with immediate vision loss in her left eye after direct inadvertent exposure to a single discharge from an occupational 750-nm Alexandrite laser used for laser hair removal. Baseline Snellen visual acuity was 20/40 in the involved left eye. One week after the initial exposure, the patient experienced subjective visual decline to 20/50, was treated with oral prednisone, and then developed a subretinal hemorrhage (SRH) in the setting of choroidal neovascularization 2 weeks later, or 3 weeks after initial trauma. The patient subsequently received 5 intravitreal ranibizumab injections over 25 weeks with resolution of the SRH. Final visual acuity was 20/50.

CONCLUSION: The present case documents development and management of subretinal hemorrhage associated with choroidal neovascularization following macular photic trauma after accidental occupational to a 750-nm Alexandrite laser.

PMID: 26584328 [PubMed - as supplied by publisher]

J Biol Chem. 2015 Nov 12. [Epub ahead of print]

Complement component C5a primes retinal pigment epithelial cells for inflammasome activation by lipofuscin-mediated photooxidative damage.

Brandstetter C, Holz FG, Krohne TU.

Abstract: Complement activation, oxidative damage, and activation of the NLRP3 inflammasome have been implicated in retinal pigment epithelium (RPE) pathology in age-related macular degeneration (AMD). Following priming of RPE cells, the NLRP3 inflammasome can be activated by various stimuli such as lipofuscin-mediated photooxidative damage to lysosomal membranes. We investigated whether products of complement activation are capable of providing the priming signal for the inflammasome in RPE cells. Incubation of primary human RPE cells and ARPE-19 cells with complement-competent human serum resulted in upregulation of C5a receptor, but not C3a receptor. Furthermore, it induced expression of pro-IL-

1β and enabled IL-1β secretion in response to lipofuscin phototoxicity, thus indicating inflammasome priming by human serum. Complement heat-inactivation, C5 depletion, and C5a receptor inhibition suppressed the priming effect of human serum whereas recombinant C5a likewise induced priming. Conditioned media of inflammasome-activated RPE cells provided an additional priming effect that was mediated by the IL-1 receptor. These results indicate that complement activation product C5a represents a priming signal for RPE cells that allows for subsequent inflammasome activation by stimuli such as lipofuscin-mediated photooxidative damage. This molecular pathway provides a functional link between key factors of AMD pathogenesis including lipofuscin accumulation, photooxidative damage, complement activation, and RPE degeneration and may provide novel therapeutic targets in this disease.

PMID: 26565031 [PubMed - as supplied by publisher]

Sci Rep. 2015 Nov 17;5:16754.

Alterations in Circulating Immune Cells in Neovascular Age-Related Macular Degeneration.

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

Abstract: Neovascular age-related macular degeneration (nAMD) is the leading cause of irreversible blindness in developed countries. Recent advances have highlighted the essential role of inflammation in the development of the disease. In addition to local retinal chronic inflammatory response, systemic immune alterations have also been observed in AMD patients. In this study we investigated the association between the frequency of circulating leukocyte populations and the prevalence as well as clinical presentations of nAMD. Leukocyte subsets of 103 nAMD patients (most of them were receiving anti-VEGF therapy prior to enrolment) and 26 controls were analysed by flow cytometry by relative cell size, granularity and surface markers. Circulating CD11b(+) cells and CD16(hi)HLA-DR(-) neutrophils were significantly increased (P = 0.015 and 0.009 respectively) in nAMD when compared to controls. The percentage of circulating CD4(+) T-cells was reduced in nAMD patients without subretinal fibrosis (P = 0.026) compared to patients with subretinal fibrosis. There was no correlation between the percentage of circulating leukocytes and the responsiveness to anti-VEGF therapy in nAMD patients. Our results suggest that higher levels of circulating CD11b(+) cells and neutrophils are associated with nAMD and that reduced levels of CD4(+) T-cells are associated with the absence of subretinal fibrosis in nAMD.

PMID: 26572732 [PubMed - in process] PMCID: PMC4648089

J Pathol. 2015 Nov 13. [Epub ahead of print]

Molecular Response of Chorioretinal Endothelial Cells to Complement Injury: Implications for Macular Degeneration.

Zeng S, Whitmore SS, Sohn EH, Riker MJ, Wiley LA, Scheetz TE, Stone EM, Tucker BA, Mullins RF.

Abstract: Age-related macular degeneration (AMD) is a common, blinding disease of the elderly in which macular photoreceptor cells, retinal pigment epithelium, and choriocapillaris endothelial cells ultimately degenerate. Recent studies have found that degeneration of the choriocapillaris occurs early in this disease and that endothelial cell dropout is concomitant with increased deposition of the complement membrane attack complex (MAC) at the choroidal endothelium. However, the impact of MAC injury to choroidal endothelial cells is poorly understood. To model this event in vitro, and to study the downstream consequences of MAC injury, endothelial cells were exposed to complement from human serum, compared to heat-inactivated serum which lacks complement components. Cells exposed to complement components in human serum showed increased labelling with antibodies directed against the MAC, time- and dose-dependent cell death as assessed by lactate dehydrogenase assay, and increased permeability. RNA-Seq analysis following complement injury revealed increased expression of genes associated with angiogenesis including matrix metalloproteinase (MMP) -3 and -9, and VEGF-A. The MAC-induced increase in MMP9 RNA expression was validated using C5 depleted serum compared to C5 reconstituted serum. Increased

levels of MMP9 were also established using Western blot and zymography. These data suggest that in addition to cell lysis, complement attack on choroidal endothelial cells promotes an angiogenic phenotype in surviving cells.

PMID: 26564985 [PubMed - as supplied by publisher]

Ophthalmic Res. 2015 Dec;55(1):37-44. Epub 2015 Nov 12.

Expression of Vascular Endothelial Growth Factor by Retinal Pigment Epithelial Cells Induced by Amyloid-β Is Depressed by an Endoplasmic Reticulum Stress Inhibitor.

Matsui A, Kaneko H, Kachi S, Ye F, Hwang SJ, Takayama K, Nagasaka Y, Sugita T, Terasaki H.

PURPOSE: Amyloid-β (Aβ) is a 36- to 43-amino-acid peptide that is a constituent of drusen, and it has been demonstrated to upregulate vascular endothelial growth factor (VEGF) expression by retinal pigment epithelial (RPE) cells. This study aimed to determine whether 4-phenylbutyl phosphonylacetate (PBA), a known endoplasmic reticulum (ER) stress inhibitor, can reduce Aβ-induced expression of VEGF in RPE cells.

METHODS: Aβ was added to the medium of regularly cultured or polarized ARPE-19 cells, a human RPE cell line, with or without PBA. The levels of VEGF and ER stress markers, namely GRP78/Bip, cleaved caspases 4 and 12 and GADD153/C-EBP homologous protein, were determined by enzyme-linked immunoassay, immunocytochemistry and Western blotting.

RESULTS: Exposure of ARPE-19 cells to Aβ induced GRP78/Bip expression and activated caspases 4 and 12; however, their expression was decreased by simultaneous exposure to PBA. Aβ increased the expression of VEGF both in regularly cultured and polarized ARPE-19 cells, but it was suppressed by PBA. PBA did not cause RPE cell apoptosis.

CONCLUSION: Aβ has been suggested to be involved in the development of age-related macular degeneration; therefore, our findings suggest that drugs that target ER stress should be considered for the treatment of age-related macular degeneration.

PMID: 26560903 [PubMed - in process]

Mol Neurobiol. 2015 Nov 12. [Epub ahead of print]

Rotenone Induces the Formation of 4-Hydroxynonenal Aggresomes. Role of ROS-Mediated Tubulin Hyperacetylation and Autophagic Flux Disruption.

Bonet-Ponce L, Saez-Atienzar S, da Casa C, Sancho-Pelluz J, Barcia JM, Martinez-Gil N, Nava E, Jordan J, Romero FJ, Galindo MF.

Abstract: Oxidative stress causes cellular damage by (i) altering protein stability, (ii) impairing organelle function, or (iii) triggering the formation of 4-HNE protein aggregates. The catabolic process known as autophagy is an antioxidant cellular response aimed to counteract these stressful conditions. Therefore, autophagy might act as a cytoprotective response by removing impaired organelles and aggregated proteins. In the present study, we sought to understand the role of autophagy in the clearance of 4-HNE protein aggregates in ARPE-19 cells under rotenone exposure. Rotenone induced an overproduction of reactive oxygen species (ROS), which led to an accumulation of 4-HNE inclusions, and an increase in the number of autophagosomes. The latter resulted from a disturbed autophagic flux rather than an activation of the autophagic synthesis pathway. In compliance with this, rotenone treatment induced an increase in LC3-II while upstream autophagy markers such as Beclin- 1, Vsp34 or Atg5-Atg12, were decreased. Rotenone reduced the autophagosome-to-lysosome fusion step by increasing tubulin acetylation levels through a ROS-mediated pathway. Proof of this is the finding that the free radical scavenger, N-acetylcysteine, restored autophagy flux and reduced rotenone-induced tubulin hyperacetylation. Indeed,

this dysfunctional autophagic response exacerbates cell death triggered by rotenone, since 3-methyladenine, an autophagy inhibitor, reduced cell mortality, while rapamycin, an inductor of autophagy, caused opposite effects. In summary, we shed new light on the mechanisms involved in the autophagic responses disrupted by oxidative stress, which take place in neurodegenerative diseases such as Huntington or Parkinson diseases, and age-related macular degeneration.

PMID: 26558631 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2015 Oct 18;8(5):991-5. eCollection 2015.

Brain-derived neurotrophic factor in patients with advanced age-related macular degeneration.

Afarid M, Torabi-Nami M, Nemati A, Khosravi A, Malekzadeh M.

AIM: To investigate the serum level of the brain-derived neurotrophic factor (BDNF) in age-related macular degeneration (AMD) and healthy control subjects. The disruption in the tight balance of neuroinflammatory and neuroprotective processes in an immune-privileged site like retina is proposed to contribute to the pathogenesis of AMD. One of the main neuroprotective mediators in the central nervous system is BDNF with its serum level notably affected in several neurodegenerative disorders.

METHODS: Thirty-six patients with AMD and 36 age-matched controls were enrolled in this study. The serum level of BDNF was measured using the enzyme-linked immunosorbent assay method. Results were analyzed to compare case and control values. Comparisons were also made between the BDNF level of wet- vs dry-AMD, and male vs female patients and controls. Analysis of variance (ANOVA) and Student's t-test were employed to analyze the data.

RESULTS: The mean BDNF levels in AMD group were significantly higher than the control group. Furthermore, our analysis revealed greater BDNF values in all AMD subgroups compared to controls (P=0.004, 0.005, 0.001 and 0.02 for male wet-AMD, male dry-AMD, female wet-AMD and female dry-AMD vs controls, respectively). The BDNF level however did not vary between wet- and dry-AMD patients (P=0.74). While within-group comparisons in males and females of AMD and control groups did not show any difference in BDNF (P=0.16, 0.64 and 0.85 for wet-AMD, dry-AMD and control groups, respectively), between-group data showed a higher mean BDNF in both male and female AMD subjects than their peer controls.

CONCLUSION: This study demonstrated that the serum BDNF level is different in patients with AMD as compared to subjects without AMD. Future attempts should be done to unravel beneficial or deleterious effect of this neurotrophin in the pathogenesis of AMD.

PMID: 26558215 [PubMed] PMCID: PMC4630989

Invest Ophthalmol Vis Sci. 2015 Nov 1;56(12):7462-72.

Melanin Pigmentation in Rat Eyes: In Vivo Imaging by Polarization-Sensitive Optical Coherence Tomography and Comparison to Histology.

Baumann B, Schirmer J, Rauscher S, Fialová S, Glösmann M, Augustin M, Pircher M, Gröger M, Hitzenberger CK.

PURPOSE: The purpose of this study was to demonstrate polarization-sensitive optical coherence tomography (PS-OCT) for imaging pigmented structures in the posterior eye segments of albino and pigmented rats and to correlate depolarization contrast of the retinal pigment epithelium (RPE) and choroid in in vivo PS-OCT to melanin pigmentation detected in postmortem histologic serial sections.

METHODS: In vivo three-dimensional PS-OCT imaging was performed in adult albino and pigmented rat eyes at 70-kHz A-line rate. Degree of polarization uniformity (DOPU) fundus maps and radial DOPU

profiles were generated. Postmortem histomorphologic analysis was performed in order to investigate melanin pigmentation of the RPE and choroid. Fundus pigmentation maps were extracted from histologic serial sections. Pigmentation profiles were correlated to DOPU profiles of the same eyes.

RESULTS: Strong depolarization was found in the RPE/choroid complex of pigmented rats, whereas the same structures exhibited uniform polarization in albino rats. The difference between the depolarization characteristics between albino and pigmented animals was statistically significant. In the fundus pigmentation maps, optical pigment density was zero in albino rat eyes. In pigmented rat eyes, a strong negative correlation between optical pigment density and DOPU was observed.

CONCLUSIONS: This in vivo and ex vivo investigation of posterior rat eyes indicates that melanin is the cause of depolarization in retinal PS-OCT images. It further demonstrates that melanin pigmentation in the RPE and choroid can be quantified via depolarization imaging and therefore suggests that PS-OCT is a useful tool for the noninvasive quantitative assessment of pigmentary changes in vision-threatening diseases such as age-related macular degeneration.

PMID: 26595606 [PubMed - in process]

Front Genet. 2015 Nov 6;6:325.

Nitroxide pharmaceutical development for age-related degeneration and disease.

Zarling JA, Brunt VE, Vallerga AK, Li W, Tao A, Zarling DA, Minson CT.

Abstract: Nitroxide small molecule agents are in development as preventative or therapeutic pharmaceutical drugs for age-related macular degeneration (AMD) and cardiovascular disease, which are two major diseases of aging. These aging diseases are associated with patient genetics, smoking, diet, oxidative stress, and chronic inflammation. Nitroxide drugs preventing aging-, smoking-, high sugar or high fat diet-, or radiation- and other environmental-induced pathophysiological conditions in aging disease are reviewed. Tempol (TP), Tempol Hydroxylamine (TP-H), and TP-H prodrug (OT-551) are evaluated in (1) non-smokers versus smokers with cutaneous microvascular dysfunction, rapidly reversed by cutaneous TP; (2) elderly cancer patients at risk for radiation-induced skin burns or hair loss, prevented by topical TP; and (3) elderly smoker or non-smoker AMD patients at risk for vision loss, prevented by daily eye drops of OT-551. The human data indicates safety and efficacy for these nitroxide drugs. Both TP and TP-H topically penetrate and function in skin or mucosa, protecting and treating radiation burns and hair loss or smoking-induced cutaneous vascular dysfunction. TP and TP-H do not penetrate the cornea, while OT-551 does effectively penetrate and travels to the back of the eye, preserving visual acuity and preserving normal and low light luminance in dry AMD smokers and non-smoker patients. Topical, oral, or injectable drug formulations are discussed.

PMID: 26594225 [PubMed - as supplied by publisher] PMCID: PMC4635221

Molecules. 2015 Nov 19;20(11):20699-708.

Cinidium officinale and its Bioactive Compound, Butylidenephthalide, Inhibit Laser-Induced Choroidal Neovascularization in a Rat Model.

Lee YM, Lee YR, Kim JS, Kim YH, Kim J.

Abstract: Choroidal neovascularization (CNV) is a common pathology in age-related macular degeneration. In this study, we evaluated in a rat model the effect of an extract of Cinidium officinale Makino and its bioactive compound, butylidenephthalide, on laser-induced CNV. Experimental CNV was induced in Long-Evans rats by laser photocoagulation. C. officinale extract (COE) and butylidenephthalide was intraperitoneally injected once per day for ten days after laser photocoagulation. Choroidal flat mounts were prepared to measure CNV areas and macrophage infiltration. We used a protein array to evaluate the expression levels of angiogenic factors. The CNV area and macrophage infiltration in COE-treated rats

were significantly lower than in vehicle-treated rats. COE decreased the expression levels of IGFBP-1, MCP-1, PAI-1, and VEGF. Additionally, butylidenephthalide also inhibited the laser-induced CNV formation and macrophage infiltration and down-regulated the expression of IGFBP-1, MCP-1 and VEGF. These results suggest that COE exerts anti-angiogenic effects on laser-induced CNV by inhibiting the expression of IGFBP-1, MCP-1, and VEGF, indicating that anti-angiogenic activities of COE may be in part due to its bioactive compound, butylidenephthalide.

Front Neurol. 2015 Nov 3;6:232.

Pathogenic microRNAs Common to Brain and Retinal Degeneration; Recent Observations in Alzheimer's Disease and Age-Related Macular Degeneration.

Hill JM, Pogue AI, Lukiw WJ.

PMID: 26579072 [PubMed - as supplied by publisher] PMCID: PMC4630578

Epidemiology

Maturitas. 2015 Nov 4. [Epub ahead of print]

Age-related macular degeneration and risk of total and cause-specific mortality over 15 years.

Gopinath B, Liew G, Burlutsky G, Mitchell P.

OBJECTIVE: We aimed to investigate the independent association between AMD and risk of ischemic heart disease (IHD), stroke, and cardiovascular (CVD) mortality, and all-cause mortality over 15 years.

METHODS: 3654 participants aged 49+ years at baseline were followed over 15 years. AMD was assessed from retinal photographs. Deaths and cause of death were confirmed by data linkage with the Australian National Death Index. Hazard ratios (HRs) and 95% confidence intervals (CIs) were assessed using Cox models.

RESULTS: 71.4% (n=162) and 34.6% (n=1037) of participants with any AMD and no AMD, respectively, died over 15 years. After multivariable-adjustment, no significant associations were observed between AMD and total- and cause-specific mortality in the overall cohort. However, among men, late AMD at baseline was associated with an increased risk of all-cause mortality (n=22; 95.7%), 15 years later: multivariable-adjusted HR, 1.80 (95% CI 1.04-3.11). Women with late AMD had 2-fold increased risk of stroke mortality (n=15; 28.9%), HR 2.10 (95% CI 1.08-4.06). Early-stage AMD was not associated with mortality risk.

CONCLUSION: Late AMD independently predicted all-cause mortality in men and stroke mortality in women, over 15 years. Although underlying mechanisms are unclear, these findings indicate that late AMD is a marker of biological aging.

PMID: 26596903 [PubMed - as supplied by publisher]

PLoS One. 2015 Nov 18;10(11):e0142968. eCollection 2015.

Age-Related Macular Degeneration and Incident Stroke: A Systematic Review and Meta-Analysis.

Fernandez AB, Panza GA, Cramer B, Chatterjee S, Jayaraman R, Wu WC.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of vision loss and blindness in people over 65 years old in the United States and has been associated with cardiovascular risk and decreased survival. There is conflicting data, however, regarding the contribution of AMD to the prediction of stroke.

AIM: To determine whether AMD is a risk indicator for incident stroke in a meta-analysis of available prospective and retrospective cohort studies published in the English literature.

METHODS: We performed a systematic literature search of all studies published in English with Pub Med and other databases from 1966 to August 2014, reporting stroke incidence in patients with macular degeneration. Two investigators independently extracted the data. A random effects model was used to report Odds ratios (OR), with corresponding 95% confidence intervals (CI). Meta-regression using a mixed linear model was used to understand potential heterogeneity amongst studies.

RESULTS: We identified 9 studies that reported stroke incidence in patients with and without early AMD (N = 1,420,978). No significant association was found between early AMD with incident stroke. Combined, these 9 studies demonstrated random effects (OR, 1.12; CI, 0.86-1.47; I2 = 96%). Meta-regression on baseline covariates of age, sex, and year of publication did not significantly relate to heterogeneity.

CONCLUSIONS: We found no significant relationship between AMD and incident stroke. Further studies are needed to clarify other causes of decreased survival in patients with AMD.

PMID: 26580396 [PubMed - in process] PMCID: PMC4651536

Sci Rep. 2015 Nov 9;5:16304.

Impact of Visual Impairment and Eye diseases on Mortality: the Singapore Malay Eye Study (SiMES).

Siantar RG, Cheng CY, Gemmy Cheung CM, Lamoureux EL, Ong PG, Chow KY, Mitchell P, Aung T, Wong TY, Cheung CY.

Abstract: We investigated the relationship of visual impairment (VI) and age-related eye diseases with mortality in a prospective, population-based cohort study of 3,280 Malay adults aged 40-80 years between 2004-2006. Participants underwent a full ophthalmic examination and standardized lens and fundus photographic grading. Visual acuity was measured using logMAR chart. VI was defined as presenting (PVA) and best-corrected (BCVA) visual acuity worse than 0.30 logMAR in the better-seeing eye. Participants were linked with mortality records until 2012. During follow-up (median 7.24 years), 398 (12.2%) persons died. In Cox proportional-hazards models adjusting for relevant factors, participants with VI (PVA) had higher all-cause mortality (hazard ratio[HR], 1.57; 95% confidence interval[CI], 1.25-1.96) and cardiovascular (CVD) mortality (HR 1.75; 95% CI, 1.24-2.49) than participants without. Diabetic retinopathy (DR) was associated with increased all-cause (HR 1.70; 95% CI, 1.25-2.36) and CVD mortality (HR 1.57; 95% CI, 1.05-2.43). Retinal vein occlusion (RVO) was associated with increased CVD mortality (HR 3.14; 95% CI, 1.26-7.73). No significant associations were observed between cataract, glaucoma and age-related macular degeneration with mortality. We conclude that persons with VI were more likely to die than persons without. DR and RVO are markers of CVD mortality.

PMID: 26549406 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Nov 1;56(12):7269-73.

Phenotype Characteristics of Fellow Eyes in Patients With Early Onset of Neovascular Age-Related Macular Degeneration.

Schick T, Ersoy L, Hoyng CB, Kirchhof B, Liakopoulos S.

PURPOSE: To investigate phenotype characteristics of fellow eyes in patients with early onset of neovascular age-related macular degeneration (NVAMD).

METHODS: Patients with new-onset unilateral NVAMD between 50 and 65 years (n = 57, early-onset choroidal neovascularization [CNV] group) or >80 years (n = 47, late-onset CNV group) or with

nonneovascular AMD (n = 98, no-CNV group) were included. Fellow eyes in both CNV groups and the eyes with the more severe AMD staging in the no-CNV group were used to evaluate number and size of macular drusen, extramacular drusen (EMD), pigmentary abnormalities, and retinal pigment epithelium (RPE) atrophy on color photographs and hyperreflective dots (HRD) and reticular pseudodrusen (RPD) on spectral-domain optical coherence tomography (SDOCT) scans. Regression analysis was used to compare groups.

RESULTS: Occurrence of >20 macular drusen was more frequent in the early-onset CNV group than the late-onset CNV group (odds ratio [OR] 2.93; P = 0.01) or the no-CNV group (OR 2.17; P = 0.02). Retinal pigment epithelium atrophy, RPD, and HRD appeared less frequently in the early-onset CNV group than in the late-onset CNV group (RPE atrophy: OR 0.11; P = 0.005; RPD: OR 0.04; P = 9.38 × 10-10, HRD: OR 0.30; P = 0.004) and no-CNV group (RPE atrophy: OR 0.12; P = 0.005; RPD: OR 0.40, P = 0.03, HRD: not significant). No differences were detected regarding presence of large drusen, pigmentary abnormalities, and EMD.

CONCLUSIONS: A large number of macular drusen in the fellow eye appeared to be characteristic for early onset of NVAMD, whereas RPE atrophy, HRD, and RPD were more frequently present in AMD patients > 80 years. Prospective trials with patients converting to NVAMD are required to further analyze morphologic characteristics for early versus late development of advanced AMD.

PMID: 26551330 [PubMed - in process]

Genetics

Graefes Arch Clin Exp Ophthalmol. 2015 Nov 25. [Epub ahead of print]

ABCA1 rs1883025 polymorphism and risk of age-related macular degeneration.

Wang Y, Wang M, Han Y, Zhang R, Ma L.

PURPOSE: To evaluate the association of the ABCA1 rs1883025 polymorphism and susceptibility to age-related macular degeneration (AMD).

METHODS: A systematic search of the PubMed, EMBASE, and ISI web of science databases was performed to identify eligible published studies without language restrictions up to September 2015. Pooled odds ratios (ORs) with 95 % confidence intervals (CIs) were estimated under different genetic models using meta-analytic methods. Stratified analysis and sensitivity analysis were performed to explore potential sources of heterogeneity.

RESULTS: A total of 12 articles with 25,445 cases and 36,460 controls were eligible in this meta-analysis. The ABCA1 rs1883025 variant showed significant association with the lower risk of overall AMD under the allelic model (OR= 0.81, 95 % CI=0.74-0.89). Stratified analysis based on ethnicity demonstrated a strong association between rs1883025 polymorphism and AMD in the Caucasian population, but not in Asian population. For late AMD, the ABCA1 rs1883025 variant was observed to have a significant association with the lower risk of this disease (OR = 0.81, 95 % CI, 0.72-0.91). In early-stage AMD, significant associations of the rs1883025 polymorphism with lower risk of early AMD were observed in different genetic models (OR ranging from 0.45 to 0.65, all P < 0.05).

CONCLUSIONS: The present meta-analysis indicated that the T allelic in rs1883025 variant was significantly associated with the risk of developing AMD, particularly at the early stage. The associations of the ABCA1 locus with AMD risk in various populations need further exploration.

PMID: 26608582 [PubMed - as supplied by publisher]

J Med Case Rep. 2015 Nov 24;9(1):269.

Association of familial macular degeneration with specific genetic markers: a case report.

Takayanagi Y, Ashida M, Go M, Gunji M, Sato I, Kato S, Miyashita M.

INTRODUCTION: Age-related macular degeneration is a serious visual disorder of the central retina and was recently reported to be associated with genetic background. Here we describe a genetic link to early onset age-related macular degeneration in members of an Asian family.

CASE PRESENTATION: A 73-year-old Asian woman developed age-related macular degeneration in the fifth decade of her life and her 49-year-old daughter developed age-related macular degeneration. Because of the family history and the early onset, family members were tested for two single nucleotide polymorphism variants (rs10490924 and rs11200638) at a recently identified susceptibility locus for age-related macular degeneration. Both alleles in the 73-year-old woman were of the high-risk variants (T/T for rs10490924 and A/A for rs11200638), and her two daughters and a grandson each carried the risk variants (T and A) one on each allele.

CONCLUSIONS: In a case where multiple family members had early onset age-related macular degeneration, we found two high-risk single nucleotide polymorphism variants in the age-related macular degeneration susceptibility locus, suggesting the combination of the known single nucleotide polymorphism variants as a potent age-related macular degeneration diagnostic indicator.

PMID: 26597887 [PubMed - in process] PMCID: PMC4657362

Stem Cells

Sci Rep. 2015 Nov 26;5:17258.

The Molecular Karyotype of 25 Clinical-Grade Human Embryonic Stem Cell Lines.

Canham MA, Van Deusen A, Brison DR, De Sousa PA, Downie J, Devito L, Hewitt ZA, Ilic D, Kimber SJ, Moore HD, Murray H, Kunath T.

Abstract: The application of human embryonic stem cell (hESC) derivatives to regenerative medicine is now becoming a reality. Although the vast majority of hESC lines have been derived for research purposes only, about 50 lines have been established under Good Manufacturing Practice (GMP) conditions. Cell types differentiated from these designated lines may be used as a cell therapy to treat macular degeneration, Parkinson's, Huntington's, diabetes, osteoarthritis and other degenerative conditions. It is essential to know the genetic stability of the hESC lines before progressing to clinical trials. We evaluated the molecular karyotype of 25 clinical-grade hESC lines by whole-genome single nucleotide polymorphism (SNP) array analysis. A total of 15 unique copy number variations (CNVs) greater than 100 kb were detected, most of which were found to be naturally occurring in the human population and none were associated with culture adaptation. In addition, three copy-neutral loss of heterozygosity (CN-LOH) regions greater than 1 Mb were observed and all were relatively small and interstitial suggesting they did not arise in culture. The large number of available clinical-grade hESC lines with defined molecular karyotypes provides a substantial starting platform from which the development of pre-clinical and clinical trials in regenerative medicine can be realised.

PMID: 26607962 [PubMed - in process]

PLoS One. 2015 Nov 25;10(11):e0143272. eCollection 2015.

Differentiation of Human Protein-Induced Pluripotent Stem Cells toward a Retinal Pigment Epithelial Cell Fate.

Gong J, Fields MA, Moreira EF, Bowrey HE, Gooz M, Ablonczy Z, Del Priore LV.

Abstract: Compared with many induced pluripotent stem cell (iPSC) lines generated using retrovirus and other non-integrating methods, the utilization of human protein-induced iPSC (piPSC) lines may provide a safer alternative for the generation of retinal pigment epithelial (RPE) cells for transplantation in retinal degenerative diseases. Here we assess the ability of piPSCs to differentiate into RPE cells, and to perform native RPE cell behavior. piPSCs were seeded in 6-well low-attachment plates to allow embryoid body formation, and then analyzed for pluripotent stem cell markers NANOG, SSEA4 and TRA-1-60 by immunofluorescence. Following colony formation, piPSCs were assessed for confirmation of RPE cell differentiation by staining for zonula occludens (ZO-1), bestrophin, microphthalmia-associated transcription factor (MITF) and retinal pigment epithelium specific protein-65 (RPE65). To evaluate piPSC-RPE cell phagocytic ability, adult bovine photoreceptor rod outer segments (ROS) were fed to piPSC-RPE cells, which were analyzed by fluorescent microscopy and flow cytometry. Undifferentiated piPSCs expressed all pluripotent markers assessed and formed embryoid body aggregates after 7 days. Differentiated piPSC-RPE cells expressed ZO-1, bestrophin, MITF and RPE65, typical RPE cell markers. Flow cytometry revealed robust ingestion of fluorescently-labeled ROS by piPSC-RPE cells, which was over four-times greater than that of undifferentiated piPSCs and comparable to that of an immortalized RPE cell line. Phagocytosis activity by piPSC-RPE cells was significantly reduced after the addition of anti-integrin αVβ5. In conclusion, piPSCs can be differentiated toward an RPE cell fate, expressing RPE cell markers and resembling native RPE cells in behavior. These results demonstrate that piPSCs can be differentiated into RPE-like cells using a method that has an increased safety profile, a critical consideration for the development of better treatments for retinal degenerative diseases such as age-related macular degeneration (AMD).

PMID: 26606685 [PubMed - in process]

J Neurosci. 2015 Nov 25;35(47):15649-65.

Human Umbilical Tissue-Derived Cells Promote Synapse Formation and Neurite Outgrowth via Thrombospondin Family Proteins.

Koh S, Kim N, Yin HH, Harris IR, Dejneka NS, Eroglu C.

Abstract: Cell therapy demonstrates great potential for the treatment of neurological disorders. Human umbilical tissue-derived cells (hUTCs) were previously shown to have protective and regenerative effects in animal models of stroke and retinal degeneration, but the underlying therapeutic mechanisms are unknown. Because synaptic dysfunction, synapse loss, degeneration of neuronal processes, and neuronal death are hallmarks of neurological diseases and retinal degenerations, we tested whether hUTCs contribute to tissue repair and regeneration by stimulating synapse formation, neurite outgrowth, and neuronal survival. To do so, we used a purified rat retinal ganglion cell culture system and found that hUTCs secrete factors that strongly promote excitatory synaptic connectivity and enhance neuronal survival. Additionally, we demonstrated that hUTCs support neurite outgrowth under normal culture conditions and in the presence of the growth-inhibitory proteins chondroitin sulfate proteoglycan, myelin basic protein, or Nogo-A (reticulon 4). Furthermore, through biochemical fractionation and pharmacology, we identified the major hUTC-secreted synaptogenic factors as the thrombospondin family proteins (TSPs), TSP1, TSP2, and TSP4. Silencing TSP expression in hUTCs, using small RNA interference, eliminated both the synaptogenic function of these cells and their ability to promote neurite outgrowth. However, the majority of the prosurvival functions of hUTC-conditioned media was spared after TSP knockdown, indicating that hUTCs secrete additional neurotrophic factors. Together, our findings demonstrate that hUTCs affect multiple aspects of neuronal health and connectivity through secreted factors, and each of these paracrine effects may individually contribute to the therapeutic function of these cells.

SIGNIFICANCE STATEMENT: Human umbilical tissue-derived cells (hUTC) are currently under clinical investigation for the treatment of geographic atrophy secondary to age-related macular degeneration. These cells show great promise for the treatment of neurological disorders; however, the therapeutic effects

of these cells on CNS neurons are not fully understood. Here we provide compelling evidence that hUTCs secrete multiple factors that work synergistically to enhance synapse formation and function, and support neuronal growth and survival. Moreover, we identified thrombospondins (TSPs) as the hUTC-secreted factors that mediate the synaptogenic and growth-promoting functions of these cells. Our findings highlight novel paracrine effects of hUTC on CNS neuron health and connectivity and begin to unravel potential therapeutic mechanisms by which these cells elicit their effects.

PMID: 26609158 [PubMed - in process]

Br Med Bull. 2015 Nov 17. [Epub ahead of print]

Human embryonic and induced pluripotent stem cells in clinical trials.

Ilic D, Devito L, Miere C, Codognotto S.

BACKGROUND: Human embryonic and induced pluripotent stem cells (hESC and hiPSC) have tremendous potential for clinical implementation. In spite of all hurdles and controversy, clinical trials in treatment of spinal cord injury, macular degeneration of retina, type 1 diabetes and heart failure are already ongoing.

SOURCES OF DATA: ClinicalTrials.gov database, International Clinical Trials Registry Platform, PubMed and press releases and websites of companies and institutions working on hESC- and iPSC-based cellular therapy.

AREAS OF AGREEMENT: The initial results from multiple clinical trials demonstrate that hESC-based therapies are safe and promising.

AREAS OF CONTROVERSY: Are iPSC cells safe in the clinical application? Is there a room for both hESC and iPSC in the future clinical applications?

GROWING POINTS: Increasing number of new clinical trials.

AREAS TIMELY FOR DEVELOPING RESEARCH: Development of hESC- and/or iPSC-based cellular therapy for other diseases.

PMID: 26582538 [PubMed - as supplied by publisher]

Stem Cell Res Ther. 2015 Nov 9;6:219.

Transplantation of rat embryonic stem cell-derived retinal progenitor cells preserves the retinal structure and function in rat retinal degeneration.

Qu Z, Guan Y, Cui L, Song J, Gu J, Zhao H, Xu L, Lu L, Jin Y, Xu GT.

INTRODUCTION: therapeutic effect for such diseases, and embryonic stem cell (ESC) is one of the sources of such donor cells. Here, we aimed to generate retinal progenitor cells (RPCs) from rat ESCs (rESCs) and to test their therapeutic effects in rat model.

METHODS: The rESCs (DA8-16) were cultured in N2B27 medium with 2i, and differentiated to two types of RPCs following the SFEBq method with modifications. For rESC-RPC1, the cells were switched to adherent culture at D10, while for rESC-RPC2, the suspension culture was maintained to D14. Both RPCs were harvested at D16. Primary RPCs were obtained from P1 SD rats, and some of them were labeled with EGFP by infection with lentivirus. To generate Rax::EGFP knock-in rESC lines, TALENs were engineered to facilitate homologous recombination in rESCs, which were cotransfected with the targeting vector and TALEN vectors. The differentiated cells were analyzed with live image, immunofluorescence staining, flow cytometric analysis, gene expression microarray, etc. RCS rats were used to mimic the degeneration of retina and test the therapeutic effects of subretinally transplanted donor cells. The structure and function of

retina were examined.

RESULTS: We established two protocols through which two types of rESC-derived RPCs were obtained and both contained committed retina lineage cells and some neural progenitor cells (NPCs). These rESC-derived RPCs survived in the host retinas of RCS rats and protected the retinal structure and function in early stage following the transplantation. However, the glia enriched rESC-RPC1 obtained through early and longer adherent culture only increased the b-wave amplitude at 4 weeks, while the longer suspension culture gave rise to evidently neuronal differentiation in rESC-RPC2 which significantly improved the visual function of RCS rats.

CONCLUSIONS: We have successfully differentiated rESCs to glia enriched RPCs and retinal neuron enriched RPCs in vitro. The retinal neuron enriched rESC-RPC2 protected the structure and function of retina in rats with genetic retinal degeneration and could be a candidate cell source for treating some degenerative retinal diseases in human trials.

PMID: 26553210 [PubMed - in process] PMCID: PMC4640237

Diet, lifestyle & low vision

Eye (Lond). 2015 Nov 27. [Epub ahead of print]

Caregiver perceptions about the impact of caring for patients with wet age-related macular degeneration.

Vukicevic M, Heraghty J, Cummins R, Gopinath B, Mitchell P.

Purpose: Caregivers of older persons with eye disease, namely age-related macular degeneration (AMD), have been reported to have a higher than expected distress. Very few studies have explored caregiver perceptions as to what is important when providing care. The aim of this study was to explore the perceptions of caregivers of persons with neovascular AMD in relation to the most important aspects of caring, as described in extended answers to self-administered survey questions.

Methods: A cross-sectional, self-administered survey of 643 caregivers of people with neovascular AMD, comprising 27 closed-response questions and 2 open ended questions. The latter were analysed as part of this study utilising and 'inductive' Grounded Theory approach.

Results: Six-hundred and forty-three caregiver responses to 2 open ended questions were analysed using an inductive approach and sorted into thematic networks. Three discrete categories arose: The Impact of Caring; Injections and Information and Activities of Daily Living.

Conclusions: Most caregivers were family caregivers and were found to be compassionate and self-sacrificing. They accepted additional responsibility whilst providing an encouraging environment for their care recipient. As a result, they experience distress and consider their own needs as secondary. Very few seek or receive respite and this added burden can have a negative impact upon the relationship between caregiver and care recipient.Eye advance online publication, 27 November 2015; doi:10.1038/eye.2015.235.

PMID: 26611848 [PubMed - as supplied by publisher]

Retina. 2015 Nov 13. [Epub ahead of print]

NUTRITIONAL SUPPLEMENTATION IN AGE-RELATED MACULAR DEGENERATION.

Parodi MB, Zucchiatti I, Cicinelli MV, Cascavilla ML, Bandello F.

PURPOSE: To evaluate the rate of adherence to prescribed nutritional supplementation in patients affected

by age-related macular degeneration, in an Italian tertiary referral tertiary center.

METHODS: Patients with age-related macular degeneration, age-related eye disease study Categories 3 and 4, were recruited and underwent an 11-item questionnaire.

RESULTS: The study included a total of 193 patients meeting the age-related eye disease study nutritional supplementation criteria (174 patients with age-related eye disease study Category 4 and 19 with Category 3). Seventy-seven (40%) were taking oral supplementation, 70 of whom (90%) 1 tablet/day. Oral supplementation was recommended by the personal ophthalmologist in 85 patients (44%), including all those currently receiving it. Eight patients of 85 (9.4%) rejected supplementation despite it being recommended, mostly because they were already taking other medicines. Ninety-four patients (48%) claimed they had not received any information from their ophthalmologist.

CONCLUSION: Our data reveal that Italian patients with age-related eye disease study Categories 3 and 4 have a low adherence to nutritional supplementation. In 65% of cases, patients were not adequately informed by their ophthalmologist of the potential benefits of oral supplementation for age-related macular degeneration; indeed, 108 patients (56%) were not even aware such nutritional treatments are available. Ophthalmologists should be aware of the importance of giving advice to persons with age-related macular degeneration regarding the benefits of oral supplements.

PMID: 26579787 [PubMed - as supplied by publisher]

Aerosp Med Hum Perform. 2015 Nov;86(11):953-61.

Solar Eye Protection Practices of Civilian Aircrew.

Chorley AC, Evans BJ, Benwell MJ.

INTRODUCTION: There is good evidence that long term exposure to ultraviolet (UV) radiation increases the risk of cataracts. The 'blue light hazard' is considered a risk factor for retinal changes similar to those seen in macular degeneration. Previous studies ascertaining the prevalence of radiation related ocular disease in pilot cohorts have not considered use of solar eye protection. The aim of this study was to explore pilot use of sunglasses and other solar eye protection habits and to gain insight into the difficulties encountered managing sunlight on the flight deck. Additionally, the prevalence of radiation related ocular pathology in the study group was calculated.

METHODS: A web based questionnaire was developed and administered to a large population of current UK professional pilots.

RESULTS: There were 2917 respondents who completed the questionnaire, demonstrating a wide range of sunglass use during flight. A number of barriers to sunglass use were identified, the most prevalent being the requirement for corrective lenses to be used. Pilots most commonly increase sunglass use due to ocular health concerns. A high level of dissatisfaction with standard aircraft sun protection systems was reported. Long haul airline pilots were the highest users of nonstandard sunlight blocking strategies. No correlation between reported pathology and flying experience was found.

DISCUSSION: The use of sunglasses during flight is complex; however, a number of practical recommendations can be made to increase the success for those pilots who wish to use sunglasses more. Aircraft manufacturers should consider how greater control of cockpit sunlight levels can be achieved.

PMID: 26564760 [PubMed - in process]

Ophthalmic Res. 2015 Nov 27;55(2):62-69. [Epub ahead of print]

Omega-3 Fatty Acids and Age-Related Macular Degeneration.

Souied EH, Aslam T, Garcia-Layana A, Holz FG, Leys A, Silva R, Delcourt C.

Abstract: Against a background of considerable epidemiological and other evidence implicating omega-3 fatty acids in the prevention of age-related macular degeneration (AMD), the negative results of the Age-Related Disease Study 2 (AREDS2) were unexpected. The possibility that the design, setting, intake or subjects of AREDS2 may not have permitted the prophylactic potential of omega-3 to be adequately demonstrated is considered. Epidemiological studies had indicated potential preventative effects of omega-3, and an earlier randomised prospective study (NAT2) showed that patients who achieved high red blood cell membrane EPA/DHA (eicosapentaenoic acid/docosahexaenoic acid) levels were significantly protected against AMD compared with those with permanently low EPA/DHA levels. Various methodological differences between these studies are considered. NAT2 included a true placebo group, whereas control subjects in AREDS2 received a nutritional formula already found to be effective in AREDS1, but no placebo for DHA/EPA supplementation. Differences in the handling of non-compliant subjects and the formulation of the test formulations are considered. Given these considerations, and other lines of evidence from laboratory and clinical studies, closing the chapter on omega-3 in AMD prevention may be premature.

PMID: 26610051 [PubMed - as supplied by publisher]

J Vis. 2015 Jul 1;15(10):16.

The effect of normal aging and age-related macular degeneration on perceptual learning.

Astle AT, Blighe AJ, Webb BS, McGraw PV.

Abstract: We investigated whether perceptual learning could be used to improve peripheral word identification speed. The relationship between the magnitude of learning and age was established in normal participants to determine whether perceptual learning effects are age invariant. We then investigated whether training could lead to improvements in patients with age-related macular degeneration (AMD). Twenty-eight participants with normal vision and five participants with AMD trained on a word identification task. They were required to identify three-letter words, presented 10° from fixation. To standardize crowding across each of the letters that made up the word, words were flanked laterally by randomly chosen letters. Word identification performance was measured psychophysically using a staircase procedure. Significant improvements in peripheral word identification speed were demonstrated following training (71% ± 18%). Initial task performance was correlated with age, with older participants having poorer performance. However, older adults learned more rapidly such that, following training, they reached the same level of performance as their younger counterparts. As a function of number of trials completed, patients with AMD learned at an equivalent rate as age-matched participants with normal vision. Improvements in word identification speed were maintained at least 6 months after training. We have demonstrated that temporal aspects of word recognition can be improved in peripheral vision with training across a range of ages and these learned improvements are relatively enduring. However, training targeted at other bottlenecks to peripheral reading ability, such as visual crowding, may need to be incorporated to optimize this approach.

PMID: 26605694 [PubMed - in process]

Rev Colomb Psiquiatr. 2012 Sep;41(3):620-6. Epub 2014 May 10.

[Depression in Patients with Age-Related Macular Degeneration]. [Article in Spanish]

Narváez YR, Gómez-Restrepo C.

Abstract: Age-related macular degeneration is a cause for disability in the elderly since it greatly affects their quality of life and increases depression likelihood. This article discusses the negative effect depression has on patients with age-related macular degeneration and summarizes the interventions available for decreasing their depression index.

PMID: 26572116 [PubMed - in process]

Ugeskr Laeger. 2015 Aug 17;177(34):1624-7.

[Physical activity benefits patients with age-related macular degeneration].[Article in Danish]

Subhi Y, Munch IC, Singh A, Sørensen TL.

Abstract: We have reviewed studies investigating the effect of physical activity on prevention of early age-related macular degeneration (AMD), progression to late AMD, and risk modulation of morbidity and mortality in patients with AMD. Regular physical activity may lower risk of developing early AMD and progression of early AMD to late AMD at a level comparable with smoking cessation or dietary supplements. Studies suggest that AMD itself is associated with physical inactivity which can result in higher morbidity levels. Patients with AMD may benefit from physical activity counselling at all stages of the disease.

PMID: 26561660 [PubMed - in process]