

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. 2016 Oct;123(10S):S78-S88.

Anti-Vascular Endothelial Growth Factor Agents in the Treatment of Retinal Disease: From Bench to Bedside.

Campochiaro PA, Aiello LP, Rosenfeld PJ.

Abstract: The association of retinal hypoxia with retinal neovascularization has been recognized for decades, causing Michaelson to postulate in 1948 that a factor secreted by hypoxic retina was involved. The isolation of vascular endothelial growth factor (VEGF), characterization of its angiogenic activity, and demonstration that its expression was increased in hypoxic tissue made it a prime candidate. Intraocular levels of VEGF are elevated in patients with retinal or iris neovascularization, and VEGF-specific antagonists markedly suppress retinal neovascularization in mice and primates with ischemic retinopathy. Vascular endothelial growth factor antagonists also suppress choroidal neovascularization, and transgenic expression of VEGF in the retina of mice causes subretinal neovascularization. Clinical trials using a VEGF antagonist that blocks all isoforms of VEGF-A in patients with neovascular age-related macular degeneration (nAMD) demonstrated dramatic benefit. Similar results have been obtained with 2 other VEGF antagonists. Retinal hypoxia also contributes to diabetic macular edema (DME), and because of the absence of good animal models, small clinical trials were used to test the role of VEGF. The results clearly implicated VEGF as a major contributor to DME and have been confirmed by several large multicenter trials. A similar strategy demonstrated that VEGF is a major contributor to macular edema resulting from retinal vein occlusion, also confirmed in multicenter trials. Secondary outcomes in these large clinical trials have shown that VEGF inhibition improves retinal hemorrhages, retinal vessel closure, and progression of nonproliferative diabetic retinopathy. Anti-VEGF agents also provide therapeutic benefits in proliferative diabetic retinopathy. Thus, the development of VEGF antagonists has revolutionized the treatment of nAMD, diabetic retinopathy, and other ischemic retinopathies, but in many patients, the upregulation of VEGF is prolonged. Although the molecular signaling by which hypoxia and some other insults lead to upregulation of VEGF has been elucidated, it has not yet led to a treatment that reliably reduces the production of VEGF, necessitating continued neutralization by repeated intraocular injections of VEGF antagonists in many patients. The next horizon in the evolution of anti-VEGF therapy is the development of longer-acting agents or delivery platforms that provide sustained neutralization with fewer injections.

Copyright © 2016 American Academy of Ophthalmology. Published by Elsevier Inc. All rights reserved.

PMID: 27664289

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

Intravitreal Aflibercept for Diabetic Macular Edema: 148-Week Results from the VISTA and VIVID Studies.

Heier JS, Korobelnik JF, Brown DM, Schmidt-Erfurth U, et al

PURPOSE: To compare efficacy and safety of intravitreal aflibercept injection (IAI) with macular laser photocoagulation for diabetic macular edema (DME) over 3 years.

DESIGN: Two similarly designed phase 3 trials: VISTADME and VIVIDME.

PARTICIPANTS: Patients (eyes; n = 872) with central-involved DME.

METHODS: Eyes received IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or laser control. From week 24, if rescue treatment criteria were met, IAI patients received active laser, and laser control patients received IAI 2q8. From week 100, laser control patients who had not received IAI rescue treatment received IAI as needed per retreatment criteria.

MAIN OUTCOME MEASURES: The primary end point was the change from baseline in best-corrected visual acuity (BCVA) at week 52. We report the 148-week results.

RESULTS: Mean BCVA gain from baseline to week 148 with IAI 2q4, IAI 2q8, and laser control was 10.4, 10.5, and 1.4 letters ($P < 0.0001$) in VISTA and 10.3, 11.7, and 1.6 letters ($P < 0.0001$) in VIVID, respectively. The proportion of eyes that gained ≥ 15 letters from baseline at week 148 was 42.9%, 35.8%, and 13.6% ($P < 0.0001$) in VISTA and 41.2%, 42.2%, and 18.9% ($P < 0.0001$) in VIVID, respectively. Greater proportions of eyes treated with IAI 2q4 and IAI 2q8 versus those treated with laser control had an improvement of ≥ 2 steps in the Diabetic Retinopathy Severity Scale (DRSS) score in both VISTA (29.9% and 34.4% vs. 20.1% [$P = 0.0350$, IAI 2q4; $P = 0.0052$, IAI 2q8]) and VIVID (44.3% and 47.8% vs. 17.4% [$P < 0.0001$ for both]). In an integrated safety analysis, the most frequent ocular serious adverse event was cataract (3.1%, 2.1%, 0.3% for 2q4, 2q8, and control).

CONCLUSIONS: Visual improvements observed with both IAI regimens (over laser control) at weeks 52 and 100 were maintained at week 148, with similar overall efficacy in the IAI 2q4 and IAI 2q8 groups. Treatment with IAI also had positive effects on the DRSS score. Over 148 weeks, the incidence of adverse events was consistent with the known safety profile of IAI.

PMID: 27651226

Ophthalmology. 2016 Oct;123(10S):S64-S77.

Historical Perspectives on the Management of Macular Degeneration, Diabetic Retinopathy, and Retinal Detachment: Personal Reminiscences.

Fine SL, Goldberg MF, Tasman W.

Abstract: We were challenged and delighted when Dr. Sharon Solomon, guest editor of this Retina Supplement, invited us to reminisce about caring for patients with common retinal disorders before there was access to the diagnostic and therapeutic tools that are readily available today. We agreed to confine our remarks to 3 common, but serious, conditions: age-related macular degeneration (Dr. Fine), diabetic retinopathy (Dr. Goldberg), and retinal detachment (Dr. Tasman). Each of us completed our ophthalmology training about half a century ago. At that time, a patient who received any 1 of the 3 diagnoses was at considerable risk of severe and irreversible loss of vision. Most readers today will have little if any experience in evaluating and treating such patients without access to a plethora of diagnostic and therapeutic technologies, including intravenous fluorescein angiography, laser photocoagulation, optical coherence tomography, ophthalmic ultrasound, angioinhibitory drugs, vitrectomy, intraocular gases, and many others. We are both pleased and privileged that each of us has practiced our profession long enough to enjoy what the enormous technological developments of the past half century, as described in this article, have meant for our patients.

PMID: 27664288

Eur J Ophthalmol. 2016 Sep 7:0.

Intravitreal ranibizumab for retinal arterial macroaneurysm: long-term results of a prospective study.

Chatziralli I, Maniatea A, Koubouni K, Parikakis E, Mitropoulos P.

PURPOSE: To evaluate the potential efficacy and safety of primary intravitreal ranibizumab in patients with symptomatic retinal arterial macroaneurysm (RAM).

METHODS: This prospective study comprised 5 eyes with RAM treated with intravitreal ranibizumab. At baseline, all patients underwent best-corrected visual acuity (BCVA) measurement, ophthalmic examination including slit-lamp biomicroscopy, and central foveal thickness (CFT) measurement using optical coherence tomography. Fluorescein angiography was also performed to confirm diagnosis. Patients were examined at 1 month after injection and monthly thereafter. Main outcome measures included changes in BCVA and CFT. Safety was assessed by ophthalmic examination and report of systemic adverse effects.

RESULTS: There was a statistically significant difference in BCVA ($p < 0.001$) and CFT ($p < 0.001$) before and after the ranibizumab injection at the end of the follow-up of 13.4 ± 3.2 months. One injection appeared to be sufficient for the resolution of macular edema and absorption of hemorrhages. No observable ocular or systemic side effects were found. One patient developed foveal atrophy.

CONCLUSIONS: Intravitreal ranibizumab seems to be effective and safe for the treatment of symptomatic RAM.

PMID: 27646333

Am J Ophthalmol. 2016 Sep 16. [Epub ahead of print]

Early and Long-term Responses to Anti-Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema: Analysis of Protocol I Data.

Gonzalez VH, Campbell J, Holekamp NM, Kiss S, Loewenstein A, Augustin AJ, Ma J, Ho AC, Patel V, Whitcup SM, Dugel PU.

PURPOSE: To determine whether early visual acuity response to ranibizumab in diabetic macular edema is associated with long-term outcome.

DESIGN: Post-hoc analysis of randomized-controlled-trial data **METHODS:** Pooled data from the ranibizumab plus prompt and deferred laser treatment arms of the Diabetic Retinopathy Clinical Research Network's Protocol I study were used to explore the relationship between early (week 12) and late (weeks 52–156) visual acuity response [mean change from baseline in best-corrected visual acuity (CFB BCVA); categorized improvement (<5 , 5–9, or ≥ 10 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in BCVA].

RESULTS: In the analysis population (340 eyes), <5 , 5–9, and ≥ 10 -letter BCVA improvements occurred in 39.7%, 23.2% and 37.1% of eyes, respectively, at 12 weeks, and 34.2%, 16.5% and 49.3% of eyes at 156 weeks. Within each early BCVA response category (<5 , 5–9, and ≥ 10 letter- improvement at 12 weeks), mean CFB BCVA at 52–156 weeks varied by <5 letters from that at 12 weeks. CFB BCVA and <5 -letter improvement at 12 weeks showed significant positive and negative association, respectively, with CFB BCVA and ≥ 10 -letter improvement at 52 and 156 weeks. Similar relationships were demonstrated in eyes with baseline BCVA < 69 letters, and associations remained significant after multivariate adjustment for potential confounders.

CONCLUSIONS: Ranibizumab $\pm$ laser therapy resulted in similar rates ($\approx 40\%$) of suboptimal (<5 -letter) and pronounced (≥ 10 -letter) BCVA improvement at 12 weeks. Eyes with suboptimal early BCVA response showed poorer long-term visual outcomes than eyes with pronounced early response (mean improvement 3.0 vs 13.8 letters at 156 weeks).

PMID: 27644589

Health Qual Life Outcomes. 2016 Sep 20;14(1):132.

Vision-related quality of life in patients receiving intravitreal ranibizumab injections in routine clinical practice: baseline data from the German OCEAN study.

Bertelmann T, Feltgen N, Scheffler M, Hufenbach U, Wiedon A, Wilhelm H, Ziemssen F.

BACKGROUND: Vision-related quality of life (vrQoL) is advancing more and more into the focus of interest in ophthalmological clinical research. However, to date only little information is available about vrQoL from large non-interventional studies in terms of "real-world evidence". The purpose of this investigation was to describe baseline VFQ-25 visual function scores, to evaluate whether they differ from previous phase III clinical trials, to determine which contributing factors (e.g. indication, age, gender) affect VFQ-25 scores and to identify its impact on driving.

METHODS: The non-interventional OCEAN study (Observation of treatment patterns with LuCentis and real life ophthalmic monitoring, including optional OCT in Approved iNdications) is the largest ophthalmic study conducted in Germany, to evaluate the real world situation of patients treated with ranibizumab (NCT02194803). The NEI-VFQ-25 questionnaire was conducted at baseline, months 4, 12 and 24. Descriptive statistics was used to analyse the baseline data. ANOVA was performed to evaluate the impact of various contributing factors on composite and selected subscale scores.

RESULTS: Overall, 4844 (84.1 %) of all 5760 OCEAN patients completed the VFQ-25 questionnaire at baseline. Thereof, 3414 treatment-naïve patients were further analysed. Overall, the VFQ subscore general health was most affected by the ocular disease, followed by general vision. No major differences were detected in comparison to corresponding VFQ-25 scores of previous phase III clinical trials, except in DME patients, or with respect to possible contributing factors. A tendency towards a more decreased VFQ-25 composite score was observed for nAMD, for elderly patients ≥ 75 years of age, for female patients, for patients with low baseline visual acuity (VA; < 50 letters) and for those with statutory health insurance. Indication, age, gender, baseline VA (all $p < 0.01$) and the interaction of age and indication, as well as baseline VA and indication ($p < 0.01$ each) had a significant impact on composite, general vision and distance vision scores (ANOVA). About 10 % of patients gave up driving due to eyesight issues.

CONCLUSIONS: The knowledge of a patient's subjective disease burden is crucial to understanding anxieties and mental anguish. Additionally, the understanding of the impact of various contributing factors on the VFQ-25 scores and the extent to which they can be influenced help to optimize patient care. It demonstrates the need for medical and mental support by all medical staff, to encourage patients' compliance with a comprehensive anti-VEGF therapy, to increase BCVA and, consecutively, VFQ-25 scores.

PMID: 27644469 PMCID: PMC5029004

Am J Ophthalmol. 2016 Sep 16. [Epub ahead of print]

Long-Term Results of Pro Re Nata Regimen of Aflibercept Treatment in Persistent Neovascular Age-Related Macular Degeneration.

Muftuoglu IK, Arcinue CA, Alam M, Gaber R, Camacho N, You Q, Tsai FF, Freeman WR.

PMID: 27646165

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

RESPONSIVENESS OF THE NATIONAL EYE INSTITUTE VISUAL FUNCTION QUESTIONNAIRE-25 TO VISUAL ACUITY GAINS IN PATIENTS WITH DIABETIC MACULAR EDEMA: Evidence From the RIDE and RISE Trials.

Suñer IJ, Bressler NM, Varma R, Dolan CM, Ward J, Turpcu A.

PURPOSE: To evaluate the responsiveness of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in patients with diabetic macular edema using data from the RIDE and RISE trials.

METHODS: Patients were randomized to monthly intravitreal ranibizumab 0.3 mg, 0.5 mg, or sham injections for 2 years. The NEI VFQ-25 was administered at baseline and at Months 6, 12, 18, and 24. The least-squares mean change in NEI VFQ-25 for ≥ 15 letters gained or lost was derived from analysis of covariance models.

RESULTS: The mean improvement in NEI VFQ-25 composite score associated with a ≥ 15 -letter gain in best-corrected visual acuity over 24 months was 9.0 (95% confidence interval, 6.3-11.7) points in RIDE and 7.1 (95% confidence interval, 4.7-9.6) points in RISE. In patients who lost ≥ 15 letters, the mean worsening in overall NEI VFQ-25 composite score was -6.6 (95% confidence interval, -13.6 to 0.5) in RIDE and -2.7 (95% confidence interval, -8.9 to 3.5) in RISE.

CONCLUSION: This exploratory analysis of data from the RIDE and RISE studies supports the responsiveness of the NEI VFQ-25 to changes in best-corrected visual acuity over time in patients with diabetic macular edema. This is an open access article distributed under the terms of the Creative Commons Attribution-Noncommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially.

PMID: 27668928

Jpn J Ophthalmol. 2016 Sep 22. [Epub ahead of print]

Efficacy of intravitreal aflibercept in Japanese patients with exudative age-related macular degeneration.

Saito M, Kano M, Itagaki K, Sekiryu T.

PURPOSE: To clarify the efficacy of aflibercept for treating exudative age-related macular degeneration (AMD).

METHODS: We prospectively studied 47 eyes with AMD. Forty-seven patients (mean age 72.2 years) received three consecutive monthly intravitreal aflibercept injections followed by an injection every 2 months until 12 months. The primary outcome was the 12-month visual results compared with baseline; the secondary outcomes were the prevalence of geography atrophy (GA), a dry macula at month 12, and anatomic changes on optical coherence tomography.

RESULTS: The mean logarithm of the minimum angle of resolution best-corrected visual acuity (BCVA) in 27 eyes with typical AMD and 20 eyes with polypoidal choroidal vasculopathy (PCV) significantly ($p < 0.0001$, $p < 0.05$, respectively) improved from 0.60 to 0.32 at baseline to 0.29 and 0.21 at month 12. At month 12, 22 (81.5 %) eyes with typical AMD and 17 (85 %) eyes with PCV had dry macula. The subfoveal choroidal thicknesses in typical AMD and PCV decreased significantly ($p < 0.0001$ for both comparisons) from 241 ± 118 and 294 ± 76 μ at baseline to 198 ± 104 and 244 ± 84 μ at month 12. Progressing or new GA was seen in three eyes with typical AMD and one eye with PCV; the mean change in the BCVA was significantly ($p = 0.0026$) worse at month 12. No other complications developed.

CONCLUSION: Intravitreal aflibercept significantly improved VA and anatomic changes in typical AMD and PCV over 12 months. Development of GA might be a risk for declining VA.

PMID: 27660164

Jpn J Ophthalmol. 2016 Sep 22. [Epub ahead of print]

Comparison between ranibizumab and aflibercept for macular edema associated with central retinal vein occlusion.

Saishin Y, Ito Y, Fujikawa M, Sawada T, Ohji M.

PURPOSE: We compared the efficacy of bimonthly intravitreal injections of ranibizumab (IVR) with that of bimonthly intravitreal injections of aflibercept (IVA) in two prospective, consecutive groups of patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO).

PATIENTS AND METHODS: Eyes with ME after CRVO received either bimonthly IVR (ranibizumab group; n = 13) or IVA (aflibercept group; n = 13) injections and were followed monthly for 6 months. Three patients in the ranibizumab group and two in the aflibercept group were lost to follow-up and excluded from the study. The best-corrected visual acuity (BCVA), central foveal thickness (CFT) on optical coherence tomography, and aqueous vascular endothelial growth factor (VEGF) concentrations were evaluated before and after treatment.

RESULTS: From baseline to month 6, significant improvements occurred in mean logMAR BCVA (ranibizumab group: 0.78-0.47; $p < 0.05$; aflibercept group: 0.74-0.54; $p < 0.05$) and mean CFT (ranibizumab group: 685-311 μm ; $p < 0.05$; aflibercept group: 695-230 μm ; $p < 0.05$). Fluctuations in CFT were seen at months 2, 4, and 6 in the ranibizumab group. Mean aqueous VEGF concentration decreased from baseline to month 2 in the ranibizumab group (509.9-348.2 pg/ml) and aflibercept group (412.1 pg/ml to undetectable limits in eight of 11 eyes and to 13.6, 15.6, and 24.1 pg/ml in the other three eyes, respectively).

CONCLUSIONS: There was no significant improvement of visual acuity in one group compared with another; VEGF may not be completely neutralized by bimonthly injections of ranibizumab.

PMID: 27660163

Retina. 2016 Sep 19. [Epub ahead of print]

INTRAVITREAL AFLIBERCEPT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION WITH LIMITED RESPONSE TO RANIBIZUMAB: A Treat-and-Extend Trial.

Hatz K, Prunte C.

PURPOSE: To evaluate aflibercept treat-and-extend regimen for treatment of neovascular age-related macular degeneration in patients with limited response to ranibizumab.

METHODS: This prospective single-arm trial included 33 patients with neovascular age-related macular degeneration pretreated with treat-and-extend regimen ranibizumab for ≥ 6 months who failed to be extended to a 6-week interval at least twice. All patients received aflibercept (2 mg/0.05 mL) at baseline, and were subsequently treated according to treat-and-extend regimen, starting with a 4-week interval and extending in 2-week steps. Evaluations included mean maximum recurrence-free treatment interval; best-corrected visual acuity; central retinal thickness; and pigment epithelium detachment height and horizontal diameter.

RESULTS: At Week 24, the maximum recurrence-free treatment interval increased to ≥ 6 weeks in $\square 35\%$ of patients, whereas the mean interval was 4.9 ± 1.3 weeks. Best-corrected visual acuity score remained stable, but significant reductions in central retinal thickness ($P < 0.001$) and pigment epithelium detachment height ($P = 0.001$) were observed compared with baseline, as was a small decrease in horizontal pigment epithelium detachment diameter ($P = 0.035$).

CONCLUSION: After switching patients with limited ranibizumab response to aflibercept, signs of choroidal neovascularization activity regressed, and an increased duration of treatment effects was seen in approximately one-third of lesions, but visual acuity was unchanged.

PMID: 27652915

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

Short-term efficacy and safety of ranibizumab for macular oedema secondary to retinal vein occlusion in Japanese patients.

Kamei M, Terasaki H, Yoshimura N, Shiraga F, Ogura Y, Grotzfeld AS, Pilz S, Ishibashi T.

PURPOSE: To evaluate the efficacy and safety of ranibizumab 0.5 mg in Japanese patients with visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO) and to support the applicability of the phase III results from Caucasian to Japanese populations.

METHODS: This is a 3-month, open-label, single-arm, multicentre, phase III study. Thirty-one patients (15 BRVO and 16 CRVO) aged ≥ 18 years with a best-corrected visual acuity (BCVA) letter score of 19-73 (BRVO) or 24-73 (CRVO) were included. The primary end-point was the mean average change in BCVA from baseline to month 1 through month 3 after three consecutive monthly intravitreal injections of ranibizumab 0.5 mg. Secondary end-points were mean change in BCVA and central subfield thickness (CSFT), categorized BCVA, and safety over 3 months.

RESULTS: At month 3, the mean average change in BCVA improved substantially from baseline for BRVO (11.3 letters, $p = 0.001$) and CRVO (6.7 letters, $p = 0.019$). The mean BCVA improved (12.8 and 9.1 letters) and the mean CSFT decreased (212.5 and 442.1 μm) from baseline to month 3. At month 3, 26.7% (BRVO) and 31.3% (CRVO) of the patients had a gain of ≥ 15 letters from baseline. Safety findings in this study were similar to those reported in the previous clinical trials.

CONCLUSION: Ranibizumab was effective in improving BCVA and was well tolerated in Japanese patients with BRVO and CRVO. The findings from this study were consistent with those reported in the Caucasian population.

PMID: 27654837

Am J Manag Care. 2016 Jul;22(10 Suppl):s292-s299.

Current approaches to the management of diabetic macular edema.

Hariprasad SM.

Abstract: Three modalities have a role in the primary management of diabetic macular edema (DME): laser photocoagulation, intravitreal vascular endothelial growth factor (VEGF) inhibitors, and intravitreal corticosteroid implants. Intravitreal VEGF inhibitors are most commonly used for center-involved DME, but laser photocoagulation and intravitreal corticosteroids also have an important role in DME management. Until recently, the selection of a VEGF inhibitor for a patient was complicated by a lack of comparative data and a much lower cost for bevacizumab compared with other agents. Two-year results of the landmark head-to-head Protocol T trial will inform treatment selection for ophthalmologists and formulary decisions for managed care organizations. The study found that patients with better baseline visual acuity benefited from aflibercept, bevacizumab, or ranibizumab. However, aflibercept and ranibizumab were more effective than bevacizumab for patients with worse baseline visual acuity. A higher rate of nonfatal stroke and vascular death with ranibizumab in the Protocol T trial has raised concern in the community and needs to be investigated further. Emerging drugs for DME include VEGF inhibitors with less-frequent dosing intervals, and new agents that target other pathologic processes that contribute to vascular leakage and angiogenesis in DME.

PMID: 27668631

Ophthalmology. 2016 Oct;123(10):e60.

Re: Clark et al.: Intravitreal aflibercept for macular edema following branch retinal vein occlusion: 52-week results of the VIBRANT Study (Ophthalmology 2016;123:330-6).

Azad SV1, Takkar B2.

PMID: 27664916

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

Aflibercept improves outcome in eyes with poor vision from neovascular age-related macular degeneration.

Tomkins-Netzer O, Seguin-Greenstein S, Woronkiewicz M, Lightman S.

PMID: 27654888

Other treatment & diagnosis

Retina. 2016 Oct;36(10):1806-22.

CLINICAL ENDPOINTS FOR THE STUDY OF GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION.

Sadda SR, Chakravarthy U, Birch DG, Staurenghi G, Henry EC, Brittain C.

PURPOSE: To summarize the recent literature describing the application of modern technologies in the study of patients with geographic atrophy (GA) secondary to age-related macular degeneration.

METHODS: Review of the literature describing the terms and definitions used to describe GA, imaging modalities used to capture and measure GA, and the tests of visual function and functional deficits that occur in patients with GA.

RESULTS: In this paper, we describe the evolution of the definitions used to describe GA. We compare imaging modalities used in the characterization of GA, report on the sensitivity and specificity of the techniques where data exist, and describe the correlations between these various modes of capturing the presence of GA. We review the functional tests that have been used in patients with GA, and critically examine their ability to detect and quantify visual deficits.

CONCLUSION: Ophthalmologists and retina specialists now have a wide range of assessments available for the functional and anatomic characterization of GA in patients with age-related macular degeneration. To date, studies have been limited by their unimodal approach, and we recommend that future studies of GA use multimodal imaging. We also suggest strategies for the optimal functional testing of patients with GA.

PMID: 27652913

Optom Vis Sci. 2016 Sep 23. [Epub ahead of print]

Fundus Autofluorescence in Age-related Macular Degeneration.

Ly A, Nivison-Smith L, Assaad N, Kalloniatis M.

Abstract: Fundus autofluorescence (FAF) provides detailed insight into the health of the retinal pigment epithelium (RPE). This is highly valuable in age-related macular degeneration (AMD) as RPE damage is a

hallmark of the disease. The purpose of this paper is to critically appraise current clinical descriptions regarding the appearance of AMD using FAF and to integrate these findings into a chair-side reference. A wide variety of FAF patterns have been described in AMD, which is consistent with the clinical heterogeneity of the disease. In particular, FAF imaging in early to intermediate AMD has the capacity to reveal RPE alterations in areas that appear normal on funduscopy, which aids in the stratification of cases and may have visually significant prognostic implications. It can assist in differential diagnoses and also represents a reliable, sensitive method for distinguishing reticular pseudodrusen. FAF is especially valuable in the detection, evaluation, and monitoring of geographic atrophy and has been used as an endpoint in clinical trials. In neovascular AMD, FAF reveals distinct patterns of classic choroidal neovascularization noninvasively and may be especially useful for determining which eyes are likely to benefit from therapeutic intervention. FAF represents a rapid, effective, noninvasive imaging method that has been underutilized, and incorporation into the routine assessment of AMD cases should be considered. However, the practicing clinician should also be aware of the limitations of the modality, such as in the detection of foveal involvement and in the distinction of phenotypes (hypo-autofluorescent drusen from small areas of geographic atrophy).

PMID: 27668639

Proteomics. 2016 Sep 20. [Epub ahead of print]

A novel, multiplexed targeted mass spectrometry assay for quantification of complement factor H (CFH) variants and CFH-related proteins 1-5 in human plasma.

Zhang P, Zhu M, Geng-Spyropoulos M, Shardell M, Gonzalez-Freire M, Gudnason V, Eiriksdottir G, Schaumberg D, Van Eyk JE, Ferrucci L, Semba RD.

Abstract: Age-related macular degeneration (AMD) is a leading cause of visual loss among older adults. Two variants in the complement factor H (CFH) gene, Y402H and I62V, are strongly associated with risk of AMD. CFH is encoded in Regulator of Complement Activation gene cluster in chromosome 1q32, which includes complement factor-related (CFHR) proteins, CFHR1 to CFHR5, with high amino acid sequence homology to CFH. Our goal was to build a selected reaction monitoring (SRM) assay to measure plasma concentrations of CFH variants Y402, H402, I62, and V62, and CFHR1-5. The final assay consisted of 36 peptides and 108 interference-free SRM transition ion pairs. Most peptides showed good linearity over 0.3-200 fmol/ μ L concentration range. Plasma concentrations of CFH variants and CFHR1-5 were measured using the SRM assay in 344 adults. Plasma CFH concentrations (mean, SE in μ g/mL) by inferred genotype were: YY402, II62 (170.1, 31.4), YY402, VV62 (188.8, 38.5), HH402, VV62 (144.0, 37.0), HY402, VV62 (164.2, 42.3), YY402, IV62 (194.8, 36.8), HY402, IV62 (181.3, 44.7). Mean (SE) plasma concentrations of CFHR1-5 were 1.63 (0.04), 3.64 (1.20), 0.020 (0.001), 2.42 (0.18), and 5.49 (1.55) μ g/mL, respectively. This SRM assay should facilitate the study of the role of systemic complement and risk of AMD. This article is protected by copyright. All rights reserved.

PMID: 27647805

Eur J Ophthalmol. 2016 Sep 17:0. [Epub ahead of print]

Choroidal thickness and visual prognosis in type 1 lesion due to neovascular age-related macular degeneration.

Hernández-Martínez P, Dolz-Marco R, Hervás-Marín D, Andreu-Fenoll M, Gallego-Pinazo R, Arévalo JF.

PURPOSE: To evaluate the association between subfoveal choroidal thickness and the visual outcome in eyes with type 1 choroidal neovascularization (CNV) due to neovascular age-related macular degeneration (nAMD).

METHODS: This was a retrospective, longitudinal, cross-sectional study including patients diagnosed with nAMD type 1 lesions managed with intravitreal injections of ranibizumab in a PRN strategy during 24

months. Retrospective chart review of patients with type 1 CNV recording the visual acuity, number of intravitreal injections, multimodal imaging data, and follow-up period was performed. Subfoveal choroidal thickness was measured using enhanced depth imaging scans obtained with spectral-domain optical coherence tomography.

RESULTS: Twenty-five eyes of 21 patients were included. The mean baseline logMAR best-corrected visual acuity was 0.52 (+0.35) (median 0.5; range 0.1-1; interquartile range (IQR) 0.3-0.8) and improved to 0.39 (+0.39) (median 0.4; range 0.1-1; IQR 0.2-0.5) by the end of the follow-up ($p = 0.038$). Subfoveal choroidal thickness was 202.8 (+60.3) μm (median 218; range 81-285; IQR 146-258). Statistical mixed effects model demonstrated an association between rate of improvement of visual acuity with subfoveal choroidal thickness after 24 months ($p < 0.001$) (95% confidence interval 0.0002-0.0001 logMAR month μm); higher thickness values were correlated with better visual acuity.

CONCLUSIONS: Thicker subfoveal choroid was associated with better visual outcomes in patients with type 1 CNV due to nAMD following a strict PRN regimen with intravitreal ranibizumab at 24 months of follow-up.

PMID: 27646337

J Fr Ophtalmol. 2016 Sep 19. [Epub ahead of print]

Follow-up after surgery for hemorrhagic AMD.

Garcia D, Mahieu L, Soubrane G, Salmon L, Renouvin A, Pagot-Mathis V, Matonti F, Soler V.

INTRODUCTION: The long-term functional results of macular hematoma (MH) surgery in exudative AMD are often limited. The goal of this study was to compare visual outcomes of monthly versus bimonthly follow-up in these patients.

METHODS: Retrospective, interventional case series. Population : 21 eyes of 21 patients with SMH associated with exudative AMD.

INCLUSION CRITERIA: first SMH associated with exudative AMD, with 1-year postoperative follow-up.

EXCLUSION CRITERIA: blood located exclusively underneath the retinal pigment epithelium on OCT imaging, SMH due to different etiology, lost to follow-up, ≤ 5 postoperative visits and a different surgical protocol as described. Patients were divided into two groups according to the number of postoperative visits (number of intravitreal injections [IVT] combined with the number of consultations, only one visit was recorded when IVT and consultation occurred on the same day) during the 1-year postoperative follow-up: group 1 had ≥ 11 visits ($n=8$); group 2 had 6 to 10 visits ($n=13$). All eyes underwent vitrectomy with subretinal injection of recombinant tissue plasminogen activator, fluid-gas exchange and anti-VEGF intravitreal injection. The main outcome was change in best-corrected visual acuity (BCVA).

RESULTS: Considering visual acuity (VA) change between 1-month and 1-year postoperative follow-up examinations, group 1 had statistically significant greater VA changes (logMAR -0.29 ± 0.44 vs logMAR 0.42 ± 0.73 ; $P=0.016$; $P=0.016$). In patients that had exudative recurrences (ER), group 1 received more anti-VEGF IVT than group 2 ($P=0.045$).

CONCLUSION: Our results showed that monthly follow-up, between the IVT series, is highly recommended to preserve postoperative VA in patients undergoing surgery for SMH associated with AMD.

PMID: 27658564

Retina. 2016 Sep 21. [Epub ahead of print]

VISUALIZING RETINAL PIGMENT EPITHELIUM PHENOTYPES IN THE TRANSITION TO GEOGRAPHIC ATROPHY IN AGE-RELATED MACULAR DEGENERATION.

Macular Disease Foundation Australia Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.
Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: research@mdfoundation.com.au | W: www.mdfoundation.com.au

Zanzottera EC, Ach T, Huisinigh C, Messinger JD, Spaide RF, Curcio CA.

PURPOSE: To inform the interpretation of clinical optical coherence tomography and fundus autofluorescence imaging in geographic atrophy (GA) of age-related macular degeneration by determining the distribution of retinal pigment epithelium (RPE) phenotypes in the transition from health to atrophy in donor eyes.

METHODS: In RPE-Bruch membrane flat mounts of two GA eyes, the terminations of organized RPE cytoskeleton and autofluorescent material were compared. In high-resolution histological sections of 13 GA eyes, RPE phenotypes were assessed at ± 500 and ± 100 μm from the descent of the external limiting membrane (ELM) toward Bruch membrane. The ELM descent was defined as curved, reflected, or oblique in shape. Thicknesses of RPE, basal laminar deposit (BLamD), and RPE plus BLamD were measured.

RESULTS: A border of atrophy that can be precisely delimited is the ELM descent, as opposed to the termination of the RPE layer itself, because of dissociated RPE in the atrophic area. Approaching the ELM descent, the percentage of abnormal RPE morphologies increases, the percentage of age-normal cells decreases, overall RPE thickens, and BLamD does not thin. The combination of RPE plus BLamD is 19.7% thicker at -100 μm from the ELM descent than that at -500 μm (23.1 ± 10.7 μm vs. 19.3 ± 8.2 μm ; $P = 0.05$).

CONCLUSION: The distribution of RPE phenotypes at the GA transition supports the idea that these morphologies represent defined stages of a degeneration sequence. The idea that RPE dysmorphia including rounding and stacking helps explain variable autofluorescence patterns in GA is supported. The ELM descent and RPE plus BLamD thickness profile may have utility as spectral domain optical coherence tomography metrics in clinical trials.

PMID: 27658287

Optom Vis Sci. 2016 Oct;93(10):1292-1295.

Type II Macular Telangiectasia Presenting as Bilateral Retinochoroidal Anastomosis.

Agarwal A, Invernizzi A, Kumari N, Singh R.

PURPOSE: Retinochoroidal anastomosis (RCA) is known to be associated with retinal angiomatous proliferans rather than idiopathic macular telangiectasia. The case report describes a rare association of bilateral RCA with type II idiopathic macular telangiectasia in an elderly woman.

CASE REPORT: A 65-year-old female patient presented with decreased vision in both eyes to the ophthalmology clinic. She was diagnosed with bilateral large serous retinal pigment epithelial detachments (PED). Atypical association of PED with IMT led to additional imaging, including fluorescein angiography (FA), spectral-domain optical coherence tomography (SD-OCT), and indocyanine green angiography (ICGA). Multimodal imaging analysis revealed characteristic signs of RCA such as the so-called kissing sign on SD-OCT. The patient was not offered any treatment due to the poor prognosis associated with the condition.

CONCLUSIONS: Although more commonly associated with retinal angiomatous proliferans (type III neovascular age-related macular degeneration), RCA can present in type II IMT Stage 5.

PMID: 27668494

Exp Eye Res. 2016 Sep 21. [Epub ahead of print]

Optical monitoring of retinal respiration in real time: 670 nm light increases the redox state of mitochondria.

Kaynezhad P, Tachtsidis I, Jeffery G.

Abstract: Mitochondria play a key role in ageing and disease. Their membrane potentials and ATP production decline with age and this is associated with progressive inflammation, cell loss and death. Here we use broadband Near-Infrared Spectroscopy (NIRS) to non-invasively measure in-vivo changes in aged retinal mitochondrial respiration following exposure to 670 nm, which improves mitochondrial performance and reduces inflammation. Low power NIR light was shone into the eye via a fibre optic and the reflection monitored to measure signature changes in the oxidation of cytochrome c oxidase (COX) in complex IV of the electron transport chain. Changes in retinal haemodynamics and oxygenation were also recorded simultaneously with COX by measuring changes in oxygenated and deoxygenated haemoglobin ($\Delta[\text{HbO}_2]$ and $\Delta[\text{HHb}]$). Retinae of aged rats exposed to 670 nm for 5 mins showed consistent progressive increases in oxidation of COX 5 mins post exposure. This remained significantly greater than baseline for up to 2 h. This was not seen when retinae were exposed to 420 nm light of the same power or when no light was applied. 670 nm exposure significantly increased total haemoglobin concentration ($\Delta[\text{HbT}] = \Delta[\text{HbO}_2] + \Delta[\text{HHb}]$) but not haemoglobin difference ($\Delta[\text{HbDiff}] = \Delta[\text{HbO}_2] - \Delta[\text{HHb}]$). There were no changes in blood metrics in association with 420 nm light or when no light exposure was given. Hence, brief 670 nm exposure that is associated with reduced inflammation has a significant positive impact on the redox state of COX in aged retinae. The relative redox state of retinal COX may provide a valuable biomarker in ageing and macular degeneration where declining mitochondrial function is implicated.

PMID: 27664904

Am J Ophthalmol. 2016 Sep 14. [Epub ahead of print]

Clinical Characteristics, Choroidal Neovascularization and Predictors of Visual Outcomes in Acquired Vitelliform Lesions.

Balaratnasingam C, Hoang QV, Inoue M, Curcio CA, Dolz-Marco R, Yannuzzi NA, Dhrami-Gavazi E, Yannuzzi LA, Freund KB.

PURPOSE: To quantify the temporal properties of the acquired vitelliform lesion (AVL) lifecycle, define the clinical characteristics of choroidal neovascularization (NV) in this setting and determine the predictors of long-term visual outcomes.

DESIGN: Retrospective cohort study

METHODS: Clinical and imaging data from 199 eyes of 124 consecutive patients with AVLs associated with age-related macular degeneration (AMD) and adult-onset foveomacular vitelliform dystrophy (AOFVD) were analyzed. Volumetric calculations of vitelliform material were determined using spectral-domain optical coherence tomography and the temporal properties of the AVL lifecycle were quantified. The clinical characteristics of NV were assessed as were the predictors of final best-corrected visual acuity (BCVA) and change in BCVA.

RESULTS: Mean age was 79.2 ± 12.1 years. AVLs grew and collapsed at approximately the same rate ($P = 0.275$). Fifteen eyes (7.5%) developed NV of which all were type 1. In 13 of these eyes, NV occurred during the collapse phase of the AVL lifecycle, after the peak AVL volume was reached. The risk of NV ($P = 0.006$) and the decline in BCVA ($P = 0.001$) were both significantly greater among eyes with AMD. Foveal atrophy was the characteristic most significantly associated with final BCVA and change in BCVA from baseline (both $P < 0.0005$). The development of NV was not predictive of long-term visual outcomes (all $P = 0.216$).

CONCLUSIONS: Complications associated with AVLs typically occur during the collapse phase of the AVL lifecycle. Visual outcomes and risk of NV are related to the underlying disease associated with AVLs.

PMID: 27640006

JAMA Ophthalmol. 2016 Sep 22. [Epub ahead of print]

Histopathological Insights Into Choroidal Vascular Loss in Clinically Documented Cases of Age-Related Macular Degeneration.

Seddon JM, McLeod DS, Bhutto IA, Villalonga MB, Silver RE, Wenick AS, Edwards MM, Luty GA.

IMPORTANCE: Age-related macular degeneration (AMD) is a multifactorial disease with genetic and environmental factors contributing to risk. Histopathologic changes underlying AMD are not fully understood, particularly the relationship between choriocapillaris (CC) dysfunction and phenotypic variability of this disease.

OBJECTIVE: To examine histopathologic changes in the CC of eyes with clinically documented AMD.

DESIGN, SETTING, AND PARTICIPANTS: The study was designed in 2011. Tissues were collected post mortem (2012-2016), and histopathological images were obtained from participants enrolled in AMD studies since 1988. Clinical records and images were collected from participants as standard protocol. Eyes without AMD (n = 4) and eyes with early (n = 9), intermediate (n = 5), and advanced stages of AMD (geographic atrophy, n = 5; neovascular disease, n = 13) were evaluated. Choroidal vasculature was labeled using Ulex europaeus agglutinin lectin and examined using confocal microscopy.

MAIN OUTCOMES AND MEASURES: A standardized classification system was applied to determine AMD stage. Ocular records and images were reviewed and histopathologic analyses performed. Viability of the choroidal vasculature was analyzed for each AMD stage.

RESULTS: All participants were white. Fourteen were male, and 16 were female. The mean age was 90.5 years among AMD patients and 88.5 years among control participants. Submacular CC dropout without retinal pigment epithelial (RPE) loss was observed in all cases with early stages of AMD. Higher vascular area loss for each AMD stage was observed compared with control participants: 20.5% in early AMD (95% CI, 11.2%-40.2%; $P < .001$), 12.5% in intermediate AMD (95% CI, 2.9%-21.4%; $P = .01$), 39.0% loss in GA (95% CI, 32.1%-45.4%; $P < .001$), and 38.2% loss in neovascular disease where RPE remained intact (95% CI, 27.7%-47.9%; $P < .001$). Hypercellular, apparent neovascular buds were adjacent to areas of CC loss in 22.2% of eyes with early AMD and 40% of eyes with intermediate AMD.

CONCLUSIONS AND RELEVANCE: Retinal pigment epithelial atrophy preceded CC loss in geographic atrophy, but CC loss occurred in the absence of RPE atrophy in 2 of 9 eyes with early-stage AMD. Given the cross-sectional nature of this study and the small number of eyes evaluated, definitive conclusions regarding this progression cannot be determined with certainty. We speculate that neovascular buds may be a precursor to neovascular disease. Hypoxic RPE resulting from reduced blood supply might upregulate production of vascular endothelial growth factor, providing the stimulus for neovascular disease.

PMID: 27657855

Acta Ophthalmol. 2016 Sep 23. [Epub ahead of print]

Optical coherence tomography angiography in age-related macular degeneration: persistence of vascular network in quiescent choroidal neovascularization.

Wirth MA, Freiberg F, Pfau M, Wons J, Becker MD, Michels S.

PMID: 27659278

JAMA Ophthalmol. 2016 Sep 22. [Epub ahead of print]

Early Insight Into Neovascular Age-Related Macular Degeneration.

Dryja TP.

PMID: 27657333

J Clin Diagn Res. 2016 Aug;10(8):NJ01-2. Epub 2016 Aug 1.

Retinal Pigment Epithelial Tear Developing in a Patient with Outer Retinal Tubulations: Pathogenic Association or Coincidence?

Tsaousis KT, Empeslidis T.

PMID: 27656475 PMCID: PMC5028436 [Available on 2016-10-01]

Pathogenesis

Open J Ophthalmol. 2016 Feb;6(1):43-50. Epub 2016 Feb 26.

Novel Mechanistic Interplay between Products of Oxidative Stress and Components of the Complement System in AMD Pathogenesis.

Du H, Xiao X, Stiles T, Douglas C, Ho D, Shaw PX.

Abstract: Age-related macular degeneration (AMD) is a leading cause of vision loss affecting tens of millions of elderly worldwide. Early AMD includes soft drusen and pigmentary changes in the retinal pigment epithelium (RPE). As people age, such soft confluent drusen can progress into two forms of advanced AMD, geographic atrophy (GA, or dry AMD) or choroidal neovascularization (CNV, or wet AMD) and result in the loss of central vision. The exact mechanism for developing early AMD and progressing to advanced stage of disease is still largely unknown. However, significant evidence exists demonstrating a complex interplay of genetic and environmental factors as the cause of AMD progression. Together, complement factor H (CFH) and HTRA1/ARMS polymorphisms contribute to more than 50% of the genetic risk for AMD. Environmentally, oxidative stress from activities such as smoking has also demonstrated a powerful contribution to AMD progression. To extend our previous finding that genetic polymorphisms in CFH results in OxPLs and the risk-form of CFH (CFH Y402H) has reduced affinity for oxidized phospholipids, and subsequent diminished capacity which subsequently diminishes the capability to attenuate the inflammatory effects of these molecules, we compared the binding properties of CFH and CFH related protein 1 (CFHR1), which is also associated with disease risk, to OxPLs and their effects on modulating inflammation and lipids uptake. As both CFH-402H and CFHR1 are associated with increased risk to AMD, we hypothesized that like CFH-402H, CFHR1 contribution to AMD risk may also be due to its diminished affinity for OxPLs. Interestingly, we found that association of CFHR1 with OxPLs was not statistically different than CFH. However, binding of CFHR1 did not elicit the same protective benefits as CFH in that both inflammation and lipid uptake are unaffected by CFHR1 association with OxPLs. These findings demonstrate a novel and interesting complexity to the potential interplay between the complement system and oxidative stress byproducts, such as OxPLs, in the mechanistic contribution to AMD. Future work will aim to identify the molecular distinctions between CFH and CFHR1 which confer protection by the former, but not latter molecules. Understanding the molecular domains necessary for protection could provide interventional insights in the generation of novel therapeutics for AMD and other diseases associated with oxidative stress.

PMID: 27668132

Lab Invest. 2016 Sep 26. [Epub ahead of print]

Tenascin-C secreted by transdifferentiated retinal pigment epithelial cells promotes choroidal neovascularization via integrin α V.

Kobayashi Y, Yoshida S, Zhou Y, Nakama T, Ishikawa K, Kubo Y, Arima M, Nakao S, Hisatomi T, Ikeda Y, Matsuda A, Sonoda KH, Ishibashi T.

Abstract: Tenascin-C is expressed in choroidal neovascular (CNV) membranes in eyes with age-related macular degeneration (AMD). However, its role in the pathogenesis of CNV remains to be elucidated. Here

we investigated the role of tenascin-C in CNV formation. In immunofluorescence analyses, tenascin-C co-stained with α -SMA, pan-cytokeratin, CD31, CD34, and integrin α V in the CNV membranes of patients with AMD and a mouse model of laser-induced CNV. A marked increase in the expression of tenascin-C mRNA and protein was observed 3 days after laser photocoagulation in the mouse CNV model. Tenascin-C was also shown to promote proliferation and inhibit adhesion of human retinal pigment epithelial (hRPE) cells in vitro. Moreover, tenascin-C promoted proliferation, adhesion, migration, and tube formation in human microvascular endothelial cells (HMVECs); these functions were, however, blocked by cilengitide, an integrin α V inhibitor. Exposure to TGF- β 2 increased tenascin-C expression in hRPE cells. Conditioned media harvested from TGF- β 2-treated hRPE cell cultures enhanced HMVEC proliferation and tube formation, which were inhibited by pretreatment with tenascin-C siRNA. The CNV volume was significantly reduced in tenascin-C knockout mice and tenascin-C siRNA-injected mice. These findings suggest that tenascin-C is secreted by transdifferentiated RPE cells and promotes the development of CNV via integrin α V in a paracrine manner. Therefore, tenascin-C could be a potential therapeutic target for the inhibition of CNV development associated with AMD. Laboratory Investigation advance online publication, 26 September 2016; doi:10.1038/labinvest.2016.99.

PMID: 27668890

Aging Cell. 2016 Sep 22. [Epub ahead of print]

Activated monocytes resist elimination by retinal pigment epithelium and downregulate their OTX2 expression via TNF- α .

Mathis T, Housset M, Eandi C, Beguier F, Touhami S, Reichman S, Augustin S, Gondouin P, Sahel JA, Kodjikian L, Goureau O, Guillonnet X, Sennlaub F.

Abstract: Orthodenticle homeobox 2 (OTX2) controls essential, homeostatic retinal pigment epithelial (RPE) genes in the adult. Using cocultures of human CD14⁺ blood monocytes (Mos) and primary porcine RPE cells and a fully humanized system using human-induced pluripotent stem cell-derived RPE cells, we show that activated Mos markedly inhibit RPE OTX2 expression and resist elimination in contact with the immunosuppressive RPE. Mechanistically, we demonstrate that TNF- α , secreted from activated Mos, mediates the downregulation of OTX2 and essential RPE genes of the visual cycle among others. Our data show how subretinal, chronic inflammation and in particular TNF- α can affect RPE function, which might contribute to the visual dysfunctions in diseases such as age-related macular degeneration (AMD) where subretinal macrophages are observed. Our findings provide important mechanistic insights into the regulation of OTX2 under inflammatory conditions. Therapeutic restoration of OTX2 expression might help revive RPE and visual function in retinal diseases such as AMD.

PMID: 27660103

Biomaterials. 2016 Sep 13;109:12-22. [Epub ahead of print]

Ultrastrong trapping of VEGF by graphene oxide: Anti-angiogenesis application.

Lai PX, Chen CW, Wei SC, Lin TY, Jian HJ, Lai IP, Mao JY, Hsu PH, Lin HJ, Tzou WS, Chen SY, Harroun SG, Lai JY, Huang CC.

Abstract: Angiogenesis is the process of formation of new blood vessels, which is essential to human biology, and also plays a crucial role in several pathologies such as tumor growth and metastasis, exudative age-related macular degeneration, and ischemia. Vascular endothelial growth factor (VEGF), in particular, VEGF-A165 is the most important pro-angiogenic factor for angiogenesis. Thus, blocking the interaction between VEGFs and their receptors is considered an effective anti-angiogenic strategy. We demonstrate for that first time that bovine serum albumin-capped graphene oxide (BSA-GO) exhibits high stability in physiological saline solution and possesses ultrastrong binding affinity towards VEGF-A165 [dissociation constant (K_d) $\approx 3 \times 10^{-12}$ M], which is at least five orders of magnitude stronger than that of

high-abundant plasma proteins such as human serum albumin, fibrinogen, transferrin, and immunoglobulin G. Due to the surprising binding specificity of BSA-GO for VEGF-A165 in complex plasma fluid, we have also studied the anti-angiogenic effects in vitro and in vivo. Results show that BSA-GO not only effectively inhibits the proliferation, migration and tube formation of human umbilical vein endothelial cells, but also strongly disturbs the physiological process of angiogenesis in chick chorioallantoic membrane and blocks VEGF-A165-induced blood vessel formation in rabbit corneal neovascularization. Our findings indicate that GO nanomaterials can potentially act as therapeutic anti-angiogenic agents via ultrastrong VEGF adsorption and its activity suppression.

PMID: 27639528

Philos Trans A Math Phys Eng Sci. 2016 Oct 28;374(2079).

Quantitative metabolomics of photoreceptor degeneration and the effects of stem cell-derived retinal pigment epithelium transplantation.

Wang J, Westenskow PD, Fang M, Friedlander M, Siuzdak G.

Abstract: Photoreceptor degeneration is characteristic of vision-threatening diseases including age-related macular degeneration. Photoreceptors are metabolically demanding cells in the retina, but specific details about their metabolic behaviours are unresolved. The quantitative metabolomics of retinal degeneration could provide valuable insights and inform future therapies. Here, we determined the metabolomic 'fingerprint' of healthy and dystrophic retinas in rat models using optimized metabolite extraction techniques. A number of classes of metabolites were consistently dysregulated during degeneration: vitamin A analogues, fatty acid amides, long-chain polyunsaturated fatty acids, acyl carnitines and several phospholipid species. For the first time, a distinct temporal trend of several important metabolites including DHA (4Z,7Z,10Z,13Z,16Z,19Z-docosahexaenoic acid), all-trans-retinal and its toxic end-product N-retinyl-N-retinylidene-ethanolamine were observed between healthy and dystrophic retinas. In this study, metabolomics was further used to determine the temporal effects of the therapeutic intervention of grafting stem cell-derived retinal pigment epithelium (RPE) in dystrophic retinas, which significantly prevented photoreceptor atrophy in our previous studies. The result revealed that lipid levels such as phosphatidylethanolamine in eyes were restored in those animals receiving the RPE grafts. In conclusion, this study provides insight into the metabolomics of retinal degeneration, and further understanding of the efficacy of RPE transplantation. This article is part of the themed issue 'Quantitative mass spectrometry'.

PMID: 27644974 PMCID: PMC5031641 [Available on 2017-10-28]

J Ethnopharmacol. 2016 Sep 19. [Epub ahead of print]

Anti-inflammatory activity of Barleria lupulina: Identification of active compounds that activate the Nrf2 cell defense pathway, organize cortical actin, reduce stress fibers, and improve cell junctions in microvascular endothelial cells.

Senger DR, Hoang MV, Kim KH, Li C, Cao S.

ETHNOPHARMACOLOGICAL RELEVANCE: Hot aqueous extracts of the plant Barleria lupulina (BL) are used for treating inflammatory conditions and diabetic vascular complications.

AIM OF THE STUDY: The goal was to identify active compounds in hot aqueous extracts of BL (HAE-BL) that are consistent with a role in reducing inflammation and reducing the vascular pathology associated with diabetes. In particular, we examined activation of the Nrf2 cell defense pathway because our initial findings indicated that HAE-BL activates Nrf2, and because Nrf2 is known to suppress inflammation. Activation of Nrf2 by HAE-BL has not been described previously.

MATERIALS AND METHODS: Human endothelial cells, real-time PCR, western blotting, cytoskeletal analyses, and assay-guided fractionation with HPLC were used to identify specific compounds in HAE-BL

that activate the Nrf2 cell defense pathway and reduce markers of inflammation in vitro.

RESULTS: HAE-BL potently activated the Nrf2 cell defense pathway in endothelial cells consistent with its traditional use and reported success in reducing inflammation. Assay guided fractionation with HPLC identified three alkyl catechols: 4-ethylcatechol, 4-vinylcatechol, and 4-methylcatechol, that are each potent Nrf2 activators. In addition to activating Nrf2, HAE-BL and alkyl catechols each profoundly improved organization of the endothelial cell actin cytoskeleton, reduced actin stress fibers, organized cell-cell junctions, and induced expression of mRNA encoding claudin-5 that is important for formation of endothelial tight junctions and reducing vascular leak.

CONCLUSIONS: HAE-BL contains important alkyl catechols that potently activate the Nrf2 cell defense pathway, improve organization of the endothelial cell cytoskeleton, and organize tight cell junctions. All of these properties are consistent with a role in reducing inflammation and reducing vascular leak. Because activation of the Nrf2 cell defense pathway also prevents cancers, neuro-degeneration, age-related macular degeneration, and also reduces the severity of chronic obstructive pulmonary disorder and multiple sclerosis, HAE-BL warrants additional consideration for these other serious disorders.

PMID: 27660013

J Pathol. 2016 Sep 23. [Epub ahead of print]

PTX3 recruits complement factor H to protect against oxidative stress-induced complement and inflammasome overactivation.

Wang L, Cano M, Datta S, Wei H, Ebrahimi KB, Gorashi Y, Garlanda C, Handa JT.

Abstract: The discovery that genetic abnormalities in complement factor H (FH) are associated with increased risk for age-related macular degeneration (AMD), the most common cause of blindness among the elderly, raised hope of new treatments for this vision threatening disease. Nonetheless, over a decade after the identification of this important association, how innate immunity contributes to AMD remains unresolved. Pentraxin 3 (PTX3), an essential component of innate immunity that plays a non-redundant role in controlling inflammation, regulates complement by interacting with complement components. Here we show that PTX3 is induced by oxidative stress, a known cause of AMD, in the retinal pigmented epithelium (RPE). PTX3 deficiency in vitro and in vivo magnified complement activation induced by oxidative stress, leading to increased C3a, FB, and C3d, but not C5b-9 complex formation. Increased C3a, resulting from PTX3 deficiency, raised levels of IL1b mRNA and secretion of activated IL1b by interacting with C3aR. Importantly, PTX3 deficiency augmented NLRP3 inflammasome activation resulting in enhanced IL-1b, but not IL-18 production by the RPE. Thus, with PTX3 deficiency, the complement and inflammasome pathways worked in concert to produce IL-1b in sufficient abundance that importantly, resulted in macrophages accumulating in the choroid. These results demonstrate that PTX3 acts as an essential brake for complement and inflammasome activation by regulating the abundance of FH in the RPE, and provide critical insight into the complex interplay between oxidative stress and innate immunity in the early stages of AMD development.

PMID: 27659908

Mol Diagn Ther. 2016 Sep 23. [Epub ahead of print]

An Eye on Age-Related Macular Degeneration: The Role of MicroRNAs in Disease Pathology.

Berber P, Grassmann F, Kiel C, Weber BH.

Abstract: Age-related macular degeneration (AMD) is the primary cause of blindness in developed countries, and is the third leading cause worldwide. Emerging evidence suggests that beside environmental and genetic factors, epigenetic mechanisms, such as microRNA (miRNA) regulation of gene expression, are relevant to AMD providing an exciting new avenue for research and therapy. MiRNAs are short, non-

coding RNAs thought to be imperative for coping with cellular stress. Numerous studies have analyzed miRNA dysregulation in AMD patients, although with varying outcomes. Four studies which profiled dysregulated circulating miRNAs in AMD yielded unique sets, and there is only minimal overlap in ocular miRNA profiling of AMD. Mouse models of AMD, including oxygen-induced retinopathy and laser-induced choroidal neovascularization, showed similarities to some extent with miRNA patterns in AMD. For example, miR-146a is an extensively researched miRNA thought to modulate inflammation, and was found to be upregulated in AMD mice and cellular systems, but also in human AMD retinae and vitreous humor. Similarly, miR-17, miR-125b and miR-155 were dysregulated in multiple AMD mouse models as well as in human AMD plasma or retinae. These miRNAs are thought to regulate angiogenesis, apoptosis, phagocytosis, and inflammation. A promising avenue of research is the modulation of such miRNAs, as the phenotype of AMD mice could be ameliorated with antagomirs or miRNA-mimic treatment. However, before meaningful strides can be made to develop miRNAs as a diagnostic or therapeutic tool, reproducible miRNA profiles need to be established for the various clinical outcomes of AMD.

PMID: 27658786

Epidemiology

Neurotoxicology. 2016 Sep 20. [Epub ahead of print]

Adult lead exposure increases blood-retinal permeability: A risk factor for retinal vascular disease.

Shen XF, Huang P, Fox DA, Lin Y, Zhao ZH, Wang W, Wang JY, Liu XQ, Chen JY, Luo WJ.

Abstract: Low-to-moderate level developmental and adult lead exposure produces retinal dysfunction and/or degeneration in humans and experimental animals. Although high level in vivo or in vitro lead disrupts blood-brain-barrier tight junctions and increases its permeability, the blood-retinal-barrier (BRB) has not been examined. There were four overall goals. First, generate environmentally relevant dose-response models of short-term lead exposure in adult rats. Second, assess retinal histology and functional integrity of the BRB. Third, investigate the transmembrane proteins occludin and claudin-5 as targets mediating the increased BRB permeability. Fourth, examine the contribution of the PI3K-Akt signaling pathway as a mechanism underlying increased BRB permeability. Young adult rats were given water, 0.01% or 0.02% lead drinking solutions for six weeks. In control, 0.01% and 0.02% groups the six week mean blood [Pb] were 1, 12.5 and 19µg/dl, respectively. We employed histology, stereology, quantitative image analysis, immunoblots and densitometry, and pharmacology techniques. Major findings were that adult lead exposure produced dose-dependent 1) decreases in outer and inner nuclear layer thickness, 2) increases in BRB permeability, 3) decreases in occludin and claudin-5 expression, 4) increases in pAkt (Ser473), but not pAkt (Thr308), expression, and 5) wortmannin partially or completely blocked the increased BRB permeability and changes in protein expression. These results indicate that lead-induced increases in PI3K-Akt signaling partially underlie the increased BRB permeability and advance our knowledge about lead-induced retinotoxicity. Furthermore, they suggest that environmental and occupational lead exposures are risk factors for increased BRB permeability in diseases such as age-related macular degeneration, diabetes and stroke.

PMID: 27663850

Genetics

PLoS One. 2016 Sep 19;11(9):e0162296. eCollection 2016.

Evaluation of 10 AMD Associated Polymorphisms as a Cause of Choroidal Neovascularization in Highly Myopic Eyes.

Velazquez-Villoria A, Recalde S, Anter J, Bezunartea J, Hernandez-Sanchez M, García-García L, Alonso E, Ruiz-Moreno JM, Araiz-Iribarren J, Fernandez-Robredo P, García-Layana A.

Abstract: Choroidal neovascularization (CNV) commonly occurs in age related macular degeneration and pathological myopia patients. In this study we conducted a case-control prospective study including 431 participants. The aim of this study was to determine the potential association between 10 single nucleotide polymorphisms (SNPs) located in 4 different genetic regions (CFI, COL8A1, LIPC, and APOE), and choroidal neovascularization in age-related macular degeneration and the development of choroidal neovascularization in highly myopic eyes of a Caucasian population. Univariate and multivariate logistic regression analysis adjusted for age, sex and hypertension was performed for each allele, genotype and haplotype frequency analysis. We found that in the univariate analysis that both single-nucleotide polymorphisms in COL8A1 gene (rs13095226 and rs669676) together with age, sex and hypertension were significantly associated with myopic CNV development in Spanish patients ($p < 0.05$). After correcting for multiple testing none of the polymorphisms studied remained significantly associated with myopic CNV ($p > 0.05$); however, analysis of the axial length between genotypes of rs13095226 revealed an important influence of COL8A1 in the development of CNV in high myopia. Furthermore we conducted a meta-analysis of COL8A1, CFI and LIPC genes SNPs (rs669676, rs10033900 and rs10468017) and found that only rs669676 of these SNPs were associated with high myopia neovascularization.

PMID: 27643879

BMC Genomics. 2016 Sep 22;17(1):752.

Erratum to: Genotype distribution-based inference of collective effects in genome-wide association studies: insights to age-related macular degeneration disease mechanism.

Woo HJ, Yu C, Kumar K, Gold B, Reifman J.

Erratum for: Genotype distribution-based inference of collective effects in genome-wide association studies: insights to age-related macular degeneration disease mechanism. [BMC Genomics. 2016]

PMID: 27660151

Adv Med. 2016;2016:3917916. Epub 2016 Aug 29.

CYP4F2 (rs2108622) Gene Polymorphism Association with Age-Related Macular Degeneration.

Sakiene R, Vilkeviciute A, Kriauciuniene L, Balciuniene VJ, Buteikiene D, Miniauskiene G, Liutkeviciene R.

Background: Age-related macular degeneration is the leading cause of blindness in elderly individuals where aetiology and pathophysiology of age-related macular degeneration are not absolutely clear.

Purpose: To determine the frequency of the genotype of rs2108622 in patients with early and exudative age-related macular degeneration.

Methods: The study enrolled 190 patients with early age-related macular degeneration, 181 patients with exudative age-related macular degeneration (eAMD), and a random sample of 210 subjects from the general population (control group). The genotyping of rs2108622 was carried out using the real-time polymerase chain reaction method.

Results: The analysis of rs2108622 gene polymorphism did not reveal any differences in the distribution of C/C, C/T, and T/T genotypes between the early AMD group, the eAMD group, and the control group. The CYP4F2 (1347C>T) T/T genotype was more frequent in males with eAMD compared to females (10.2% versus 0.8%; $p = 0.0052$); also T/T genotype was less frequently present in eAMD females compared to healthy control females (0.8% versus 6.2%; $p = 0.027$).

Conclusion: Rs2108622 gene polymorphism had no predominant effect on the development of early AMD and eAMD. The T/T genotype was more frequent in males with eAMD compared to females and less frequently present in eAMD females compared to healthy females.

PMID: 27652291 PMCID: PMC5019857

Sci Rep. 2016 Sep 20;6:33742.

CCT2 Mutations Evoke Leber Congenital Amaurosis due to Chaperone Complex Instability.

Minegishi Y, Sheng X, Yoshitake K, Sergeev Y, Iejima D, Shibagaki Y, Monma N, Ikeo K, Furuno M, Zhuang W, Liu Y, Rong W, Hattori S, Iwata T.

Abstract: Leber congenital amaurosis (LCA) is a hereditary early-onset retinal dystrophy that is accompanied by severe macular degeneration. In this study, novel compound heterozygous mutations were identified as LCA-causative in chaperonin-containing TCP-1, subunit 2 (CCT2), a gene that encodes the molecular chaperone protein, CCT β . The zebrafish mutants of CCT β are known to exhibit the eye phenotype while its mutation and association with human disease have been unknown. The CCT proteins (CCT α - θ) forms ring complex for its chaperon function. The LCA mutants of CCT β , T400P and R516H, are biochemically unstable and the affinity for the adjacent subunit, CCT γ , was affected distinctly in both mutants. The patient-derived induced pluripotent stem cells (iPSCs), carrying these CCT β mutants, were less proliferative than the control iPSCs. Decreased proliferation under Cct2 knockdown in 661W cells was significantly rescued by wild-type CCT β expression. However, the expression of T400P and R516H didn't exhibit the significant effect. In mouse retina, both CCT β and CCT γ are expressed in the retinal ganglion cells and connecting cilium of photoreceptor cells. The Cct2 knockdown decreased its major client protein, transducing β 1 (G β 1). Here we report the novel LCA mutations in CCT β and the impact of chaperon disability by these mutations in cellular biology.

PMID: 27645772

Stem Cells

Stem Cell Reports. 2016 Sep 15. [Epub ahead of print]

Lack of T Cell Response to iPSC-Derived Retinal Pigment Epithelial Cells from HLA Homozygous Donors.

Sugita S, Iwasaki Y, Makabe K, Kimura T, Futagami T, Suegami S, Takahashi M.

Abstract: Allografts of retinal pigment epithelial (RPE) cells have been considered for the treatment of ocular diseases. We recently started the transplantation of induced pluripotent stem cell (iPSC)-derived RPE cells for patients with age-related macular degeneration (autogenic grafts). However, there are at least two problems with this approach: (1) high cost, and (2) uselessness for acute patients. To resolve these issues, we established RPE cells from induced iPSCs in HLA homozygote donors. In vitro, human T cells directly recognized allogeneic iPSC-derived RPE cells that expressed HLA class I/II antigens. However, these T cells failed to respond to HLA-A, -B, and -DRB1-matched iPSC-derived RPE cells from HLA homozygous donors. Because of the lack of T cell response to iPSC-derived RPE cells from HLA homozygous donors, we can use these allogeneic iPSC-derived RPE cells in future clinical trials if the recipient and donor are HLA matched.

Copyright © 2016 The Authors. Published by Elsevier Inc. All rights reserved.

PMID: 27641646

Diet, lifestyle & low vision

Transl Vis Sci Technol. 2016 Sep 9;5(5):5. eCollection 2016.

Bioptic Telescope Use and Driving Patterns of Drivers with Age-Related Macular Degeneration.

Bowers AR, Sheldon SS, DeCarlo DK, Peli E.

PURPOSE: To investigate the telescope use and driving patterns of bioptic drivers with age-related macular degeneration (AMD).

METHODS: A questionnaire addressing telescope use and driving patterns was administered by telephone interview to three groups of bioptic drivers: AMD (n = 31; median 76 years); non-AMD first licensed with a bioptic (n = 38; 53 years); and non-AMD first licensed without a bioptic (n = 47; 37 years). Driving patterns of bioptic AMD drivers were also compared with those of normal vision (NV) drivers (n = 36; 74 years) and nonbioptic AMD drivers (n = 34; 79 years).

RESULTS: Bioptic usage patterns of AMD drivers did not differ from those of the younger bioptic drivers and greater visual difficulty without the bioptic was strongly correlated with greater bioptic helpfulness. Bioptic AMD drivers were more likely to report avoidance of night driving than the age-similar NV drivers ($P = 0.06$). However, they reported less difficulty than the nonbioptic AMD drivers in all driving situations ($P \leq 0.02$). Weekly mileages of bioptic AMD drivers were lower than those of the younger bioptic drivers ($P < 0.001$), but not the NV group ($P = 0.54$), and were higher than those of the nonbioptic AMD group ($P < 0.001$).

CONCLUSIONS: Our results suggest that bioptic telescopes met the visual demands of drivers with AMD and that those drivers had relatively unrestricted driving habits.

TRANSLATIONAL RELEVANCE: Licensure with a bioptic telescope may prolong driving of older adults with AMD; however, objective measures of bioptic use, driving performance, and safety are needed.

PMID: 27642541 PMCID: PMC5024559

Semin Ophthalmol. 2016 Aug 10:1-9. [Epub ahead of print]

Risk Factors for Poor Quality of Life among Patients with Age-Related Macular Degeneration.

Chatziralli I, Mitropoulos P, Parikakis E, Niakas D, Labiris G.

PURPOSE: The purpose of this study was to evaluate the quality of life in patients with age-related macular degeneration (AMD) and compare it with that of healthy controls. Additionally, our study aims to investigate the possible risk factors for poor quality of life in AMD patients.

METHODS: Participants in the study were 114 patients with AMD, 63 male and 51 female, mean-aged 76.5 ± 6.1 years. Demographic data, lifestyle factors, and medical history were recorded. All patients underwent a routine examination for AMD, including best-corrected visual acuity measurement, dilated fundoscopy and optical coherence tomography, and completed three questionnaires assessing quality of life (SF-36, EQ-5D, NEI VFQ-25). In addition, 100 controls, adjusted for gender and age, were included in the study. Risk factors for quality of life in AMD patients were investigated. Univariate analysis was performed using SPSS 22.0.

RESULTS: Patients with AMD scored lower in vision- and health-related quality-of-life questionnaires compared to controls. Risk factors associated with quality of life in patients with AMD were found to be the female gender, alcohol consumption, the presence of hypertension, diabetes mellitus, cardiovascular diseases, myoskeletal problems, migraine, anxiety/depression, subretinal or intraretinal fluid, pigment epithelium detachment, previous treatment for AMD, visual acuity, the stage of the disease, and the integrity of the ellipsoid zone.

CONCLUSION: Patients with AMD presented lower quality of life in comparison with controls. Potential risk factors should be taken into account and clinicians should thus focus on the most vulnerable subgroups.

PMID: 27648680

Arch Pharm Res. 2016 Sep 22. [Epub ahead of print]

Protective effects of resveratrol and its analogs on age-related macular degeneration in vitro.

Kang JH, Choung SY.

Abstract: Damage of retinal pigment epithelial (RPE) cells by A2E may be critical for age-related macular degeneration (AMD) management. Accumulation and photooxidation of A2E are known to be one of the critical causes in AMD. Here, we evaluated the protective effect of resveratrol (RES), piceatannol (PIC) and RES glycones on blue-light-induced RPE cell death caused by A2E photooxidation. A2E treatment followed by blue light exposure caused significant damages on human RPE cells (ARPE-19). But the damages were attenuated by post- and pre-treatment of RES and PIC in our in vitro models. The results of cell free system and FAB-MS analysis clearly showed that the reduction of A2E by blue light exposure was significantly rescued, and that oxidized forms of A2E were significantly reduced by RES or PIC treatment. Besides, RES or PIC inhibited the intracellular accumulation of A2E. Not only RES and PIC but RES glycones showed protection of ARPE-19 cells against A2E and blue-light-induced photo-damage. These findings demonstrate that RES and its analogs may have protective effects against A2E and blue-light-induced ARPE-19 cell death through regulation of A2E accumulation as well as photooxidation of A2E. Thus RES and its analogs may be beneficial for AMD treatment.

PMID: 27659166

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