

Issue 311

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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.

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Drug treatment

Clin Ophthalmol. 2016 Dec 15;10:2505-2513. eCollection 2016.

Physician, patient, and caregiver experience of different wet age-related macular degeneration anti-VEGF treatment regimens in Japan: a qualitative assessment.

Iida T, Ishii K.

PURPOSE: The purpose of this study was to monitor anti-vascular endothelial growth factor (anti-VEGF) treatment regimens for wet age-related macular degeneration (wAMD) in clinical practice and to determine how they impact the physician, patient, and caregiver treatment experience.

MATERIALS AND METHODS: This was a qualitative analysis based on semistructured interviews with 20 ophthalmologists who had practiced both pro re nata (PRN) and treat-and-extend (T&E) anti-VEGF regimens for wAMD. Interview questions were constructed to assess how the different regimens affected patient and caregiver experiences (in the opinion of the ophthalmologist) in addition to the ophthalmologist's own experience. The interview included questions relating to 1) issues and benefits of PRN and T&E; 2) logistical and operational issues of introducing proactive therapy, especially T&E, to PRN practice; and 3) actions taken to handle the issues raised in 2).

RESULTS: A total of 18 interview results were eligible for analysis. The study demonstrated that the benefits of T&E compared with PRN included decreased burden of patient consultations, decreased patient and caregiver emotional burden, and a sustained period of macular dryness. The issues associated with T&E were increased number of injections and financial burden from prolonged treatment duration. The ophthalmologists also experienced difficulty explaining the significance of proactive injections to patients. Countermeasures to operational issues experienced by ophthalmologists varied by practice.

CONCLUSION: Patients, caregivers, and the practicing ophthalmologists experienced benefits associated with a T&E regimen. However, in order to encourage better understanding of the T&E regimen, including its smooth implementation and significance for patients, a formal T&E treatment guideline providing standard practice should be considered.

PMID: 28008223 PMCID: PMC5170788

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

Intravitreal Aflibercept Injection in Eyes With Substantial Vision Loss After Laser Photocoagulation for Diabetic Macular Edema: Subanalysis of the VISTA and VIVID Randomized Clinical Trials.

Wykoff CC, Marcus DM, Midena E, Korobelnik JF, Saroj N, Gibson A, Vitti R, Berliner AJ, Williams Liu Z, Zeitz O, Metzger C, Schmelter T, Heier JS.

IMPORTANCE: Information on the effect of anti-vascular endothelial growth factor therapy in eyes with

diabetic macular edema (DME) with vision loss after macular laser photocoagulation is clinically valuable.

OBJECTIVE: To evaluate visual and anatomic outcomes in a subgroup of macular laser photocoagulation treatment control (hereafter laser control) eyes with substantial vision loss receiving treatment with intravitreal aflibercept injection.

DESIGN, SETTING, AND PARTICIPANTS: This investigation was a post hoc analysis of a subgroup of laser control eyes in 2 phase 3 trials-VISTA (Study of Intravitreal Aflibercept Injection in Patients With Diabetic Macular Edema) and VIVID (Intravitreal Aflibercept Injection in Vision Impairment Due to DME)-in a multicenter setting. One hundred nine laser control eyes with center-involving DME were included.

INTERVENTIONS: Treatment with intravitreal aflibercept injection (2 mg) every 8 weeks after 5 monthly doses with sham injections on nontreatment visits starting at week 24 was initiated on meeting prespecified criteria of at least a 10-letter visual acuity loss at 2 consecutive visits or at least a 15-letter visual acuity loss from the best previous measurement at 1 visit and vision not better than at baseline.

MAIN OUTCOMES AND MEASURES: Visual and anatomic outcomes in a subgroup of laser control eyes receiving treatment with intravitreal aflibercept injection.

RESULTS: Through week 100, a total of 63 of 154 eyes (40.9%) in VISTA and 46 of 133 eyes (34.6%) in VIVID initially randomized to laser control received treatment with intravitreal aflibercept injection. The median time from week 24 to the first intravitreal aflibercept injection treatment was 34.0 (VISTA) and 83.5 (VIVID) days. In this subgroup, the mean (SD) visual gain from baseline to week 100 was 2.2 (12.5) (VISTA) and 3.8 (10.1) (VIVID) letters. At the time of intravitreal aflibercept injection initiation, these eyes had a mean (SD) loss of 11.0 (10.1) (VISTA) and 10.0 (6.5) (VIVID) letters from baseline, and they subsequently gained a mean (SD) of 17.4 (9.7) (VISTA) and 13.6 (8.6) (VIVID) letters from the initiation of treatment with intravitreal aflibercept injection through week 100. There was a minimal mean change in central subfield thickness from baseline in these eyes at the time of intravitreal aflibercept injection initiation (an increase of 3.9 μ m in VISTA and a decrease of 3.0 μ m in VIVID), after which further mean (SD) reductions of 285.6 (202.6) μ m (VISTA) and 313.4 (181.9) μ m (VIVID) occurred through week 100.

CONCLUSIONS AND RELEVANCE: Intravitreal aflibercept injection improves visual and anatomic outcomes in eyes experiencing substantial vision loss after macular laser photocoagulation treatment for DME.

PMID: 28006063

Invest Ophthalmol Vis Sci. 2016 Dec 1;57(15):6911-6918.

Beyond VEGF-The Weisenfeld Lecture.

Miller JW.

PURPOSE: To review advances made in the treatment of age-related macular degeneration (AMD) and share perspectives on the future of AMD treatment.

METHODS: Review of published clinical and experimental studies.

RESULTS: Inhibitors of vascular endothelial growth factor (VEGF) truly revolutionized the treatment of AMD. However, available results from longer-term studies suggest that a degenerative process is unveiled, and continues to occur, even when neovascularization is controlled. Furthermore, anti-VEGF therapy may play a role in the development of atrophic changes. We have proposed using neuroprotection to prevent atrophy, and multiple models of retinal degeneration have shown that it is necessary to block both apoptotic and necrotic cell death pathways. Despite the success of anti-VEGF therapy and the promise of neuroprotection, neither addresses the underlying cause of AMD. It has been postulated that in early AMD, the retention and abnormal accumulation of lipids in Bruch's membrane and below the retinal pigmented epithelium (RPE) lead to drusen. Thus, it is conceivable to target the retained lipoproteins and seek to remove them. In a case study and pilot multicenter clinical trial, we observed significant regression of

drusen and an improvement in visual acuity in patients taking high-dose statin therapy. These results, though preliminary, warrant further investigation.

CONCLUSION: Future treatment of AMD should be based on biology, which will require continued elucidation of the pathogenic mechanisms of AMD development. Neuroprotection represents a potential therapeutic approach, and other promising targets include immune pathways (e.g., inflammation, complement, and inflammasomes) and lipid/lipoprotein accumulation. Finally, due to the heterogeneity of AMD, future progress in therapy will benefit from improved phenotyping and classification.

PMID: 28027565 PMCID: PMC5214225

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

Evaluating Effects of Switching Anti-Vascular Endothelial Growth Factor Drugs for Age-Related Macular Degeneration and Diabetic Macular Edema.

Ferris FL 3rd, Maguire MG, Glassman AR, Ying GS, Martin DF.

IMPORTANCE: When a patient with neovascular age-related macular degeneration or diabetic macular edema does not respond to an initial anti-vascular endothelial growth factor agent, usually after several injections, ophthalmologists may switch to another anti-vascular endothelial growth factor agent. Authors of case series have suggested beneficial effects from switching. However, to our knowledge, there are no studies with an appropriate control group to evaluate how such patients would do without switching agents.

OBJECTIVE: To assess outcomes in patients who have a poor initial response but continue treatment without switching agents.

DESIGN, SETTING, AND PARTICIPANTS: We obtained data from 2 multicenter clinical trials, the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and the Diabetic Retinopathy Clinical Research Network (DRCR.net). Based on typical clinical reasons for switching agents, we developed "switching rules" at both 3 and 6 months after initiation of treatment. Using these switching rules, we identified a 3-month and a 6-month cohort of "treatment failures" from both CATT and DRCR.net studies.

INTERVENTIONS: Although the cohorts from each study met criteria for switching, they were treated with the initial agent throughout the study (bevacizumab or ranibizumab in CATT and ranibizumab in DRCR.net).

MAIN OUTCOMES AND MEASURES: Primary outcomes were change in visual acuity and change in central retinal thickness on optical coherence tomography from the 3- or 6-month visit at which switching rules were met.

RESULTS: The 126 patients from CATT and the 59 patients from DRCR.net who were selected for the switching analysis were similar in age, sex and race/ethnicity to the overall study populations. Among the participants who met the criteria for switching, the CATT participants were a mean (SD) of 79.7 (7.8) years of age, 65.9% women, and 97.6% white, while the DRCR.net participants were a mean (SD) of 65.5 (9.3) years of age, 44.1% women, and 76.3% white. In all 4 cohorts, there was a 3- to 5-letter improvement in mean visual acuity over the 3 months after the switching rules were met, although all patients continued on their originally assigned treatment. Mean central retinal thickness also improved by 40 to 70 μ m.

CONCLUSIONS AND RELEVANCE: These results demonstrate the importance of having a comparison group to evaluate the effect of switching anti-vascular endothelial growth factor agents for treatment of neovascular age-related macular degeneration or diabetic macular edema. Without a comparison group, it is impossible to know whether any improvement observed after switching was related to the new treatment or was related to regression to the mean and time effects as observed in the 4 cohorts presented here. Randomization to switching or not switching drugs would provide a basis for valid conclusions about the effects of switching.

PMID: 28006042

Retina. 2016 Dec 28. [Epub ahead of print]

FACTORS INFLUENCING VISUAL ACUITY IN PATIENTS RECEIVING ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR FOR MYOPIC CHOROIDAL NEOVASCULARIZATION.

Iacono P, Battaglia Parodi M, Selvi F, Parravano MC, Chiaravalloti A, Varano M, Bandello F.

PURPOSE: To identify the prognostic variables relative to myopic choroidal neovascularization (CNV) treated with intravitreal ranibizumab/bevacizumab.

METHODS: Forty-eight patients with myopic CNV were enrolled in a prospective, interventional, non-randomized 12-month study. Intravitreal ranibizumab/bevacizumab was administered in a pro-re-nata regimen and re-treatment was performed in the presence of angiographic leakage, intraretinal/subretinal fluid on optical coherence tomography, new hemorrhages, five-letter decrease and increased metamorphosis. The primary outcome measures were the identification of the predictive value of symptom duration, patient's age, refractive error, best-corrected visual acuity (BCVA), central macular thickness (CMT), CNV area, CNV location, retinal hemorrhages, atrophy, lacquer cracks, and CNV-fundus autofluorescence pattern (hyper-fundus autofluorescence/patchy pattern). The secondary outcomes were patients requiring either one or two injections to achieve CNV stabilization.

RESULTS: The mean BCVA improved from 0.49 ± 0.30 (logarithm of minimal angle resolution, Snellen equivalent 20/63) to 0.39 ± 0.32 (20/49) at 1-year follow-up ($P = 0.043$). Univariate and multiple stepwise linear regression analysis identified baseline BCVA ($P = 0.0003$), symptom duration ($P = 0.005$), CMT ($P = 0.02$), and fundus autofluorescence pattern ($P = 0.005$) as the explanatory variables on the final BCVA and the change in the mean BCVA. Overall, patients with better baseline BCVA, early diagnosis, lower CMT, or disclosing a hyperfundus autofluorescence CNV pattern achieved better visual outcomes. Patients responding with just one to two intravitreal injections (45.8%) obtained better visual outcomes compared with patients receiving three or more injections, and this group consisted of younger patients with lesser CMT, smaller CNV area, and fewer baseline hemorrhages.

CONCLUSION: Ranibizumab/bevacizumab therapy was effective in improving and maintaining visual acuity in myopic choroidal neovascularization. Early diagnosis, better baseline BCVA, and hyperfundus autofluorescence CNV pattern were strongly associated with better functional outcomes. Moreover, CNV distinguished by its small size and low CMT responded more favorably, achieving a better visual outcome.

PMID: 28033235

Eye (Lond). 2017 Jan 6. [Epub ahead of print]

Short-term effects of intravitreal ranibizumab and bevacizumab administration on 24-h ambulatory blood pressure monitoring recordings in normotensive patients with age-related macular degeneration.

Sengul A, Rasier R, Ciftci C, Artunay O, Kockar A, Bahcecioglu H, Yuzbasioglu E.

Purpose: To evaluate effects of intravitreal ranibizumab and bevacizumab administration on ambulatory blood pressure monitoring (ABPM) recordings in normotensive patients with age-related macular degeneration (AMD).

Patients and methods: A total of 72 patients (mean age: 61.8(6.2) years, 52.8% were females) diagnosed with AMD were included in this study as divided into ranibizumab (n=34) and bevacizumab (n=38) treatment groups. Twenty-four hour, nighttime, and daytime ABPM values for systolic and diastolic BP were recorded in study groups before and after the third intravitreal injection of ranibizumab or bevacizumab.

Results: Ranibizumab injection had no impact on ABPM recordings and dipping status. In the bevacizumab group, increased daytime (129.0(6.6) vs 127.7(6.6) mm Hg, $P=0.002$) and nighttime systolic (116.9(7.5) vs 112.6(7.1) mmHg, $p<0.001$) BP and decreased daytime diastolic (80.1(6.5) vs 82.4(6.1)mm Hg, $P=0.001$) BP were noted in the post-injection period. Also, percentage of non-dippers was significantly increased

from 5.3% at pre-injection to 28.9% ($P=0.004$) at the post-injection period.

Conclusion: In conclusion, given that it has no significant impact on ABPM recordings and dipping status, in our study, intravitreal ranibizumab injection may be the better choice in the management of AMD.

PMID: 28060360

Retina. 2017 Jan 2. [Epub ahead of print]

SHORT-TERM SAFETY OF 2 MG INTRAVITREAL ZIV-AFLIBERCEPT.

Chhablani J, Dedhia CJ, Peguda HK, Stewart M.

PURPOSE: To evaluate the safety of single intravitreal 2 mg ziv-aflibercept (0.08 mL) injections for the treatment of choroidal neovascular membranes (CNVM).

METHODS: Eyes with choroidal neovascular membranes because of several conditions each received single intravitreal injections of 2 mg ziv-aflibercept (0.08 mL). Comprehensive ophthalmic examinations and detailed systemic evaluations were performed at baseline and Days 1, 7, and 30 after injections. Standard electroretinography was performed at baseline and Day 30. Primary outcome measures consisted of safety assessments (signs of clinical toxicity and electroretinographic abnormalities). Secondary outcome measures included changes in best-corrected visual acuity (BCVA) and central subfield thickness (CST) of the macula.

RESULTS: Twenty-one eyes of 20 patients (12 males) received injections. Etiologies responsible for the choroidal neovascular membranes included age-related macular degeneration (14), polypoidal choroidal vasculopathy (PCV) (3), myopia (2), and idiopathic juxtafoveal telangiectasia (2). None of the patients complained of worsening vision or pain after the intravitreal injections and no intraocular inflammation was seen. No significant changes in the electroretinographic b/a ratio from baseline to 1 month were measured (scotopic: $P = 0.89$; photopic: $P = 0.13$) and mean intraocular pressures were unchanged (14.2 ± 3.6 vs. 13.7 ± 3.0 mmHg; $P = 0.62$). Mean best-corrected visual acuity did not change significantly from baseline to 1 month (0.66 ± 0.37 logMAR [Snellen equivalent: 20/100] vs. 0.61 ± 0.35 logMAR [Snellen equivalent: 20/80]; $P = 0.72$) but significant improvements in central subfield thickness were seen (343 ± 177 vs. 210 ± 133 μ m; $P = 0.01$).

CONCLUSION: Single intravitreal injections of 2 mg ziv-aflibercept (0.08 mL) appear to be safe through 1 month.

PMID: 28060148

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

Dual Antagonism of PDGF and VEGF in Neovascular Age-Related Macular Degeneration: A Phase IIb, Multicenter, Randomized Controlled Trial.

Jaffe GJ, Ciulla TA, Ciardella AP, Devin F, Dugel PU, Eandi CM, Masonson H, Monés J, Pearlman JA, Quaranta-El Maftouhi M, Ricci F, Westby K, Patel SC.

PURPOSE: To assess the safety and efficacy of E10030 (Fovista; Ophthotech, New York, NY), a platelet-derived growth factor (PDGF) antagonist, administered in combination with the anti-vascular endothelial growth factor (VEGF) agent ranibizumab (Lucentis; Roche, Basel, Switzerland) compared with ranibizumab monotherapy in patients with neovascular age-related macular degeneration (nAMD).

DESIGN: Phase IIb global, multicenter, randomized, prospective, double-masked, controlled superiority trial.

PARTICIPANTS: Four hundred forty-nine patients with treatment-naïve nAMD.

METHODS: Participants were randomized in a 1:1:1 ratio to 1 of the following 3 intravitreal treatment groups: E10030 0.3 mg in combination with ranibizumab 0.5 mg, E10030 1.5 mg in combination with ranibizumab 0.5 mg, and sham in combination with ranibizumab 0.5 mg (anti-VEGF monotherapy). Drugs were administered monthly in each of the groups for a total duration of 24 weeks.

MAIN OUTCOME MEASURES: The prespecified primary end point was the mean change in visual acuity (VA; Early Treatment Diabetic Retinopathy [ETDRS] letters) from baseline to 24 weeks.

RESULTS: No significant safety issues were observed in any treatment group. The E10030 (1.5 mg) combination therapy regimen met the prespecified primary end point of superiority in mean VA gain compared with anti-VEGF monotherapy (10.6 compared with 6.5 ETDRS letters at week 24; $P = 0.019$). A dose-response relationship was evident at each measured time point commencing at 4 weeks. Visual acuity outcomes favored the E10030 1.5 mg combination therapy group regardless of baseline VA, lesion size, or central subfield thickness on optical coherence tomography. All clinically relevant treatment end points of visual benefit (≥ 15 ETDRS letter gain, final VA $\geq 20/40$ or $\geq 20/25$) and visual loss (≥ 1 ETDRS line loss, ≥ 2 ETDRS line loss, final VA $\leq 20/125$ or $\leq 20/200$) favored the E10030 1.5 mg combination group.

CONCLUSIONS: In this phase IIb clinical trial, a 62% relative benefit from baseline was noted in the E10030 1.5 mg combination therapy group compared with the anti-VEGF monotherapy group. A favorable safety and efficacy profile of E10030 combination therapy for nAMD was evident across multiple clinically relevant end points. This highly powered study provides strong rationale for a confirmatory phase III clinical trial.

PMID: 28029445

Retina. 2016 Dec;36 Suppl 1:S50-S64.

TYPE 1 VERSUS TYPE 3 NEOVASCULARIZATION IN PIGMENT EPITHELIAL DETACHMENTS ASSOCIATED WITH AGE-RELATED MACULAR DEGENERATION AFTER ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY: A Prospective Study.

Chen X, Al-Sheikh M, Chan CK, Hariri AH, Abraham P, Lalezary M, Lin SG, Sadda S, Sarraf D.

PURPOSE: To evaluate the response to aflibercept therapy for Type 1 and Type 3 neovascularization in pigment epithelial detachments associated with treatment-naïve, neovascular age-related macular degeneration.

METHODS: In this multicentered, prospective study, eligible eyes underwent an intravitreal aflibercept injection protocol for 12 months. Visual acuity and morphologic features of the pigment epithelial detachments were compared at baseline and follow-up intervals between eyes with Type 1 versus Type 3 neovascularization.

RESULTS: Thirty-six eyes were analyzed. At 12 months, Type 1 lesions showed a 4.5 ± 23 Early Treatment of Diabetic Retinopathy Study letter improvement ($P = 0.1665$) versus a 14 ± 11 ($P = 0.0072$) letter improvement with Type 3 lesions. Both Type 1 and 3 eyes showed a significant decrease in pigment epithelial detachment size, subretinal fluid, and subretinal hyperreflective material; however, Type 3 eyes had a greater reduction in pigment epithelial detachment size and subretinal hyperreflective material, as well as a reduction in central retinal thickness. Type 1 eyes required an average of 1.636 (range, 1-4) injections to resolve fluid, which was greater than Type 3 eyes, which required an average of 1.143 (range, 1-2) injections ($P = 0.0251$).

CONCLUSION: Intravitreal aflibercept injections were efficacious for pigment epithelial detachments, but baseline and follow-up anatomical and functional outcomes differed in Type 1 versus Type 3 neovascularization. The better response of Type 3 eyes with fewer injections suggests that differentiation of the neovascularization subtype at the initial diagnosis may allow for a more tailored, optimal therapy.

PMID: 28005663

Saudi J Ophthalmol. 2016 Oct-Dec;30(4):227-232. Epub 2016 Nov 9.

Aflibercept in refractory wet AMD treated with ranibizumab: Anatomical and visual outcome.

Abou-Ltaif S.

PURPOSE: To assess the anatomical outcome of patients with exudative age-related macular degeneration resistant to ranibizumab treated with aflibercept.

METHOD: Prospective, interventional, case series, where we treated a group of patients deemed resistant to Ranibizumab after 6 months of persistence of intra- or subretinal fluid despite continuous treatment.

RESULTS: The study included 17 patients, 3 males and 14 females. The average males age was 85 (range 83-87), and that of females was 79.64 (range 68-88). At the start of the study, the central foveal thickness CFT average was 534.76 μ m (range 252-999). At 1 month and after 1 injection of Aflibercept, the CFT average was 324.82 μ m (range 222-585). At 4 months and after 3 consecutive injections of Aflibercept the CFT average was 294.76 μ m (range 184-640). At 6 months the CFT average was 356 μ m (range 206-609). At the 5th visit only 8 out of 17 (47%) patients required repeated injection either for persistent fluids or for recurrence. At the 6th and final visit only 4 out of 17 (23.5%) needed repeated injections, of them only one was treated on the visit before and treatment was given as very little response was observed from last injection, and all other 3 were not treated on the visit before.

CONCLUSION: Our results showed that aflibercept was able to dry the macula even in advanced case of wet AMD resistant to Ranibizumab.

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Retina. 2016 Dec 20. [Epub ahead of print]

EFFICACY OF INTRAVITREAL AFLIBERCEPT IN MACULAR TELANGIECTASIA TYPE 1 IS LINKED TO THE OCULAR ANGIOGENIC PROFILE.

Kowalczyk L, Matet A, Dirani A, Daruich A, Ambresin A, Mantel I, Spaide RF, Turck N, Behar-Cohen F.

PURPOSE: To evaluate intravitreal aflibercept in macular telangiectasia Type 1 (MacTel 1) patients and measure their ocular angiogenic profile.

METHODS: Eight subjects with MacTel 1 refractory to bevacizumab, ranibizumab, or laser therapy and switched to aflibercept were included. Best-corrected visual acuity, central macular thickness, and cystic areas quantified on optical coherence tomography B-scans were assessed during 12 months. Perifoveal capillary densities were measured on optical coherence tomography angiography. Aqueous humor was sampled from six patients and eight control subjects undergoing cataract extraction. Growth factors were quantified using a multiarray immunoassay.

RESULTS: Over 12 months, patients received 6.6 ± 1.4 (range, 5-8) intravitreal aflibercept injections. Twelve months after switching to aflibercept, best-corrected visual acuity increased by ≥ 5 letters in 5 of 8 patients, compared with preaflibercept levels. Mean best-corrected visual acuity improved from 79.6 (~20/50) to 88.0 (~20/35) Early Treatment Diabetic Retinopathy Study letters ($P = 0.042$), and central macular thickness decreased from 434 ± 98 μ m to 293 ± 59 μ m ($P = 0.014$). Compared with control subjects, the profile of angiogenic factors in MacTel 1 eyes revealed no difference in vascular endothelial growth factor-A levels but significantly higher levels of placental growth factor ($P = 0.029$), soluble vascular endothelial growth factor receptor-1 (sFlt-1; $P = 0.013$), vascular endothelial growth factor-D ($P = 0.050$), and Tie-2 ($P = 0.019$). Placental growth factor levels inversely correlated with both superficial and deep capillary plexus densities on optical coherence tomography angiography ($P = 0.03$).

CONCLUSION: The clinical response to aflibercept coupled to the angiogenic profile of MacTel 1 eyes support the implication of the placental growth factor/Flt-1 pathway in MacTel 1.

PMID: 28002269

Retina. 2016 Dec 20. [Epub ahead of print]

CHOROIDAL THICKNESS AS A PROGNOSTIC FACTOR OF PHOTODYNAMIC THERAPY WITH AFLIBERCEPT OR RANIBIZUMAB FOR POLYPOIDAL CHOROIDAL VASCULOPATHY.

Sakurada Y, Sugiyama A, Tanabe N, Kikushima W, Kume A, Iijima H.

PURPOSE: To investigate factors associated with visual improvement and retreatment 12 months after a combination therapy of intravitreal injection of ranibizumab or aflibercept followed by photodynamic therapy for polypoidal choroidal vasculopathy.

METHODS: Changes in the best-corrected visual acuity and the subfoveal thickness of the retina and choroid were studied in 56 consecutive eyes with polypoidal choroidal vasculopathy treated initially with a combination therapy of either intravitreal ranibizumab injection (n = 23) or intravitreal aflibercept injection (n = 33) followed by photodynamic therapy. Factors associated with visual improvement and retreatment were investigated.

RESULTS: Best-corrected visual acuity significantly improved with significant reduction in central macular thickness and subfoveal choroidal thickness at all points irrespective of treatment modalities ($P < 0.001$). Better best-corrected visual acuity and improvement of best-corrected visual acuity at 12 months were associated with baseline greater subfoveal choroidal thickness ($P = 0.028$ and $P = 0.028$) and baseline smaller greatest linear dimension ($P = 0.0077$ and $P = 0.0077$). Retreatment during 12-month follow-up was associated with baseline lesser subfoveal choroidal thickness ($P = 0.036$).

CONCLUSION: Irrespective of treatment modalities, the visual outcome at 12 months is favorable in eyes with polypoidal choroidal vasculopathy treated by photodynamic therapy combined with intravitreal ranibizumab or aflibercept. Baseline greater subfoveal choroidal thickness was associated with a better visual outcome and with reduction in the need for retreatment.

PMID: 28002268

Ophthalmologica. 2016 Dec 21. [Epub ahead of print]

One-Year Outcomes of the Treat-and-Extend Approach with Aflibercept in Age-Related Macular Degeneration: Effects on Typical Choroidal Neovascularization and Retinal Angiomatous Proliferation.

Castro-Navarro V, Cervera-Taulet E, Montero-Hernández J, Navarro-Palop C.

OBJECTIVE: To investigate functional/morphological outcomes of the treat-and-extend regimen (TER) with aflibercept in typical choroidal neovascularization (CNV) and retinal angiomatous proliferation (RAP) secondary to exudative age-related macular degeneration (AMD).

METHODS: This was a retrospective study of 37 eyes treated with 2 mg aflibercept according to a TER protocol. Examinations included best corrected visual acuity (BCVA), numbers of injections, and visits needed. Additionally, quantitative/qualitative analyses with fluorescein angiography and spectral-domain optical coherence tomography were conducted at baseline as well as at 3, 6, and 12 months.

RESULTS: BCVA significantly improved from 0.6 ± 0.27 to 0.4 ± 0.34 logMAR. The final mean numbers of injections were 8.03 ± 1.27 and 7.28 ± 0.75 and the numbers of visits 6.5 ± 1.09 and 7.14 ± 1.57 in typical CNV and in RAP or atypical CNV, respectively, and they did not differ between the different subtypes of CNV ($p > 0.05$).

CONCLUSIONS: Aflibercept in TER is effective for all exudative AMD subtypes. The patient's visual gain, the mean number of injections, and the number of visits needed did not depend on the subtype of CNV.

PMID: 27997921

Retina. 2016 Dec 16. [Epub ahead of print]

SEMI-AUTOMATED QUANTITATIVE APPROACH TO CHARACTERIZE TREATMENT RESPONSE IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: A Real-World Study.

Roberts PK, Nesper PL, Gill MK, Fawzi AA.

PURPOSE: To perform a quantitative study of the vascular microstructure in actively treated choroidal neovascularization by optical coherence tomographic angiography.

METHODS: Patients undergoing individualized anti-vascular endothelial growth factor therapy of minimum 12 months duration were included in this cross-sectional observational study and imaged using optical coherence tomographic angiography. En face optical coherence tomographic angiography images were analyzed for quantitative features, such as junction density, vessel length, and lacunarity using validated software (Angiotool). Patients were divided into 2 groups depending on their individualized treatment interval: "good responders, treated less frequently than 6 weeks" versus "poor responders, treated every 6 weeks or more frequently." Nonparametric testing was used to assess differences between these groups.

RESULTS: Twenty-five eyes of 23 consecutive patients with a median 58-month history of choroidal neovascularization, treated by median of 34 anti-vascular endothelial growth factor injections, were included in the analysis. There was no significant difference between any of the microvascular choroidal neovascularization features between the 2 groups ($P > 0.05$).

CONCLUSION: The semiautomated vessel segmentation software provides an objective and quantitative approach for choroidal neovascularization characterization. The consistently nonsignificant outcomes between the groups may provide evidence to support the "normalization hypothesis." This would suggest that regardless of treatment interval, individualized therapy in these eyes established vessel stability.

PMID: 27997513

J Ophthalmol. 2016;2016:9875741. Epub 2016 Dec 1.

Differentiation between Good and Low-Responders to Intravitreal Ranibizumab for Macular Edema Secondary to Retinal Vein Occlusion.

Menke MN, Ebnetter A, Zinkernagel MS, Wolf S.

Background: Ranibizumab is approved for treatment of macular edema in eyes with retinal vein occlusion (RVO). Some eyes show low-response to treatment with regard to visual acuity gain (VA) and OCT central retinal thickness (CRT) reduction. The goal of this study was to quantify the percentage of low-responders.

Methods: Treatment of naïve eyes with macular edema secondary to RVO was included and monthly VA and CRT were analyzed. Four weeks after the loading phase, and at the end of the study, eyes were grouped into low- and good responders based on predefined criteria. The responder and low-responder groups were then compared at various time points.

Results: Forty-three eyes were included. Regarding VA, 27.9% were low-responders after the loading phase and 30.2% at the end of the study. For CRT, 34.9% were low-responders after the loading phase versus 27.9% at the end of the study. 75% of patients that were VA low-responders and 73.3% of CRT low-responders after loading phase remained low-responders at the end of the study.

Conclusion: Approximately 30% of patients showed low response to ranibizumab after the loading phase and after 1 year of treatment. Two-thirds of patients that were low-responders after the loading phase remained low-responders after 1 year.

PMID: 28044102 PMCID: PMC5156818

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

Further Scrutiny of Vision Outcomes When Aflibercept Is Used as Rescue Treatment for Eyes With Diabetic Macular Edema Treated With Laser.

Maguire MG.

PMID: 28006049

Arch Soc Esp Oftalmol. 2016 Dec 27. [Epub ahead of print]

Coats' disease with macular oedema responsive to aflibercept and argon laser. [Article in English, Spanish]

Guixeres Esteve MC, Pardo Saiz AO.

CLINICAL CASE: A 14 year-old boy with Coats' disease in his right eye, presented with a visual acuity (VA) of 0.1, micro-aneurysms, exudates, a macular oedema of 959 microns, and peripheral telangiectasias. After 12 months follow-up with 6 ranibizumab injections and 3 sessions of argon laser photocoagulation, the macular oedema remained and VA was 0.2. Following 4 aflibercept injections and another 2 laser sessions, he had a good foveal slope and a VA of 0.5, with no recurrences in the last 12 months.

DISCUSSION: Treatment with aflibercept and argon laser was effective in our patient with stage 2B Coats' disease and macular oedema unresponsive to ranibizumab.

PMID: 28038924

Ophthalmology. 2017 Jan;124(1):e5.

Re: Wells et al.: Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial

Shanmugam MP, Harshey KB, Ramanjulu R, Mishra DK.

PMID: 27993278

Am J Ophthalmol. 2016 Dec 23. [Epub ahead of print]

Long-term Outcomes of Aflibercept Treatment for Neovascular Age-related Macular Degeneration in a Clinical Setting.

Călugăru D, Călugăru M.

PMID: 28024647

Am J Ophthalmol. 2016 Dec 23. [Epub ahead of print]

Long-term Outcomes of Aflibercept Treatment for Neovascular Age-related Macular Degeneration in a Clinical Setting.

Eleftheriadou M, Vazquez-Alfageme C, Citu CM, Crosby-Nwaobi R, Sivaprasad S, Hykin P, Hamilton RD, Patel PJ.

PMID: 28024646

Other treatment & diagnosis

Acta Ophthalmol. 2016 Dec 18. [Epub ahead of print]

Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration.

Merry GF, Munk MR, Dotson RS, Walker MG, Devenyi RG.

PURPOSE: To evaluate the efficacy of photobiomodulation (PBM) treatment for patients with dry age-related macular degeneration (AMD).

METHODS: Assessments on 42 eyes with dry AMD (age related eye disease study (AREDS) 2-4) were conducted. Multiwavelength light emitting diode (LED) light comprising of yellow (590 nm), red (670 nm) and near-infrared (790 nm) bandwidths was applied to subjects' eyes for a treatment course of 3 weeks. Outcome measures were changes in best-corrected visual acuity (BCVA), contrast sensitivity (CS), drusen volume and central drusen thickness.

RESULTS: Significant improvement in mean BCVA of 5.90 letters ($p < 0.001$) was seen on completion of the 3-week treatment and 5.14 letters ($p < 0.001$) after 3 months. Contrast sensitivity improved significantly (log unit improvement of 0.11 ($p = 0.02$) at 3 weeks and 3 months (log unit improvement of 0.16 ($p = 0.02$) at three cycles per degree. Drusen volume decreased by 0.024 mm³ ($p < 0.001$) and central drusen thickness was significantly reduced by a mean of 3.78 μ m ($p < 0.001$), while overall central retinal thickness and retinal volume remained stable.

CONCLUSION: This is the first study demonstrating improvements in functional and anatomical outcomes in dry AMD subjects with PBM therapy. These findings corroborate an earlier pilot study that looked at functional outcome measures. The addition of anatomical evidence contributes to the basis for further development of a non-invasive PBM treatment for dry AMD.

PMID: 27989012 eCollection 2016.

Medicine (Baltimore). 2016 Dec;95(52):e5729.

Stereotactic radiotherapy in neovascular age-related macular degeneration: Real-life efficacy and morphological evaluation of the outer retina-choroid complex.

Ranjbar M, Kurz M, Holzhey A, Melchert C, Rades D, Grisanti S.

Abstract: Stereotactic radiotherapy (SRT) is a new approach to treat neovascular age-related macular degeneration (nAMD). The INTREPID trial suggested that SRT could reduce the frequency of regular intravitreal injections (IVIs) with anti-vascular endothelial growth factor drugs, which are necessary to control disease activity. However, the efficacy of SRT in nAMD and resulting morphological changes have not been validated under real-life circumstances, an issue, which we would like to address in this retrospective analysis. Patients who met the INTREPID criteria for best responders were eligible for SRT. A total of 32 eyes of 32 patients were treated. Thereafter, patients were examined monthly for 12 months and received pro re nata IVI of aflibercept or ranibizumab. Outcome measures were: mean number of injections, best-corrected visual acuity, and morphological changes of the outer retina-choroid complex as well as patient safety. Mean number of IVI decreased by almost 50% during the 12 months after SRT compared to the year before, whereas visual acuity increased by one line (logMAR). Morphological evaluation showed that most changes affect outer retinal layers. Stereotactic radiotherapy significantly reduced IVI retreatment in nAMD patients under real-life circumstances. Therefore, SRT might be the first step to stop visual loss as a result of IVI undertreatment, which is a major risk.

PMID: 28033280

Clin Ophthalmol. 2016 Dec 21;11:63-70. eCollection 2017.

Neovascular age-related macular degeneration without drusen in the fellow eye: clinical spectrum and therapeutic outcome.

Chung WH, van Dijk EH, Mohabati D, Dijkman G, Yzer S, de Jong EK, Fauser S, Schlingemann RO, Hoyng CB, Boon CJ.

PURPOSE: To investigate the clinical characteristics and therapeutic outcome of patients with neovascular age-related macular degeneration (nAMD) in 1 eye, without drusen in the fellow eye.

PATIENTS AND METHODS: Medical records of 381 patients were analyzed to identify the cases. The main outcomes included Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) and change in central retinal thickness (CRT). These parameters were reviewed at baseline, first follow-up visit, and after 6, 12, and 24 months.

RESULTS: Out of 381 patients, 29 cases (8%) were included (of whom 3 had polypoidal choroidal vasculopathy [PCV]) who were treated with anti-vascular endothelial growth factor (anti-VEGF) therapy which was supplemented by photodynamic therapy (PDT) in the PCV patients. Overall, no statistically significant change in mean BCVA was observed during follow-up. BCVA improved or remained stable (defined as a gain in BCVA, a stable BCVA, or a loss of <5 ETDRS letters) in 22 patients (76%), and 7 patients (23%) had lost ≥ 5 ETDRS letters at final follow-up. A gain of ≥ 15 ETDRS letters at final follow-up was seen in 5 patients (17%). Mean CRT had decreased significantly with 99 μm ($P < 0.001$) at 24 months after the initial visit.

CONCLUSION: There is a clinical spectrum of nAMD that is not associated with drusen in the fellow eye. Patients with nAMD without drusen in the fellow eye respond to anti-VEGF treatment and, in cases of PCV, to supplemental PDT. The pathophysiology of this spectrum of nAMD may be different from drusen-associated age-related macular degeneration.

PMID: 28053502 PMCID: PMC5189970

Clin Exp Ophthalmol. 2016 Nov 6. [Epub ahead of print]

Impact of retinal pigment epithelium pathology on spectral-domain optical coherence tomography-derived macular thickness and volume metrics and their intersession repeatability.

Hanumunthadu D, Wang JP, Chen W, Wong EN, Chen Y, Morgan WH, Patel PJ, Chen FK.

BACKGROUND: To determine the impact of retinal pigment epithelium (RPE) pathology on intersession repeatability of retinal thickness and volume metrics derived from Spectralis spectral-domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany).

DESIGN: Prospective cross-sectional single centre study.

PARTICIPANTS: A total of 56 eyes of 56 subjects were divided into three groups: (i) normal RPE band (25 eyes); (ii) RPE elevation: macular soft drusen (13 eyes); and (iii) RPE attenuation: geographic atrophy or inherited retinal diseases (18 eyes).

METHODS: Each subject underwent three consecutive follow-up macular raster scans (61 B-scans at 119 μm separation) at 1-month intervals.

MAIN OUTCOME MEASURES: Retinal thicknesses and volumes for each zone of the macular subfields before and after manual correction of segmentation error. Coefficients of repeatability (CR) were calculated.

RESULTS: Mean (range) age was 57 (21-88) years. Mean central subfield thickness (CST) and total macular volume were 264 and 258 μm ($P = 0.62$), and 8.0 and 7.8 mm^3 ($P = 0.31$), before and after manual correction. Intersession CR (95% confidence interval) for CST and total macular volume were reduced from

40 (38-41) to 8.3 (8.1-8.5) and 0.62 to 0.16 mm³ after manual correction of segmentation lines. CR for CST were 7.4, 23.5 and 66.7 μ m before and 7.0, 10.9 and 7.6 μ m after manual correction in groups i, ii and iii.

CONCLUSIONS: Segmentation error in eyes with RPE disease has a significant impact on intersession repeatability of Spectralis spectral-domain optical coherence tomography macular thickness and volume metrics. Careful examination of each B-scan and manual adjustment can enhance the utility of quantitative measurement. Improved automated segmentation algorithms are needed.

PMID: 28052542

Int Ophthalmol. 2016 Dec 30. [Epub ahead of print]

Evaluation of the effect of fluorescein angiography on retinal vessel diameter: an optical coherence tomography study.

Unlu M, Sevim DG, Karaca C, Duzgun B, Oner AO, Mirza E.

PURPOSE: To evaluate the effect of fluorescein angiography on retinal vessel diameter with Optical Coherence Tomography (OCT).

METHODS: In this cross-sectional study, a total of 81 eyes of 81 patients who were performed fluorescein angiography (FA) procedure were included. Retinal vessels were examined with the Spectral-domain OCT at baseline and immediately after FA procedure. A cube scan consisting of seven horizontal scans were placed at the inferior border of the disk to include the inferior temporal retinal vessels. Vessels diameters were measured at five measurement points (480-1440 μ m inferiorly from the optic disk border).

RESULTS: The mean age of the study subjects was 58.02 ± 14.1 years. At baseline, the mean diameter of the retinal artery was 120.16 ± 24.56 μ m and of the vein 157.94 ± 32.34 μ m at the measurement point of 480 μ m, with a gradual decrease to 114.91 ± 25.59 and 152.17 ± 28.17 μ m, respectively, at 1440 μ m. After FA procedure, the mean diameter of the retinal artery was 122.85 ± 26.35 and of the vein 158.30 ± 32.21 μ m at the measurement point of 480 μ m, with a gradual decrease to 115.22 ± 22.91 and 151.94 ± 28.93 μ m, respectively, at 1440 μ m. There were no statistical differences for either of these comparisons at any of the points of both artery and vein measurements.

CONCLUSION: There was not any clinically significant change in retinal artery diameter such as a dilatatory response after FA procedure in patients with hypertension, diabetes, and age-related macular degeneration (AMD).

PMID: 28039673

Proc Natl Acad Sci U S A. 2017 Jan 3. [Epub ahead of print]

Imaging individual neurons in the retinal ganglion cell layer of the living eye.

Rossi EA, Granger CE, Sharma R, Yang Q, Saito K, Schwarz C, Walters S, Nozato K, Zhang J, Kawakami T, Fischer W, Latchney LR, Hunter JJ, Chung MM, Williams DR.

Abstract: Although imaging of the living retina with adaptive optics scanning light ophthalmoscopy (AOSLO) provides microscopic access to individual cells, such as photoreceptors, retinal pigment epithelial cells, and blood cells in the retinal vasculature, other important cell classes, such as retinal ganglion cells, have proven much more challenging to image. The near transparency of inner retinal cells is advantageous for vision, as light must pass through them to reach the photoreceptors, but it has prevented them from being directly imaged in vivo. Here we show that the individual somas of neurons within the retinal ganglion cell (RGC) layer can be imaged with a modification of confocal AOSLO, in both monkeys and humans. Human images of RGC layer neurons did not match the quality of monkey images for several reasons, including safety concerns that limited the light levels permissible for human imaging. We also show that the same

technique applied to the photoreceptor layer can resolve ambiguity about cone survival in age-related macular degeneration. The capability to noninvasively image RGC layer neurons in the living eye may one day allow for a better understanding of diseases, such as glaucoma, and accelerate the development of therapeutic strategies that aim to protect these cells. This method may also prove useful for imaging other structures, such as neurons in the brain.

PMID: 28049835

Med Phys. 2016 Jun;43(6):3674-3675.

SU-G-TeP3-05: In Vitro Demonstration of Endothelial Dose Enhancement Due to Gold Nanoparticles During Low-Voltage Radiotherapy.

Yasmin-Karim S, Moreau M, Kumar R, Makrigiorgos GM, Hanlon J, Arnoldussen M, Hempstead J, Celli J, Ngwa W.

PURPOSE: Oraya Therapy uses low-voltage, stereotactic, highly targeted X-rays for the treatment of wet age-related macular degeneration (AMD) - offering a new option for patients worldwide. Neovascular endothelial cells play a crucial role in the pathogenesis of this disease. This in-vitro study investigates the potential of gold nanoparticles (GNP) to enhance endothelial cell damage during low-voltage radiotherapy towards potential applications in the treatment of wet-AMD.

METHODS: Primary human umbilical cord vein endothelium cells (HUVEC) were treated with 1.4 nm sized GNPs for 24 hrs and then irradiated with variable X-ray doses using an Oraya therapy system (100 kVp) or a Small Animal Radiation and Research platform (SARRP) at other beam qualities (up to 220 kVp). Radio-sensitization was assessed by clonogenic assays. Variable concentrations of GNPs (0.05 mg/ml, 0.1 mg/ml, 0.25 mg/ml, 0.5 mg/ml, and 1 mg/ml) were employed. The dose enhancement factor (DEF) was calculated as the ratio of radiation doses required to give the same biological effect (survival factor, SF) with and without GNPs.

RESULTS: Preliminary results show DEFs of up to 2.62 for the different combinations of x-ray doses and GNP concentrations and beam qualities. In general the DEF increased with increase in GNP concentration. However, for high doses the effect of GNP becomes less apparent likely due to already high cell kill by the radiation alone.

CONCLUSION: The findings suggest that targeted GNPs can play a significant synergistic role in enhancing stereotactic radiosurgery for wet AMD. The results also provide impetus for ongoing studies to find the optimal synergy between the doses or beam energies and GNPs concentration. This will benefit in-vivo studies towards development of nanoparticle-aided radiotherapy for treatment of wet-AMD and potentially ocular cancers.

PMID: 28046346

Retina. 2016 Dec 30. [Epub ahead of print]

IMAGING AND MEASUREMENT OF THE PRERETINAL SPACE IN VITREOMACULAR ADHESION AND VITREOMACULAR TRACTION BY A NEW SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY ANALYSIS.

Stopa M, Marciniak E, Rakowicz P, Stankiewicz A, Marciniak T, Dąbrowski A.

PURPOSE: To evaluate a new method for volumetric imaging of the preretinal space (also known as the subhyaloid, subcortical, or retrocortical space) and investigate differences in preretinal space volume in vitreomacular adhesion (VMA) and vitreomacular traction (VMT).

METHODS: Nine patients with VMA and 13 with VMT were prospectively evaluated. Automatic inner

limiting membrane line segmentation, which exploits graph search theory implementation, and posterior cortical vitreous line segmentation were performed on 141 horizontal spectral domain optical coherence tomography B-scans per patient. Vertical distances (depths) between the posterior cortical vitreous and inner limiting membrane lines were calculated for each optical coherence tomography B-scan acquired. The derived distances were merged and visualized as a color depth map that represented the preretinal space between the posterior surface of the hyaloid and the anterior surface of the retina. The early treatment diabetic retinopathy study macular map was overlaid onto final virtual maps, and preretinal space volumes were calculated for each early treatment diabetic retinopathy study map sector.

RESULTS: Volumetric maps representing preretinal space volumes were created for each patient in the VMA and VMT groups. Preretinal space volumes were larger in all early treatment diabetic retinopathy study map macular regions in the VMT group compared with those in the VMA group. The differences reached statistical significance in all early treatment diabetic retinopathy study sectors, except for the superior outer macula and temporal outer macula where significance values were $P = 0.05$ and $P = 0.08$, respectively. Overall, the relative differences in preretinal space volumes between the VMT and VMA groups varied from 2.7 to 4.3 in inner regions and 1.8 to 2.9 in outer regions.

CONCLUSION: Our study provides evidence of significant differences in preretinal space volume between eyes with VMA and those with VMT. This may be useful not only in the investigation of preretinal space properties in VMA and VMT, but also in other conditions, such as age-related macular degeneration, diabetic retinopathy, and central retinal vein occlusion.

PMID: 28045789

Retina. 2016 Dec;36 Suppl 1:S26-S39.

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

Zanzottera EC, Ach T, Huisinigh C, Messinger JD, Freund KB, Curcio CA.

PURPOSE: To enable future studies of retinal pigment epithelium (RPE) fate in the macular atrophy occurring in eyes with neovascular age-related macular degeneration (nvAMD), the authors determined how RPE morphology changes across the transition from health to atrophy in donor eyes with nvAMD.

METHOD: In RPE-Bruch membrane flat mounts of 5 nvAMD eyes, the terminations of organized RPE cytoskeleton and autofluorescent material were compared. In high-resolution histologic sections of 27 nvAMD eyes, RPE phenotypes were assessed at $\pm 500 \mu\text{m}$ and $\pm 100 \mu\text{m}$ from the descent of the external limiting membrane (ELM) toward the Bruch membrane. Thicknesses of RPE, basal laminar deposit (BLamD), and RPE + BLamD were determined. Shapes of the ELM descent were recorded.

RESULTS: Approaching the ELM descent, the percentage of different RPE phenotypes and the thickness of RPE, BLamD, and RPE + BLamD each stayed roughly constant. Compared with a separately described cohort of eyes with geographic atrophy, eyes with nvAMD were more likely to have RPE dysmorphia that did not worsen toward the atrophy border, thinner BLamD overall ($3.25 \pm 3.46 \mu\text{m}$ vs. $7.99 \pm 7.49 \mu\text{m}$ for geographic atrophy), and a higher proportion of oblique ELM descents (47.9 vs. 31.9%).

CONCLUSION: The distribution of RPE phenotypes at the transition to macular atrophy in eyes with nvAMD differs from that in primary geographic atrophy, likely reflecting greater photoreceptor loss and the effects of exudation in nvAMD. This distribution, the shape of ELM descents, and thickness profiles may be useful metrics in clinical studies of macular atrophy using optical coherence tomography and fundus autofluorescence.

PMID: 28005661

Retina. 2016 Dec;36 Suppl 1:S12-S25.

VISUALIZING RETINAL PIGMENT EPITHELIUM PHENOTYPES IN THE TRANSITION TO

GEOGRAPHIC ATROPHY IN AGE-RELATED MACULAR DEGENERATION.

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: 28005660

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

ASSOCIATION BETWEEN THE VITREOMACULAR INTERFACE AND OPTICAL COHERENCE TOMOGRAPHY CHARACTERISTICS IN WET AGE-RELATED MACULAR DEGENERATION.

Ashraf M, Souka A, Adelman RA.

PURPOSE: To study the effect of the vitreomacular interface on various wet age-related macular degeneration (AMD) characteristics including the size and type of choroidal neovascularization (CNV), choroidal thickness, and activity of the CNV.

METHODS: This was a retrospective observational cross-sectional study. The study included 43 patients (51 eyes) with treatment-naïve age-related macular degeneration. Twenty-six patients with wet AMD in one eye and dry AMD in the other eye were included in a paired-eye analysis. Patients underwent optical coherence tomography examination using Heidelberg Spectralis (spectral domain optical coherence tomography) at presentation to determine the type of CNV and the vitreomacular status. In addition, various parameters were measured including the choroidal thickness and horizontal width and vertical height measurements of the CNV.

RESULTS: There was no correlation between the height, width, activity or type of the CNV, and the presence or absence of vitreomacular adhesion. The mean choroidal thickness (using enhanced depth imaging) in cases with vitreomacular adhesion was 272.57 μm compared with 197.32 μm in cases with no vitreomacular adhesion, a statistically significant difference ($P = 0.003$). In the paired-eye study (21 patients), there was no significant difference between the eyes with wet AMD and dry AMD with regard to vitreomacular status or the choroidal thickness. In a subgroup analysis, patients with Type 1 CNV had a significantly higher percentage of vitreomacular adhesion compared with the other eye with dry AMD ($P = 0.034$).

CONCLUSION: In conclusion, the vitreomacular interface does seem to be associated with an increased

choroidal thickness in cases of wet AMD. Furthermore, the association between the vitreomacular interface and wet AMD is more significant for Type 1 CNV.

PMID: 28005632

Clin Ophthalmol. 2016 Dec 14;10:2497-2503. eCollection 2016.

Evaluation of peripheral fundus autofluorescence in eyes with wet age-related macular degeneration.

Suetsugu T, Kato A, Yoshida M, Yasukawa T, Nishiwaki A, Hasegawa N, Usui H, Ogura Y.

PURPOSE: We aimed to evaluate the prevalence of abnormal peripheral fundus autofluorescence (FAF) in wet age-related macular degeneration (AMD) using wide-field imaging instrument.

PATIENTS AND METHODS: A retrospective, case-controlled study involving 66 eyes of 46 Japanese wet AMD patients and 32 eyes of 20 control patients was performed. Wide-field FAF images were obtained for typical AMD (37 eyes/28 patients), polypoidal choroidal vasculopathy (PCV) (22 eyes/20 patients), and retinal angiomatous proliferation (RAP) (seven eyes/four patients). Two masked ophthalmologists independently graded the images for mottled, granular, and nummular patterns. Main outcome measures were abnormal peripheral FAF frequencies and relative risks by disease subgroups and treatments.

RESULTS: Abnormal peripheral FAF patterns were found in 51.5% of wet AMD eyes compared with 18.8% of control eyes ($P<0.001$). Mottled, granular, and nummular patterns were found in 45.5%, 31.8%, and 16.7%, respectively, of wet AMD eyes. Each disease subgroup (typical AMD, 54.1%; PCV, 36.4%; and RAP, 85.7%) showed significantly higher frequencies of peripheral FAF ($P<0.001$, $P=0.03$, and $P<0.001$, respectively) than control eyes (18.8%). There were no significant differences ($P=0.76$) between the frequencies in untreated and treated eyes.

CONCLUSION: Eyes of Japanese wet AMD patients had a higher abnormal FAF prevalence compared with control eyes. Among the three disease subtypes, abnormal patterns were least prevalent in PCV eyes.

PMID: 28008222 PMCID: PMC5167462

Retina. 2016 Dec;36 Suppl 1:S137-S146.

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

Heiferman MJ, Fawzi AA.

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

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

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

CONCLUSION: Our findings indicate that variations in the distribution of lipofuscin, melanin and melanolipofuscin account for the majority of discordance between BL-AF and NI-AF. Given our finding of

missed geographic atrophy lesions on BL-AF in 24% of eyes with geographic atrophy (7/29 eyes), clinicians should consider multimodal imaging, including NI-AF and optical coherence tomography, especially in clinical trials of geographic atrophy.

PMID: 28005672 PMCID: PMC5193230

Retina. 2016 Dec;36 Suppl 1:S127-S136.

HYPERSPECTRAL AUTOFLUORESCENCE IMAGING OF DRUSEN AND RETINAL PIGMENT EPITHELIUM IN DONOR EYES WITH AGE-RELATED MACULAR DEGENERATION.

Tong Y, Ben Ami T, Hong S, Heintzmann R, Gerig G, Ablonczy Z, Curcio CA, Ach T, Smith RT.

PURPOSE: To elucidate the molecular pathogenesis of age-related macular degeneration (AMD) and interpretation of fundus autofluorescence imaging, the authors identified spectral autofluorescence characteristics of drusen and retinal pigment epithelium (RPE) in donor eyes with AMD.

METHODS: Macular RPE/Bruch membrane flat mounts were prepared from 5 donor eyes with AMD. In 12 locations (1-3 per eye), hyperspectral autofluorescence images in 10-nm-wavelength steps were acquired at 2 excitation wavelengths (λ_{ex} 436, 480 nm). A nonnegative tensor factorization algorithm was used to recover 5 abundant emission spectra and their corresponding spatial localizations.

RESULTS: At λ_{ex} 436 nm, the authors consistently localized a novel spectrum (SDr) with a peak emission near 510 nm in drusen and sub-RPE deposits. Abundant emission spectra seen previously (S0 in Bruch membrane and S1, S2, and S3 in RPE lipofuscin/melanolipofuscin, respectively) also appeared in AMD eyes, with the same shapes and peak wavelengths as in normal tissue. Lipofuscin/melanolipofuscin spectra localizations in AMD eyes varied widely in their overlap with drusen, ranging from none to complete.

CONCLUSION: An emission spectrum peaking at ~510 nm (λ_{ex} 436 nm) appears to be sensitive and specific for drusen and sub-RPE deposits. One or more abundant spectra from RPE organelles exhibit characteristic relationships with drusen.

PMID: 28005671 PMCID: PMC5193241

Retina. 2016 Dec;36 Suppl 1:S118-S126.

TOWARD QUANTITATIVE OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY: Visualizing Blood Flow Speeds in Ocular Pathology Using Variable Interscan Time Analysis.

Ploner SB, Moulton EM, Choi W, Waheed NK, Lee B, Novais EA, Cole ED, Potsaid B, Husvogt L, Schottenhamml J, Maier A, Rosenfeld PJ, Duker JS, Hornegger J, Fujimoto JG.

PURPOSE: Currently available optical coherence tomography angiography systems provide information about blood flux but only limited information about blood flow speed. The authors develop a method for mapping the previously proposed variable interscan time analysis (VISTA) algorithm into a color display that encodes relative blood flow speed.

METHODS: Optical coherence tomography angiography was performed with a 1,050 nm, 400 kHz A-scan rate, swept source optical coherence tomography system using a 5 repeated B-scan protocol. Variable interscan time analysis was used to compute the optical coherence tomography angiography signal from B-scan pairs having 1.5 millisecond and 3.0 milliseconds interscan times. The resulting VISTA data were then mapped to a color space for display.

RESULTS: The authors evaluated the VISTA visualization algorithm in normal eyes ($n = 2$), nonproliferative diabetic retinopathy eyes ($n = 6$), proliferative diabetic retinopathy eyes ($n = 3$), geographic atrophy eyes ($n = 4$), and exudative age-related macular degeneration eyes ($n = 2$). All eyes showed blood flow speed

variations, and all eyes with pathology showed abnormal blood flow speeds compared with controls.

CONCLUSION: The authors developed a novel method for mapping VISTA into a color display, allowing visualization of relative blood flow speeds. The method was found useful, in a small case series, for visualizing blood flow speeds in a variety of ocular diseases and serves as a step toward quantitative optical coherence tomography angiography.

PMID: 28005670 PMCID: PMC5193243

Retina. 2016 Dec;36 Suppl 1:S83-S92.

CLINICAL TRIAL ENDPOINTS FOR OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Cole ED, Ferrara D, Novais EA, Louzada RN, Waheed NK.

PURPOSE: To describe qualitative and quantitative optical coherence tomography (OCT) angiography (OCTA) parameters for choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) and their applicability as potential clinical trial endpoints.

METHODS: A review of current literature related to the topic of OCTA and AMD.

RESULTS: There are a number of promising OCTA parameters that can be used to diagnose the presence of CNV and to monitor the activity and progression of the lesion, pre- and post-treatment morphological characteristics, CNV dimensions, and automated quantitative parameters such as vessel density.

CONCLUSION: The OCTA parameters described in this review have promise for the future development of clinical trial endpoints, but require further validation before they can be widely used.

PMID: 28005666

Retina. 2016 Dec;36 Suppl 1:S65-S72.

RETINAL PIGMENT EPITHELIUM APERTURE: A Previously Unreported Finding in the Evolution of Avascular Pigment Epithelium Detachment.

Querques G, Capuano V, Costanzo E, Corvi F, Querques L, Introini U, Souied EH, Bandello F.

PURPOSE: To describe retinal pigment epithelium (RPE) aperture and to generate hypotheses about pathogenesis of this previously unreported finding in the evolution of avascular pigment epithelium detachment (PED) secondary to age-related macular degeneration.

METHODS: Medical records and multimodal imaging results from 10 patients with RPE apertures were reviewed between January 2009 and December 2014 by 2 institutions. Main outcome measures were analysis of RPE aperture imaging characteristics, including aperture areas and PED diameters, and their temporal course. Lesions preceding RPE aperture development were also evaluated.

RESULTS: Eleven RPE apertures were identified in 10 eyes of 10 patients (1 male, 9 females; mean age 73.1 ± 6.7 years) and included for analysis. The RPE apertures appeared as round discontinuities either at the apex or at the base of avascular PED. No rippling or retraction of the RPE was found at the sites of aperture. The RPE apertures enlarged homogeneously (mean round area of hypoautofluorescence significantly increased from 0.18 ± 0.13 to 0.93 ± 1.2 ; $P = 0.005$), and PED flattened (PED maximal height on spectral domain optical coherence significantly decreased from 445.2 ± 259 to 206.4 ± 218 ; $P = 0.04$) after a mean of 38.6 ± 16.3 months. Analysis of lesions preceding RPE apertures revealed areas of focal hyperautofluorescence at the site of development, in some cases appearing as drusenoid material connected with the base of avascular PED.

CONCLUSION: The RPE aperture represents a previously unreported possible evolution of avascular PED, which should be distinguished by typical RPE tears. Analysis of lesions preceding RPE apertures suggests focal atrophic progression of drusenoid material in its pathogenesis.

PMID: 28005664

Retina. 2016 Dec 28. [Epub ahead of print]

ASSOCIATIONS BETWEEN MACULAR EDEMA AND CIRCULATORY STATUS IN EYES WITH RETINAL VEIN OCCLUSION: An Adaptive Optics Scanning Laser Ophthalmoscopy Study.

Iida Y, Muraoka Y, Uji A, Ooto S, Murakami T, Suzuma K, Tsujikawa A, Arichika S, Takahashi A, Miwa Y, Yoshimura N.

PURPOSE: To investigate associations between parafoveal microcirculatory status and foveal pathomorphology in eyes with macular edema (ME) secondary to retinal vein occlusion (RVO).

METHODS: Ten consecutive patients (10 eyes) with acute retinal vein occlusion were enrolled, 9 eyes of which received intravitreal ranibizumab (IVR) injections. Foveal morphologic changes were examined via optical coherence tomography (OCT), and parafoveal circulatory status was assessed via adaptive optics scanning laser ophthalmoscopy (AO-SLO).

RESULTS: The mean parafoveal aggregated erythrocyte velocity (AEV) measured by adaptive optics scanning laser ophthalmoscopy in eyes with retinal vein occlusion was 0.99 ± 0.43 mm/second at baseline, which was significantly lower than that of age-matched healthy subjects (1.41 ± 0.28 mm/second, $P = 0.042$). The longitudinal adaptive optics scanning laser ophthalmoscopy examinations of each patient showed that parafoveal AEV was strongly inversely correlated with optical coherence tomography-measured central foveal thickness (CFT) over the entire observation period. Using parafoveal AEV and central foveal thickness measurements obtained at the first and second examinations, we investigated associations between differences in parafoveal AEV and central foveal thickness, which were significantly and highly correlated ($r = -0.84$, $P = 0.002$).

CONCLUSION: Using adaptive optics scanning laser ophthalmoscopy in eyes with retinal vein occlusion macular edema, we could quantitatively evaluate the parafoveal AEV. A reduction or an increase in parafoveal AEV may be a clinical marker for the resolution or development/progression of macular edema respectively.

PMID: 28033234

J Biochem Mol Toxicol. 2016 Dec 22. [Epub ahead of print]

Amyloid β induces NLRP3 inflammasome activation in retinal pigment epithelial cells via NADPH oxidase- and mitochondria-dependent ROS production.

Wang K, Yao Y, Zhu X, Zhang K, Zhou F, Zhu L.

Abstract: Amyloid β ($A\beta$)-induced chronic inflammation is believed to be a key pathogenic process in early-stage age-related macular degeneration (AMD). Nucleotide oligomerization domain (NOD)-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome activation triggered by $A\beta$ is responsible for retinal pigment epithelium (RPE) dysfunction in the onset of AMD; however, the detailed molecular mechanism remains unclear. In this study, we investigated the involvement of NADPH oxidase- and mitochondria-derived reactive oxygen species (ROS) in the process of $A\beta$ 1-40-induced NLRP3 inflammasome activation in LPS-primed ARPE-19 cells. The results showed that $A\beta$ 1-40 could induce excessive ROS generation, MAPK/NF- κ B signaling activation and subsequently NLRP3 inflammasome activation in LPS-primed ARPE-19 cells. Furthermore, the inductive effect of $A\beta$ 1-40 on NLRP3 inflammasome activation was mediated in a manner dependent on NADPH oxidase- and mitochondria-

derived ROS. Our findings may provide a novel insight into the molecular mechanism by which A β contributes to the early-stage AMD.

PMID: 28004443

J Mol Med (Berl). 2016 Dec 21. [Epub ahead of print]

The HIF-1 antagonist acriflavine: visualization in retina and suppression of ocular neovascularization.

Zeng M, Shen J, Liu Y, Lu LY, Ding K, Fortmann SD, Khan M, Wang J, Hackett SF, Semenza GL, Campochiaro PA.

Abstract: Acriflavine, a fluorescent drug previously used for bacterial and trypanosomal infections, reduces hypoxia-inducible factor-1 (HIF-1) and HIF-2 transcriptional activity. In mice with oxygen-induced ischemic retinopathy, intraocular or intraperitoneal injections of acriflavine caused dose-dependent suppression of retinal neovascularization (NV) and significantly reduced expression of HIF-1-responsive genes. Intraocular injection of 100 ng caused inner retina fluorescence within 1 h that was seen throughout the entire retina between 1 and 5 days, and at 7 days after injection, strongly suppressed choroidal NV at Bruch's membrane rupture sites. After suprachoroidal injection of 300 ng in rats, there was retinal fluorescence in the quadrant of the injection at 1 h that spread throughout the entire retina and choroid by 1 day, was detectable for 5 days, and dramatically reduced choroidal NV 14 days after rupture of Bruch's membrane. After topical administration of acriflavine in mice, fluorescence was seen in the retina and retinal pigmented epithelium within 5 min and was detectable for 6-12 h. Administration of 0.5% drops to the cornea twice a day significantly reduced choroidal NV in mice. Electroretinographic b-wave amplitudes were normal 7 days after intravitreal injection of 100 ng of acriflavine in mice, showed mild threshold reductions at highest stimulus intensities after injection of 250 ng, and more extensive changes after injection of 500 ng. These data provide additional evidence for an important role for HIF-1 in retinal and choroidal NV and suggest that acriflavine can target HIF-1 through a variety of modes of administration and has good potential to provide a novel therapy for retinal and choroidal vascular diseases.

KEY MESSAGE: Acriflavine, an inhibitor of HIF-1, suppresses retinal and choroidal neovascularization. HIF-1 plays a critical role in ocular neovascularization. Acriflavine's fluorescence provides a mean to track its entry and exit from the retina. Acriflavine has therapeutic potential for the treatment of ocular neovascularization.

PMID: 28004126

Int J Ophthalmol. 2016 Dec 18;9(12):1779-1784. eCollection 2016.

Evaluation of fundus autofluorescence patterns in age-related macular degeneration.

Venkatesh P, Sagar P, Chawla R, Gogia V, Vohra R, Sharma YR.

AIM: To study the various morphological patterns of fundus autofluorescence (FAF) images in patients with age-related macular degeneration (AMD) in Indian population.

METHODS: Totally 179 eyes of 104 patients with clinical diagnosis of AMD were recruited into the study. Autofluorescence images were captured using confocal scanning laser ophthalmoscope and the patterns of FAF were classified.

RESULTS: Of 179 eyes, 27 (15.08%) were early AMD, 58 (32.41%) were intermediate AMD, 94 eyes (52.51%) were late AMD. Of 94 eyes with late AMD, 79 (84.04%) were neovascular AMD and 15 (15.96%) were central geographic atrophy. In eyes with early and intermediate AMD, 9 patterns of FAF were noted. Six patterns (normal, minimal change, focal increased, patchy increased, linear, reticular) were similar to that in the published classification. Two patterns (lacelike and speckled) described in the published

classification were not found. Three new patterns (focal hypo-fluorescence, patchy hypo-fluorescence, mixed focal hypo-fluorescence and hyper-fluorescence) were detected. In eyes with neovascular AMD, 6 morphological patterns of FAF were noted. Two patterns (mixed hypo-fluorescence and hyper-fluorescence, central hypo-fluorescence with hyper-fluorescent rim) were similar to that in published classification. Two patterns (normal, near normal or normal background fluorescence in the centre of hypo-fluorescent area) described in the published classification were not found. Four new patterns (minimal change, hypo-fluorescent patch, central hypo-fluorescence with surrounding reticular, bull's eye) were recognized. In eye with central geographic atrophy 5 morphological patterns were noted and these were similar to that in published classification.

CONCLUSION: Phenotypic differences in the pattern of FAF exist in the study population compared to existing classification systems.

PMID: 28003979 PMCID: PMC5154992

PLoS One. 2016 Dec 19;11(12):e0168474. eCollection 2016.

Optical Coherence Tomographic Features and Prognosis of Pneumatic Displacement for Submacular Hemorrhage.

Bae K, Cho GE, Yoon JM, Kang SW.

PURPOSE: To identify prognostic factors, including optical coherence tomographic features, of visual outcome in exudative age-related macular degeneration with submacular hemorrhage treated with pneumatic displacement.

METHODS: This retrospective interventional case series included 37 eyes with exudative age-related macular degeneration and submacular hemorrhage, all of which underwent pneumatic displacement. The best-corrected visual acuity (BCVA) was measured at diagnosis and at 3 and 6 months after treatment. In addition to demographic and fundusoscopic parameters, tomographic features such as reflectance of the submacular hemorrhage were analyzed with regard to BCVA at 6 months.

RESULTS: After pneumatic displacement and a subsequent treatment such as laser or anti-vascular endothelial growth factor therapy, the BCVA at 3 and 6 months improved significantly ($P < 0.001$, respectively). Higher baseline BCVA ($P < 0.001$), shorter symptom duration ($P = 0.007$), and younger age ($P = 0.014$) were significant positive prognostic factors on regression analysis. Among optical coherence tomography characteristics, reflectance of the submacular hemorrhage, the shortest radius of the submacular hemorrhage centered on the fovea, and defects in the ellipsoid zone, and external limiting membrane affected the BCVA at 6 months ($P < 0.05$).

CONCLUSION: A favorable visual outcome was demonstrated after initial pneumatic displacement and subsequent treatment for submacular hemorrhage. The submacular hemorrhages exhibiting lower reflectance on optical coherence tomography and a smaller shortest radius from the foveal center were found to be good candidates for pneumatic displacement.

PMID: 27992524 PMCID: PMC5167395

J Ocul Pharmacol Ther. 2016 Dec 19. [Epub ahead of print]

Antiangiogenic Effects of Doxazosin on Experimental Choroidal Neovascularization in Mice.

Guo J, Luo X, Liang J, Xiao M, Sun X.

PURPOSE: The present study was designed to evaluate the effects of doxazosin on experimental choroidal neovascularization (CNV) in mice.

METHODS: Six- to 8-week-old male C57BL/6 mice were divided into a control group and a doxazosin-treated group (5 mg/kg, i.p., daily). Experimental CNV was induced by laser photocoagulation. Seven and 14 days after laser induction, fluorescein angiography, choroidal flat mounts, and histological studies were performed to evaluate the fluorescence leakage, area, and thickness of CNV lesions, respectively. In addition, western blot analysis was carried out to assess the inhibitory effects of doxazosin on the PI3K/Akt/mTOR signaling pathway and the expression levels of hypoxia-inducible factor 1 α (HIF-1 α) and vascular endothelial growth factor (VEGF), which are involved in CNV model.

RESULTS: Compared with the control group, the doxazosin-treated group demonstrated significantly less fluorescence leakage on day 7 and 14 after laser induction. Both the area and the thickness of CNV lesions in the doxazosin-treated group were significantly decreased. Mechanistically, PI3K/Akt/mTOR signaling pathway activation was significantly suppressed in the doxazosin-treated group. The expression of HIF-1 α and VEGF was also notably reduced by systemic doxazosin treatment.

CONCLUSIONS: Doxazosin exerts antiangiogenic actions in an experimental mouse model of CNV and may be a potential adjunctive therapy for neovascular age-related macular degeneration in humans.

PMID: 27992238

Clin Rheumatol. 2016 Dec 28. [Epub ahead of print]

The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases.

Fabiani C, Sota J, Tosi GM, Franceschini R, Frediani B, Galeazzi M, Rigante D, Cantarini L.

Abstract: Interleukin (IL)-1 plays a key role in the pathogenesis and thereafter in the search for specific treatments of different inflammatory and degenerative eye diseases. Indeed, an overactivity of IL-1 might be an initiating factor for many immunopathologic sceneries in the eye, as proven by the efficacy of the specific IL-1 blockade in different ocular diseases. For instance, the uveitis in monogenic autoinflammatory disorders, such as Blau syndrome and cryopyrin-associated periodic syndrome, or in complex polygenic autoinflammatory disorders, such as Behçet's disease, has been successfully treated with IL-1 blockers. Similarly, therapy with the IL-1 receptor antagonist anakinra has proven successful also in scleritis and episcleritis in the context of different rheumatic conditions. Moreover, interesting findings deriving from animal models of ocular disease have set a rational basis from a therapeutic viewpoint to manage patients also with dry eye disease and a broadening number of ocular inflammatory and degenerative conditions, which start from an imbalance between IL-1 and its receptor antagonist.

PMID: 28032234

Clin Exp Ophthalmol. 2016 Dec 19. [Epub ahead of print]

Hypertensive eye disease: a review.

Fraser-Bell S, Symes R, Vaze A.

Abstract: Hypertension is a risk factor for a number of vision-threatening eye conditions including retinal vascular occlusion, retinal macroaneurysm and non arteritic anterior ischaemic optic neuropathy. In addition, hypertension may exacerbate the vision-threatening effects of diabetic retinopathy and has been implicated in the pathogenesis of age-related macular degeneration. The effects of sustained hypertension are directly visible in the eye as hypertensive retinopathy and choroidopathy, reflecting a pathological process occurring throughout the body. Close collaboration between ophthalmologists and general practitioners/physicians is needed to ensure that hypertensive patients are identified and treated. Timely intervention in these patients may reduce the risk of both vision-threatening and systemic complications.

PMID: 27990740

Biomed Opt Express. 2016 Nov 3;7(12):4928-4940. eCollection 2016.

Machine learning based detection of age-related macular degeneration (AMD) and diabetic macular edema (DME) from optical coherence tomography (OCT) images.

Wang Y, Zhang Y, Yao Z, Zhao R, Zhou F.

Abstract: Non-lethal macular diseases greatly impact patients' life quality, and will cause vision loss at the late stages. Visual inspection of the optical coherence tomography (OCT) images by the experienced clinicians is the main diagnosis technique. We proposed a computer-aided diagnosis (CAD) model to discriminate age-related macular degeneration (AMD), diabetic macular edema (DME) and healthy macula. The linear configuration pattern (LCP) based features of the OCT images were screened by the Correlation-based Feature Subset (CFS) selection algorithm. And the best model based on the sequential minimal optimization (SMO) algorithm achieved 99.3% in the overall accuracy for the three classes of samples.

PMID: 28018716 PMCID: PMC5175542

Turk J Ophthalmol. 2016 Oct;46(5):215-220. Epub 2016 Oct 17.

Clinical Features and Course of Patients with Peripheral Exudative Hemorrhagic Chorioretinopathy.

Cebeci Z, Dere Y, Bayraktar Ş, Tuncer S, Kır N.

OBJECTIVES: To evaluate the clinical characteristics of patients who were followed in our clinic with the diagnosis of peripheral exudative hemorrhagic chorioretinopathy (PEHC).

MATERIALS AND METHODS: Medical records of 12 patients who were diagnosed with PEHC in İstanbul University İstanbul Faculty of Medicine, Department of Ophthalmology between July 2006 and June 2014 were reviewed retrospectively.

RESULTS: This study included 21 eyes of 12 patients. Four (33.3%) of the patients were male and 8 (66.7%) were female and ages ranged between 73 and 89 years. Eight (66.7%) of the patients were referred to us with the diagnosis of choroidal mass. Unilateral involvement was found in 3 and bilateral involvement in 9 patients. Temporal quadrants were involved in all eyes. Fifteen eyes (71.4%) had subretinal hemorrhage and hemorrhagic/serous retinal pigment epithelial detachment, 11 (52.4%) had lipid exudation, 5 (23.8%) had chronic retinal pigment epithelium alterations, 2 (9.5%) had subretinal fibrosis and 1 (4.8%) had vitreous hemorrhage. PEHC lesions were accompanied by drusen in 11 eyes (52.4%), geographic atrophy in 2 eyes (9.5%), and choroidal neovascularization scar in 2 eyes (9.5%). Treatment was done in both eyes of a patient for lesions which threatened the macula, in a patient with bilateral macular edema and in a patient with vitreous hemorrhage. The remaining eyes were followed-up without any treatment because the lesions did not threaten the macula and they showed no progression during follow-up.

CONCLUSION: PEHC is a degenerative disease of peripheral retina that is seen in older patients, and signs of age-related macular degeneration (AMD) may accompany this pathology. Especially in patients with AMD findings, the peripheral retina must be evaluated carefully for existing PEHC lesions.

PMID: 28058163 PMCID: PMC5200833

Br J Ophthalmol. 2017 Jan 5. [Epub ahead of print]

Choroid morphometric analysis in non-neovascular age-related macular degeneration by means of optical coherence tomography angiography.

Cicinelli MV, Rabiolo A, Marchese A, de Vitis L, Carnevali A, Querques L, Bandello F, Querques G.

AIMS: To describe the vascular changes in patients affected by non-neovascular age-related macular

degeneration (AMD), featuring reticular pseudodrusen (RPD), drusen, or both RPD and drusen by means of optical coherence tomography angiography (OCT-A).

METHODS: Cross-sectional observational case series. Patients with non-neovascular AMD presenting at the Medical Retina Service of the Department of Ophthalmology, University Vita-Salute San Raffaele in Milan were recruited. Patients underwent best-corrected visual acuity, biomicroscopy, infrared reflectance, short-wavelength fundus autofluorescence and OCT-A (AngioPlex, CIRRUS HD-OCT 5000, Carl Zeiss Meditech, Dublin, USA). Main outcome was quantification of vessel density, stromal tissue, and vascular/stromal (V/S) ratio at the choriocapillaris (CC), the Sattler and Haller's and the whole choroid layers among different groups of patients with non-neovascular AMD by means of binarised OCT-A scans.

RESULTS: 45 eyes of 34 patients were enrolled (15 eyes of 11 patients with RPD, group 1; 15 eyes of 11 patients with drusen, group 2; 15 eyes of 12 patients with mixed phenotype, group 3). The CC, the Sattler and Haller's and the whole choroid vessel density were reduced in all groups of patients ($p=0.023$, $p=0.007$ and $p=0.011$ in group 1, group 2 and group 3 for the CC; $p=0.021$, $p=0.037$ and $p=0.043$ in group 1, group 2 and group 3 for the Sattler and Haller's density; $p=0.016$, $p=0.002$ and $p<0.001$ in group 1, group 2 and group 3 for the choroidal density), with significantly lower V/S ratios compared with healthy controls.

CONCLUSIONS: Patients with non-neovascular AMD show significant choroidal vascular depletion and fibrotic replacement, suggesting a possible role in the pathogenesis and progression of the disease.

PMID: 28057649

J Neural Eng. 2017 Jan 3. [Epub ahead of print]

Topographic prominence discriminator for the detection of short-latency spikes of retinal ganglion cells.

Choi MH, Ahn J, Park D, Lee SM, Kim K, Cho DI, Senok S, Koo KI, Goo Y.

Objective: Direct stimulation of retinal ganglion cells in degenerate retinas by implanting epi-retinal prostheses is a recognized strategy for restoration of visual perception in patients with retinitis pigmentosa or age-related macular degeneration. Elucidating the best stimulus-response paradigms in the laboratory using multielectrode arrays (MEA) is complicated by the fact that the short-latency spikes (within 10 ms) elicited by direct retinal ganglion cell (RGC) stimulation are obscured by the stimulus artifact which is generated by the electrical stimulator.

Approach: We developed an artifact subtraction algorithm based on topographic prominence discrimination, wherein the duration of prominences within the stimulus artifact is used as a strategy for identifying the artifact for subtraction and clarifying the obfuscated spikes which are then quantified using standard thresholding.

Main results: We found that the prominence discrimination based filters perform creditably in simulation conditions by successfully isolating randomly inserted spikes in the presence of simple and even complex residual artifacts. We also show that the algorithm successfully isolated short-latency spikes in an MEA-based recording from degenerate mouse retinas, where the amplitude and frequency characteristics of the stimulus artifact vary according to the distance of the recording electrode from the stimulating electrode. By ROC analysis of false positive and false negative first spike detection rates in a dataset of one hundred and eight RGCs from four retinal patches, we found that the performance of our algorithm is comparable to that of a generally-used artifact subtraction filter algorithm which uses a strategy of local polynomial approximation (SALPA).

Significance: We conclude that the application of topographic prominence discrimination is a valid and useful method for subtraction of stimulation artifacts with variable amplitudes and shapes. We propose that our algorithm may be used as stand-alone or supplementary to other artifact subtraction algorithms like SALPA.

PMID: 28045002

Pathogenesis

Diabetes Metab Syndr. 2016 Dec 9. [Epub ahead of print]

VEGF, the underlying factor for metabolic syndrome; fact or fiction?

Mazidi M, Rezaie P, Pascal Kengne A, Stathopoulou MG, Azimi-Nezhad M, Siest S.

Abstract: Metabolic syndrome (MetS) is currently diagnosed by the co-presence of at least three of the five following abnormalities: abdominal obesity, dysglycaemia, elevated serum triglycerides, low high-density cholesterol (HDL) and finally elevated blood pressure. Metabolic syndrome increases the risk of developing cardiovascular disease and diabetes. This review is on the associations between MetS and vascular endothelial growth factor (VEGF). VEGF induces migration and proliferation of endothelial cells (ECs), increases vascular permeability and has a role in tumor growth, adipose tissue expansion, age-related macular degeneration and diabetic retinopathy. Circulating levels of VEGFs are elevated in obese individuals and it has also been suggested that VEGF is secreted from adipose tissues, especially from intra-abdominal adipose tissue. There is abundant evidence to support that poor glycemic control in diabetic patients is associated with increased plasma VEGF, which in turn may cause hypertension and several vascular complications in diabetic patients. Circulating VEGF levels are increased in children and young adults with type 1 diabetes mellitus and middle-aged diabetic patients with proliferative retinopathy. It has been revealed that plasma VEGF increases in patients with hyperlipidemia and may trigger the development of atherosclerosis. It can be concluded that there is a positive association between VEGF and components of MetS. Because of the importance of this relationship, more investigations are needed in this field.

PMID: 28040466

Mol Vis. 2016 Dec 10;22:1387-1404. eCollection 2016.

Accumulation of cholesterol and increased demand for zinc in serum-deprived RPE cells.

Mishra S, Peterson K, Yin L, Berger A, Fan J, Wistow G.

PURPOSE: Having observed that confluent ARPE-19 cells (derived from human RPE) survive well in high-glucose serum-free medium (SFM) without further feeding for several days, we investigated the expression profile of RPE cells under the same conditions.

METHODS: Expression profiles were examined with microarray and quantitative PCR (qPCR) analyses, followed by western blot analysis of key regulated proteins. The effects of low-density lipoprotein (LDL) and zinc supplementation were examined with qPCR. Immunofluorescence was used to localize the LDL receptor and to examine LDL uptake. Cellular cholesterol levels were measured with filipin binding. Expression patterns in primary fetal RPE cells were compared using qPCR.

RESULTS: Microarray analyses of gene expression in ARPE-19, confirmed with qPCR, showed upregulation of lipid and cholesterol biosynthesis pathways in SFM. At the protein level, the cholesterol synthesis control factor SRBEF2 was activated, and other key lipid synthesis proteins increased. Supplementation of SFM with LDL reversed the upregulation of lipid and cholesterol synthesis genes, but not of cholesterol transport genes. The LDL receptor relocated to the plasma membrane, and LDL uptake was activated by day 5-7 in SFM, suggesting increased demand for cholesterol. Confluent ARPE-19 cells in SFM accumulated intracellular cholesterol, compared with cells supplemented with serum, over 7 days. Over the same time course in SFM, the expression of metallothioneins decreased while the major zinc transporter was upregulated, consistent with a parallel increase in demand for zinc. Supplementation with zinc reversed expression changes for metallothionein genes, but not for other zinc-related genes. Similar patterns of regulation were also seen in primary fetal human RPE cells in SFM.

CONCLUSIONS: ARPE-19 cells respond to serum deprivation and starvation with upregulation of the lipid and cholesterol pathways, accumulation of intracellular cholesterol, and increased demand for zinc. Similar

trends are seen in primary fetal RPE cells. Cholesterol accumulation basal to RPE is a prominent feature of age-related macular degeneration (AMD), while dietary zinc is protective. It is conceivable that accumulating defects in Bruch's membrane and dysfunction of the choriocapillaris could impede transport between RPE and vasculature in AMD. Thus, this pattern of response to serum deprivation in RPE-derived cells may have relevance for some aspects of the progression of AMD.

PMID: 28003730 PMCID: PMC5166821

EMBO Mol Med. 2016 Dec 21. [Epub ahead of print]

Polysialic acid blocks mononuclear phagocyte reactivity, inhibits complement activation, and protects from vascular damage in the retina.

Karlstetter M, Kopatz J, Aslanidis A, Shahraz A, Caramoy A, Linnartz-Gerlach B, Lin Y, Lückoff A, Fauser S, Düker K, Claude J, Wang Y, Ackermann J, Schmidt T, Hornung V, Skerka C, Langmann T, Neumann H.

Abstract: Age-related macular degeneration (AMD) is a major cause of blindness in the elderly population. Its pathophysiology is linked to reactive oxygen species (ROS) and activation of the complement system. Sialic acid polymers prevent ROS production of human mononuclear phagocytes via the inhibitory sialic acid-binding immunoglobulin-like lectin-11 (SIGLEC11) receptor. Here, we show that low-dose intravitreal injection of low molecular weight polysialic acid with average degree of polymerization 20 (polySia avDP20) in humanized transgenic mice expressing SIGLEC11 on mononuclear phagocytes reduced their reactivity and vascular leakage induced by laser coagulation. Furthermore, polySia avDP20 prevented deposition of the membrane attack complex in both SIGLEC11 transgenic and wild-type animals. In vitro, polySia avDP20 showed two independent, but synergistic effects on the innate immune system. First, polySia avDP20 prevented tumor necrosis factor- α , vascular endothelial growth factor A, and superoxide production by SIGLEC11-positive phagocytes. Second, polySia avDP20 directly interfered with complement activation. Our data provide evidence that polySia avDP20 ameliorates laser-induced damage in the retina and thus is a promising candidate to prevent AMD-related inflammation and angiogenesis.

PMID: 28003336

Am J Physiol Cell Physiol. 2016 Dec 21;ajpcell.00057.2016. [Epub ahead of print]

C-reactive protein isoforms differentially affect outer blood retinal barrier integrity and function.

Molins B, Pascual Méndez A, Llorenç V, Zarranz-Ventura J, Mesquida M, Adan A, Martorell J.

Abstract: The retinal pigment epithelium (RPE) forms the outer blood-retinal barrier (oBRB) and is the prime target of early age-related macular degeneration (AMD). C-reactive protein (CRP), a serum biomarker for chronic inflammation and AMD, presents two different isoforms, monomeric (mCRP) and pentameric (pCRP) that may have a different effect on inflammation and barrier function in the RPE. The results reported in this study suggest that mCRP but not pCRP impairs RPE functionality by increasing paracellular permeability and disrupting the tight junction proteins ZO-1 and occludin in RPE cells. Additionally, we evaluated the effect of drugs commonly used in the clinical setting over the mCRP-induced barrier dysfunction. We found that corticosteroids (methylprednisolone) and anti-VEGF agents (bevacizumab) prevented mCRP-induced ARPE-19 barrier disruption and IL-8 production. Furthermore, bevacizumab was also able to revert mCRP-induced IL-8 increase after mCRP stimulation. In conclusion, the presence of mCRP within retinal tissue may lead to disruption of the oBRB, effect that may be modified in the presence of corticosteroids or anti-VEGF drugs.

PMID: 28003224

Neurobiol Aging. 2016 Dec 10;51:71-82. [Epub ahead of print]

Proangiogenic characteristics of activated macrophages from patients with age-related macular degeneration.

Hagbi-Levi S, Grunin M, Jaouni T, Tiosano L, Rinsky B, Elbaz-Hayoun S, Peled A, Chowers I.

Abstract: Macrophages were previously implicated in the pathogenesis of neovascular age-related macular degeneration (nvAMD). It is unclear if a specific macrophage phenotype is associated with nvAMD, and if macrophages from nvAMD patients are more pathogenic as compared with controls. To address these issues, we evaluated macrophages derived from peripheral blood monocytes of nvAMD patients and age-matched controls. Macrophages were assessed in terms of their expression profile and of their angiogenic potential in the choroid sprouting assay and the rat model of laser-induced choroidal neovascularization. Results showed a proangiogenic and inflammatory gene and protein expression profiles in classic (M[IFN γ and LPS]) and alternative (M[IL-4 and IL-13]) polarized macrophages. Furthermore, activated macrophages, particularly of the M(IFN γ and LPS) phenotype from nvAMD patients, were proangiogenic *ex vivo* and *in vivo*. These findings implicate activated human macrophages, particularly M(IFN γ and LPS) macrophages from nvAMD patients, in nvAMD. Further research is required to determine whether activated macrophages can serve as therapeutic targets in nvAMD.

PMID: 28039766

Ochsner J. 2016 Winter;16(4):502-510.

Age-Related Macular Degeneration and Intracrine Biology: An Hypothesis.

Abstract: This laboratory has studied the intracellular actions of angiotensin II and other signaling proteins that can act in the intracellular space-peptides/proteins we have called intracrines. Moreover, we have suggested that general principles of intracrine action exist and can help explain the progression of some chronic degenerative diseases such as diabetic nephropathy and congestive heart failure. Here, a similar analysis is carried out in the case of age-related macular degeneration. We propose that intracrine mechanisms are operative in this disorder. In particular, we hypothesize that intracrine loops involving renin, angiotensin II, transforming growth factor-beta, vascular endothelial growth factor, bone morphogenetic protein-4, and p53, among other factors, are involved. If this analysis is correct, it suggests a commonality of mechanism linking chronic progressive renal diseases, congestive heart failure, and macular degeneration.

PMID: 27999510 PMCID: PMC5158158

PLoS One. 2016 Dec 16;11(12):e0167793. eCollection 2016.

Norbixin Protects Retinal Pigmented Epithelium Cells and Photoreceptors against A2E-Mediated Phototoxicity In Vitro and In Vivo.

Fontaine V, Monteiro E, Brazhnikova E, Lesage L, Balducci C, Guibout L, Feraille L, Elena PP, Sahel JA, Veillet S, Lafont R.

Abstract: The accumulation of N-retinylidene-N-retinylethanolamine (A2E, a toxic by-product of the visual pigment cycle) in the retinal pigment epithelium (RPE) is a major cause of visual impairment in the elderly. Photooxidation of A2E results in retinal pigment epithelium degeneration followed by that of associated photoreceptors. Present treatments rely on nutrient supplementation with antioxidants. 9'-cis-Norbixin (a natural diapocarotenoid, 97% purity) was prepared from Bixa orellana seeds. It was first evaluated in primary cultures of porcine retinal pigment epithelium cells challenged with A2E and illuminated with blue light, and it provided an improved photo-protection as compared with lutein or zeaxanthin. In Abca4 $^{-/-}$ Rdh8 $^{-/-}$ mice (a model of dry AMD), intravitreally-injected norbixin maintained the electroretinogram and protected photoreceptors against light damage. In a standard rat blue-light model of photodamage, norbixin

was at least equally as active as phenyl-N-tert-butyl nitron, a free radical spin-trap. Chronic experiments performed with Abca4^{-/-} Rdh8^{-/-} mice treated orally for 3 months with norbixin showed a reduced A2E accumulation in the retina. Norbixin appears promising for developing an oral treatment of macular degeneration. A drug candidate (BIO201) with 9'-cis-norbixin as the active principle ingredient is under development, and its potential will be assessed in a forthcoming clinical trial.

PMID: 27992460 PMCID: PMC5161507

Exp Eye Res. 2016 Dec 15. [Epub ahead of print]

Retinal pigment epithelium and microglia express the CD5 antigen-like protein, a novel autoantigen in age-related macular degeneration.

Iannaccone A, Hollingsworth TJ, Koirala D, New DD, Lenchik NI, Beranova-Giorgianni S, Gerling IC, Radic MZ, Giorgianni F.

Abstract: We report on a novel autoantigen expressed in human macular tissues, identified following an initial Western blot (WB)-based screening of sera from subjects with age-related macular degeneration (AMD) for circulating auto-antibodies (AAbs) recognizing macular antigens. Immunoprecipitation, 2D-gel electrophoresis (2D-GE) and liquid chromatography-tandem mass spectrometry (LC-MS/MS), direct enzyme-linked immunosorbent assays (ELISA), WBs, immunohistochemistry (IHC), human primary and ARPE-19 immortalized cell cultures were used to characterize this novel antigen. An approximately 40-kDa autoantigen in AMD was identified as the scavenger receptor CD5 antigen-like protein (CD5L), also known as apoptosis inhibitor of macrophage (AIM). CD5L/AIM was localized to human RPE by IHC and WB methods and to retinal microglial cells by IHC. ELISAs with recombinant CD5L/AIM on a subset of AMD sera showed a nearly 2-fold higher anti-CD5L/AIM reactivity in AMD vs. Control sera ($p = 0.000007$). Reactivity ≥ 0.4 was associated with 18-fold higher odds of having AMD ($\chi^2 = 21.42$, $p = 0.00063$). Circulating CD5L/AIM levels were also nearly 2-fold higher in AMD sera compared to controls ($p = 0.0052$). The discovery of CD5L/AIM expression in the RPE and in retinal microglial cells adds to the known immunomodulatory roles of these cells in the retina. The discovery of AAbs recognizing CD5L/AIM identifies a possible novel disease biomarker and suggest a potential role for CD5L/AIM in the pathogenesis of AMD in situ. The possible mechanisms via which anti-CD5L/AIM AAbs may contribute to AMD pathogenesis are discussed. In particular, since CD5L is known to stimulate autophagy and to participate in oxidized LDL uptake in macrophages, we propose that anti-CD5L/AIM auto-antibodies may play a role in drusen biogenesis and inflammatory RPE damage in AMD.

PMID: 27989757

PLoS One. 2016 Dec 30;11(12):e0168122. eCollection 2016.

A Sema3C Mutant Resistant to Cleavage by Furin (FR-Sema3C) Inhibits Choroidal Neovascularization.

Toledano S, Lu H, Palacio A, Ziv K, Kessler O, Schaal S, Neufeld G, Barak Y.

Abstract: In age-related macular degeneration (AMD), abnormal sub retinal choroidal neovascularization (CNV) is a major cause of blindness. FR-sema3C is a point mutated form of semaphorin-3C that is resistant to cleavage by furin like pro-protein convertases (FPPC). We have found in previous work that FR-sema3C functions as an anti-angiogenic factor. In this study we investigated the possible use of FR-sema3C as an inhibitor of CNV. FR-sema3C inhibits VEGF as well as PDGF-BB signal transduction in endothelial cells and to less extent bFGF induced signal transduction using a mechanism that does not depend upon the binding of VEGF like the drugs that are currently the mainstay treatment for AMD. CNV was induced in eyes of C57 black mice by laser photocoagulation. Intravitreal injection of FR-Sema3C or aflibercept (VEGF-trap) was then used to inhibit CNV formation. Invading choroidal vessels were visualized a week later by injection of FITC-dextran into the circulation, followed by the measurement of the area of the invading blood

vessels. Injection of 0.1 µg FR-Sema3C inhibited CNV by 55% ($P < 0.01$) and was as effective as 5 µg aflibercept. FR-sema3C did not display any adverse effects on retinal function following its injection into eyes of healthy mice as assessed by optokinetic reflex (OKR) and Electro-retinogram (ERG) criteria. Furthermore, FR-sema3C did not induce apoptosis in the retina as determined by TUNEL nor was there any discernable structural damage to the retina as assessed by several immuno-histochemical criteria. Our results suggest that FR-sema3C could perhaps be used for the treatment of AMD, and that it may perhaps be of benefit to patients that do not respond well to current treatments relying on VEGF sequestering agents.

PMID: 28036336

J Pathol. 2016 Dec 27. [Epub ahead of print]

Activating the AKT2/NFκB/LCN-2 axis elicits an inflammatory response in age-related macular degeneration.

Ghosh S, Shang P, Yazdankhah M, Bhutto I, Hose S, Montezuma SR, Luo T, Chattopadhyay S, Qian J, Luttly GA, Ferrington DA, Samuel Zigler J Jr, Sinha D.

Abstract: Age-related macular degeneration (AMD) is a complex and progressive degenerative eye disease resulting in severe loss of central vision. Recent evidence indicates that immune system dysregulation could contribute to the development of AMD. We hypothesize that defective lysosome-mediated clearance causes accumulation of waste products in the retinal pigmented epithelium (RPE), activating the immune system and leading to retinal tissue injury and AMD. We have generated unique genetically engineered mice in which lysosome-mediated clearance (both by phagocytosis and autophagy) in RPE cells is compromised, causing development of features of early AMD. Our recent data indicate a link between Lipocalin-2 (LCN-2) and the inflammatory responses induced in this mouse model. We show that NFκB and STAT-1 may function as a complex in our animal model system, together controlling the up-regulation of LCN-2 expression in the retina and stimulating an inflammatory response. This study revealed increased infiltration of LCN-2 positive neutrophils in the choroid and retina of early AMD patients as compared to age-matched controls. Our results demonstrate that both in our animal model and in human AMD the AKT2/NFκB/LCN-2 signalling axis is involved in activating the inflammatory response, making this pathway a potential target for AMD treatment.

PMID: 28026019

Hum Mol Genet. 2016 Dec 26. [Epub ahead of print]

Dysfunction of cGMP signalling in photoreceptors by a macular dystrophy-related mutation in the calcium sensor GCAP1.

Vocke F, Weisschuh N, Marino V, Malfatti S, Jacobson SG, Reiff CM, Dell'Orco D, Koch KW.

Abstract: Macular dystrophy leads to progressive loss of central vision and shows symptoms similar to age-related macular degeneration. Genetic screening of patients diagnosed with macular dystrophy disclosed a novel mutation in the GUCA1A gene, namely a c.526C > T substitution leading to the amino acid substitution p.L176F in the guanylate cyclase-activating protein 1 (GCAP1). The same variant was found in three families showing an autosomal dominant mode of inheritance. For a full functional characterization of the L176F mutant we expressed and purified the mutant protein and measured key parameters of its activating properties, its Ca²⁺/Mg²⁺-binding, and its Ca²⁺-induced conformational changes in comparison to the wildtype protein. The mutant was less sensitive to changes in free Ca²⁺, resulting in a constitutively active form under physiological Ca²⁺-concentration, showed significantly higher activation rates than the wildtype (90-fold versus 20-fold) and interacted with an higher apparent affinity with its target guanylate cyclase. However, direct Ca²⁺-binding of the mutant was nearly similar to the wildtype; binding of Mg²⁺ occurred with higher affinity. We performed molecular dynamics simulations for comparing the Ca²⁺-

saturated inhibiting state of GCAP1 with the Mg²⁺-bound activating states. The L176F mutant exhibited significantly lower flexibility, when three Ca²⁺ or two Mg²⁺ were bound forming probably the structural basis for the modified GCAP1 function.

PMID: 28025326

Exp Eye Res. 2017 Jan 2. [Epub ahead of print]

Iron importers Zip8 and Zip14 are expressed in retina and regulated by retinal iron levels.

Sterling J, Guttha S, Song Y, Song D, Hadziahmetovic M, Dunaief JL.

Abstract: Intracellular retinal iron accumulation has been implicated in the pathogenesis of age-related macular degeneration (AMD), the leading cause of irreversible blindness among individuals over the age of 50. Ceruloplasmin/hephaestin double knockout mice (Cp/Heph DKO) and hepcidin knockout mice (Hepc KO) accumulate retinal iron and model some features of AMD. Two canonical pathways govern cellular iron import - transferrin-bound iron import and non-transferrin bound iron import. In Cp/Heph DKO and Hepc KO iron-loaded retinas, transferrin-bound iron import is downregulated. Despite this effort to reduce cellular iron burden, iron continues to accumulate in these retinas in an age-dependent manner. Quantitative RT-PCR and Western analysis were used to quantify the expression of three ferrous iron importers, Dmt1, Zip8, and Zip14, in wild-type (Wt), Cp/Heph DKO, and Hepc KO retinas. Zip8 and Zip14 protein levels were analyzed using Western analysis in mice injected intravitreally with either apo- or holo-transferrin to elucidate one possible mechanism of Zip14 regulation in the retina. Both zip8 and zip14 were expressed in the mouse retina. Paradoxically, protein levels of non-transferrin bound iron importers were upregulated in both Cp/Heph DKO and Hepc KO retinas. Intravitreal holo-transferrin injection decreased Zip 14 protein levels. These data indicate that Zip8 and Zip14 may take up increasing amounts of non-transferrin bound iron in these two mouse models of retinal iron accumulation. Their upregulation in these already iron-loaded retinas suggests a vicious cycle leading to toxicity.

PMID: 28057442

Cell Death Dis. 2017 Jan 5;8(1):e2526.

AIF-independent parthanatos in the pathogenesis of dry age-related macular degeneration.

Jang KH, Do YJ, Son D, Son E, Choi JS, Kim E.

Abstract: Cell death of retinal pigment epithelium (RPE) is characterized as an essential late-stage phenomenon of dry age-related macular degeneration (AMD). The aim of this study was to elucidate the molecular mechanism underlying RPE cell death after exposure to oxidative stress, which occurs often because of the anatomical location of RPE cells. ARPE-19, an established RPE cell line, exhibited necrotic features involving poly (ADP-ribose) polymerase-1 (PARP-1) activation in response to hydrogen peroxide (H₂O₂). ARPE-19 cells were resistant to H₂O₂ when PARP-1 was depleted using siRNA or inhibited by a pharmacological inhibitor of PARP-1, olaparib. Our data suggest a causal relationship between PARP-1 activation and ARPE-19 cell death in response to H₂O₂. Next, we investigated downstream molecular events in PARP-1 activation. Increased mitochondrial depolarization, mitochondrial fission and alterations of the cellular energy dynamics with reduced NAD⁺ and ATP were observed in H₂O₂-treated ARPE-19 cells. H₂O₂-triggered mitochondrial dysfunction was inhibited by olaparib. Nevertheless, translocation of apoptosis-inducing factor (AIF), a biochemical signature for PARP-1-dependent cell death (parthanatos), was not observed in our study. Moreover, the depletion of AIF did not affect the amplitude of cell death, demonstrating the lack of a role for AIF in the death of ARPE-19 cells in response to H₂O₂. This feature distinguishes the type of death observed in this study from canonical parthanatos. Next, we examined the in vivo role of PARP-1 in a dry AMD animal model system. Histological analysis of the outer nuclear layer in the mouse retina revealed protection against sodium iodate (SI) following treatment with olaparib. Moreover, retina fundus and electroretinograms also confirmed such a protective effect in the SI-treated

rabbit. Collectively, we report that AIF-independent PARP-1-dependent necrosis constitutes a major mechanism of RPE cell death leading to retinal degeneration in dry AMD.

PMID: 28055012

Cell Death Dis. 2017 Jan 5;8(1):e2537.

Dysfunctional autophagy in RPE, a contributing factor in age-related macular degeneration.

Golestaneh N, Chu Y, Xiao YY, Stoleru GL, Theos AC.

Abstract: Age-related macular degeneration (AMD) is a devastating neurodegenerative disease and a major cause of blindness in the developed world. Owing to its complexity and the lack of an adequate human model that recapitulates key aspects of the disease, the molecular mechanisms of AMD pathogenesis remain poorly understood. Here we show that cultured human retinal pigment epithelium (RPE) from AMD donors (AMD RPE) are functionally impaired and exhibit distinct phenotypes compared with RPE cultured from normal donors (normal RPE). Accumulation of lipid droplets and glycogen granules, disintegration of mitochondria, and an increase in autophagosomes were observed in AMD RPE cultures. Compared with normal RPE, AMD RPE exhibit increased susceptibility to oxidative stress, produce higher levels of reactive oxygen species (ROS) under stress conditions, and showed reduced mitochondrial activity. Measurement of the ratio of LC3-II/ LC3-I, revealed impaired autophagy in AMD RPE as compared with normal RPE. Autophagic flux was also reduced in AMD RPE as compared with normal RPE, as shown by inability of AMD RPE to downregulate p62 levels during starvation. Impaired autophagic pathways were further shown by analyzing late autophagic vesicles; immunostaining with lysosome-associated membrane protein 1 (LAMP-1) antibody revealed enlarged and annular LAMP-1-positive organelles in AMD RPE as opposed to smaller discrete puncta observed in normal RPE. Our study provides insights into AMD cellular and molecular mechanisms, proposes dysfunctional autophagy as an underlying mechanism contributing to the pathophysiology of the disease, and opens up new avenues for development of novel treatment strategies.

PMID: 28055007

Autophagy. 2017 Jan 3:0. [Epub ahead of print]

Autophagy and KRT8/keratin 8 protect degeneration of retinal pigment epithelium under oxidative stress.

Baek A, Yoon S, Kim J, Baek YM, Park H, Lim D, Chung H, Kim DE.

Abstract: Contribution of autophagy and regulation of related proteins to the degeneration of retinal pigment epithelium (RPE) in age-related macular degeneration (AMD) remain unknown. We report that upregulation of KRT8 (keratin 8) as well as its phosphorylation are accompanied with autophagy and attenuated with the inhibition of autophagy in RPE cells under oxidative stress. KRT8 appears to have a dual role in RPE pathophysiology. While increased expression of KRT8 following autophagy provides a cytoprotective role in RPE, phosphorylation of KRT8 induces pathologic epithelial-mesenchymal transition (EMT) of RPE cells under oxidative stress, which is mediated by MAPK1/ERK2 (mitogen-activated protein kinase 1) and MAPK3/ERK1. Inhibition of autophagy further promotes EMT, which can be reversed by inhibition of MAPK. Thus, regulated enhancement of autophagy with concurrent increased expression of KRT8 and the inhibition of KRT8 phosphorylation serve to inhibit oxidative stress-induced EMT of RPE cells as well as to prevent cell death, suggesting that pharmacological manipulation of KRT8 upregulation through autophagy with combined inhibition of the MAPK1/3 pathway may be attractive therapeutic strategies for the treatment of AMD.

PMID: 28045574

Oxid Med Cell Longev. 2016;2016:2370252. Epub 2016 Dec 7.

Integrated Approaches to Drug Discovery for Oxidative Stress-Related Retinal Diseases.

Nishimura Y, Hara H.

Abstract: Excessive oxidative stress induces dysregulation of functional networks in the retina, resulting in retinal diseases such as glaucoma, age-related macular degeneration, and diabetic retinopathy. Although various therapies have been developed to reduce oxidative stress in retinal diseases, most have failed to show efficacy in clinical trials. This may be due to oversimplification of target selection for such a complex network as oxidative stress. Recent advances in high-throughput technologies have facilitated the collection of multilevel omics data, which has driven growth in public databases and in the development of bioinformatics tools. Integration of the knowledge gained from omics databases can be used to generate disease-related biological networks and to identify potential therapeutic targets within the networks. Here, we provide an overview of integrative approaches in the drug discovery process and provide simple examples of how the approaches can be exploited to identify oxidative stress-related targets for retinal diseases.

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Epidemiology

Probl Radiac Med Radiobiol. 2016 Dec;21:172-177.

The risk of macular degeneration development in persons antenatally irradiated as a result of Chernobyl NPP accident. [Article in English, Ukrainian]

Babenko TF, Fedirko PA, Dorichevska RY, Denysenko NV, Samoteikina LA, Tyshchenko OP.

OBJECTIVE: Assess the risk of macular degeneration development in persons exposed in utero as a result of Chernobyl NPP accident.

MATERIALS AND METHODS: The object of the study was the state of the macular area of the retina of 84 individuals exposed in utero as a result of the Chernobyl disaster. They were surveyed at the age of 14-30. The results of standardized ophthalmic examinations conducted between 2000 and 2016 were used. The control group consisted of 165 persons who have not undergone prenatal exposure and were examined at the same age as the core group. All patients were examined according to the formalized ophthalmic protocol procedure, examination included ophthalmoscopy and fundus camera photography (VISUCAM lite Digital Camera, Zeiss). Statistical analysis of the survey results was carried out using the free trial version of «Open Epi 2.2.1» software package.

RESULTS: It is shown that the prevalence of macular degeneration of the retina at the age of 14-30 for persons exposed in utero was 95.23 ± 32.03 in 1000 and compared with control age (17.86 ± 10.31 in 1000) was significantly higher ($\chi^2 = 7.827$, $p = 0.0026$).

CONCLUSIONS: In the under 30 age group of the antenatally exposed there already appear macular degenerations whose clinical picture resembles age related macular degeneration. It is proved that the prevalence of macular degeneration was significantly higher in the group of antenatally exposed as compared with non irradiated control at the same age.

PMID: 28027551

Eye Vis (Lond). 2016 Dec 22;3:34. eCollection 2016.

Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors.

Pennington KL, DeAngelis MM.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in adults over 50 years old. Genetic, epidemiological, and molecular studies are beginning to unravel the intricate mechanisms underlying this complex disease, which implicate the lipid-cholesterol pathway in the pathophysiology of disease development and progression. Many of the genetic and environmental risk factors associated with AMD are also associated with other complex degenerative diseases of advanced age, including cardiovascular disease (CVD). In this review, we present epidemiological findings associating AMD with a variety of lipid pathway genes, cardiovascular phenotypes, and relevant environmental exposures. Despite a number of studies showing significant associations between AMD and these lipid/cardiovascular factors, results have been mixed and as such the relationships among these factors and AMD remain controversial. It is imperative that researchers not only tease out the various contributions of such factors to AMD development but also the connections between AMD and CVD to develop optimal precision medical care for aging adults.

PMID: 28032115 PMCID: PMC5178091

Clin Ophthalmol. 2016 Dec 19;11:23-30. eCollection 2017.

Long-term follow-up of patients with choroidal neovascularization due to angioid streaks.

Martinez-Serrano MG, Rodriguez-Reyes A, Guerrero-Naranjo JL, Salcedo-Villanueva G, Fromow-Guerra J, García-Aguirre G, Morales-Canton V, Velez-Montoya R.

BACKGROUND: The following case series describes the long-term anatomical and functional outcome of a group of seven patients with choroidal neovascularization (CNV), secondary to angioid streaks (AS), who were treated with antiangiogenic drugs in a pro re nata (PRN) regimen. After the 4-year mark, visual acuity tends to return to pretreatment level. Treatment delays and lack of awareness and self-referral by the patients are believed to be the cause of the PRN regimen failure.

PURPOSE: To assess the long-term outcomes (>4 years) of patients with CNV due to AS treated with a PRN regimen of antiangiogenic.

METHODS: This was a retrospective, case series, single-center study. We reviewed the electronic medical records from patients with CNV due to AS. From each record, we noted general demographic data and relevant medical history; clinical presentation, changes in best-corrected visual acuity (BCVA) over time, optical coherent tomography parameters, treatment and retreatment details, and systemic associations. Changes in BCVA and central macular thickness were assessed with a Wilcoxon two-sample test, with an alpha value of ≤ 0.05 for statistical significance.

RESULTS: The mean follow-up time was 53.8 ± 26.8 months. BCVA at baseline was: 1.001 ± 0.62 logMAR; at the end of follow-up: 0.996 ± 0.56 logMAR ($P=0.9$). Central macular thickness at baseline was: 360.85 ± 173.82 μm ; at the end of follow-up: 323.85 ± 100.34 μm ($P=0.6$). Mean number of intravitreal angiogenic drugs: 6 ± 4.16 injections (range 4-15). Mean time between injections was 3.8 ± 2.7 months (range 1.9-5.8 months).

CONCLUSION: Despite initial anatomical and functional improvement, patients at the end of the follow-up had no visual improvement after a pro re nata regimen of antiangiogenic drugs. The amount of retreatments, number of recurrences, and time between intravitreal injections were similar to previous reports with shorter follow-up.

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Cancer Epidemiol Biomarkers Prev. 2017 Jan 6. [Epub ahead of print]

The association between age-related macular degeneration and renal cell carcinoma: a nested case-

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control study.

Keizman D, Yang YX, Gottfried M, Dresler H, Leibovitch I, Haynes K, Mamtani R, Boursi B.

BACKGROUND: Overexpression of vascular endothelial growth factor is implicated in the pathogenesis of both renal cell carcinoma (RCC) and age-related macular degeneration (AMD). We evaluated the association between age-related macular degeneration and RCC risk.

METHODS: We conducted a matched case-control study within a population-representative database from the United Kingdom (UK). Study cases were defined as individuals with any diagnostic code of RCC. For every case, four eligible controls were matched on age, sex, practice site, calendar time and duration of follow-up. Exposure of interest was diagnosis of AMD prior to cancer diagnosis. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for RCC were estimated using conditional logistic regression. In a secondary analysis, we evaluated the association between other retinopathies and RCC and AMD and the hypovascular pancreatic cancer.

RESULTS: The study population included 1,547 patients with RCC and 6,066 matched controls. Median follow-up time was 6 years (IQR 3-9). AMD diagnosis was associated with a significantly increased RCC risk (OR 1.89, 95%CI 1.09-3.29). In contrast, there was no association between other retinopathies and RCC risk (OR 0.8, 95%CI 0.56-1.15). AMD was associated with a lower risk for pancreatic cancer (OR 0.47, 95%CI 0.35-0.64).

CONCLUSIONS: Patients with AMD may be at higher risk for RCC. Providers should be aware of this potential link and consider screening for RCC within this population.

IMPACT: Providers should be aware of the potential link between AMD and RCC.

PMID: 28062400

Genetics

Int Ophthalmol. 2016 Dec 22. [Epub ahead of print]

Association of ARMS2/LOC387715 A69S, CFH Y402H, and CFH I62V polymorphisms with retinal angiomatous proliferation compared with typical age-related macular degeneration: a meta-analysis.

Jabbarpoor Bonyadi MH, Yaseri M, Bonyadi M, Soheilian M.

PURPOSE: To compare the published results of studies on the genotype association of ARMS2/LOC387715 A69S, CFH Y402H, and CFH I62V in cases diagnosed as retinal angiomatous proliferation (RAP) versus neovascular age-related macular degeneration (AMD) or healthy controls.

METHODS: Heterogeneity of studies was evaluated using Cochran's Q test and I-square index. To modify the heterogeneity in the variables, we used random effects model. Meta-analysis was performed using STATA.

RESULTS: Four studies were included with 1076 neovascular AMD patients, 222 RAP cases, and 2276 control subjects. Pooled overall odds ratios for RAP/AMD were 1.15 (95% CI 0.60-2.18) for GT versus GG, 3.52 (95% CI 1.25-9.91) for TT versus GG ARMS2, 0.98 (95% CI 0.22-4.29) for GA versus AA, 1.00 (95% CI 0.25-4.02) for GG versus AA CFHI62V, 0.57 (95% CI 0.35-0.93) for CT versus TT CFH Y402H, and 0.40 (95% CI 0.22-0.74) for CC versus TT CFH Y402H. Regression analysis showed that ARMS2 TT genotype has a statistically significant effect on RAP versus AMD compared to CFH genotypes ($P < 0.001$).

CONCLUSION: This meta-analysis disclosed a stronger effect of ARMS2 genotypes in RAP cases compared with CFH Y402H and I62V genotypes.

PMID: 28005184

Genet Mol Res. 2016 Dec 19;15(4).

Effect of ARMS2 gene polymorphism on intravitreal ranibizumab treatment for neovascular age-related macular degeneration.

Bardak H, Bardak Y, Ercalik Y, Turkseven Kumral E, Imamoglu S, Gunay M, Ozbas H, Bagci O.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness in developed countries. The ARMS2 gene has been found to be associated with AMD. Currently, intravitreal ranibizumab (IVR) treatment is one of the widely used treatments for neovascular AMD. The aim of this study was to investigate the association between the genotype of ARMS2 rs10490924 polymorphism and IVR treatment responsiveness in patients with neovascular AMD. The study included 39 patients with advanced neovascular AMD (patient group) and 250 healthy individuals with exome sequencing data (control group). The patient group was divided into three subgroups: GG (N = 10), TG (N = 14), and TT (N = 15). Before IVR treatment, all patients had intraretinal or subretinal fluid or both. They received three monthly IVR-injection treatments. One month after the third injection, the patients were evaluated as either "responders" or "non-responders" based on the presence or absence of intraretinal or subretinal fluid or both. The patient subgroups TG and TT had an 8.56- and 39-fold higher risk of AMD, respectively, than patient subgroup GG had. The allele frequency was 0.537 and 0.10 in the patient and control groups, respectively. Within the patient subgroup TT, there was a significant difference between the "responders" and "non-responders" (P = 0.025). In conclusion, in neovascular AMD patients undergoing IVR treatment, TT genotype tended to be a better predictor of good short-term treatment response, compared to the GG and TG genotypes. Further studies using confirmed genetic biomarkers for individualized optimal treatments are required.

PMID: 28002601

Yale J Biol Med. 2016 Dec 23;89(4):597-600. eCollection 2016.

Epigenetics and Common Ophthalmic Diseases.

Li W, Liu J, Galvin JA.

Abstract: The study of ocular diseases and epigenetic dysregulation is an emerging area of research. The knowledge from the epigenetic mechanisms of DNA methylation, histone modifications, chromatin remodeling, and non-coding RNAs regarding the pathogenesis of ocular diseases will be helpful for improved treatment modalities for our patients. In particular, we focus upon the how epigenetic regulatory mechanisms impact five common ocular diseases: age related macular degeneration, age-related cataract, pterygium, retinoblastoma, and uveal melanoma. Hence, the foundation of this research paves the way for future specific therapeutic targets to treat and prevent vision loss.

PMID: 28018148 PMCID: PMC5168835

Hum Mol Genet. 2016 Dec 22. [Epub ahead of print]

Protective coding variants in CFH and PELI3 and a variant near CTRB1 are associated with age-related macular degeneration.

Yu Y, Wagner EK, Souied EH, Seitsonen S, Immonen IJ, Häppölä P, Raychaudhuri S, Daly MJ, Seddon JM.

Abstract: Although numerous common frequency age-related macular degeneration (AMD) alleles have been discovered using genome-wide association studies, substantial disease heritability remains unexplained. We sought to identify additional common and rare variants associated with advanced AMD. A total of 4,332 cases and 25,268 controls of European ancestry from three different populations were genotyped using the Illumina Infinium HumanExome BeadChip. We performed meta-analyses to identify associations with common variants, and single variant and gene-based burden tests to identify rare

variants. Two protective, low-frequency, non-synonymous variants were significantly associated with a decrease in AMD risk: A307V in PELI3 (odds ratio [OR] = 0.14, $P = 4.3 \times 10^{-10}$) and N1050Y in CFH (OR = 0.76, $P = 6.2 \times 10^{-12}$). The new variants have a large effect size, similar to most rare mutations we reported previously in a targeted sequencing study, which remain significant in this analysis: CFH R1210C (OR = 18.82, $P = 3.5 \times 10^{-07}$), C3 K155Q (OR = 3.27, $P = 1.5 \times 10^{-10}$), and C9 P167S (OR = 2.04, $P = 2.8 \times 10^{-07}$). We also identified a strong protective signal for a common variant (rs8056814) near CTRB1 associated with a decrease in AMD risk (logistic regression: OR = 0.71, $P = 1.8 \times 10^{-07}$). Suggestive protective loci were identified in the COL4A3 and APOH genes. Our results support the involvement of common and low-frequency protective variants in this vision-threatening condition. This study expands the roles of the innate immune pathway as well as the extracellular matrix and high-density lipoprotein pathways in the etiology of AMD.

PMID: 28011711

Dis Markers. 2016;2016:8486406. Epub 2016 Nov 23.

Association between Vascular Endothelial Growth Factor Polymorphisms and Age-Related Macular Degeneration: An Updated Meta-Analysis.

Barchitta M, Maugeri A.

Abstract: Age-related macular degeneration (AMD) is the most common cause of blindness in elderly people worldwide and the major degenerative disease of the retina that leads to progressive impairment of central vision. Several polymorphisms in different genes have been proposed as factors that increase the disease susceptibility. The aim of the present study is to carry out a systematic review and an updated meta-analysis in order to summarize the current published studies and to evaluate the associations between four common vascular endothelial growth factor (VEGF) polymorphisms (rs833061, rs1413711, rs3025039, and rs2010963) and AMD risk, also stratifying for AMD subtypes and ethnicity. A systematic literature search in the Medline database, using PubMed, was carried out for epidemiological studies, published before June 2016. Associations of VEGF polymorphisms with AMD were estimated by calculating pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) based on different models. Twelve articles were included in the analysis. The present meta-analysis constitutes a useful guide for readers to study AMD and adds new evidence to the growing literature on the role of VEGF polymorphisms in the risk of AMD. Significant associations with AMD risk were showed for rs833061, rs1413711, and rs3025039 polymorphisms but not for rs2010963.

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Stem cells

J Transl Med. 2016 Dec 20;14(1):344.

Repressed SIRT1/PGC-1 α pathway and mitochondrial disintegration in iPSC-derived RPE disease model of age-related macular degeneration.

Golestaneh N, Chu Y, Cheng SK, Cao H, Poliakov E, Berinstein DM.

BACKGROUND: Study of age related macular degeneration (AMD) has been hampered by lack of human models that represent the complexity of the disease. Here we have developed a human in vitro disease model of AMD to investigate the underlying AMD disease mechanisms.

METHODS: Generation of iPSCs from retinal pigment epithelium (RPE) of AMD donors, age-matched normal donors, skin fibroblasts of a dry AMD patient, and differentiation of iPSCs into RPE (AMD RPE-iPSC-RPE, normal RPE-iPSC-RPE and AMD Skin-iPSC-RPE, respectively). Immunostaining, cell viability assay and reactive oxygen species (ROS) production under oxidative stress conditions, electron

microscopy (EM) imaging, ATP production and glycogen concentration assays, quantitative real time PCR, western blot, karyotyping.

RESULTS: The AMD RPE-iPSC-RPE and AMD Skin-iPSC-RPE present functional impairment and exhibit distinct disease phenotypes compared to RPE-iPSC-RPE generated from normal donors (Normal RPE-iPSC-RPE). The AMD RPE-iPSC-RPE and AMD Skin-iPSC-RPE show increased susceptibility to oxidative stress and produced higher levels of reactive oxygen species (ROS) under stress in accordance with recent reports. The susceptibility to oxidative stress-induced cell death in AMD RPE-iPSC-RPE and Skin-iPSC-RPE was consistent with inability of the AMD RPE-iPSC-RPE and Skin-iPSC-RPE to increase SOD2 expression under oxidative stress. Phenotypic analysis revealed disintegrated mitochondria, accumulation of autophagosomes and lipid droplets in AMD RPE-iPSC-RPE and AMD Skin-iPSC-RPE. Mitochondrial activity was significantly lower in AMD RPE-iPSC-RPE and AMD Skin-iPSC-RPE compared to normal cells and glycogen concentration was significantly increased in the diseased cells. Furthermore, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), a regulator of mitochondrial biogenesis and function was repressed, and lower expression levels of NAD-dependent deacetylase sirtuin1 (SIRT1) were found in AMD RPE-iPSC-RPE and AMD Skin-iPSC-RPE as compared to normal RPE-iPSC-RPE.

CONCLUSIONS: Our studies suggest SIRT1/PGC-1 α as underlying pathways contributing to AMD pathophysiology, and open new avenues for development of targeted drugs for treatment of this devastating neurodegenerative disease of the visual system.

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Yakugaku Zasshi. 2017;137(1):23-29.

Development of Cellular and Tissue-based Products for Retinal Regenerative Medicine.

Osakada F.

Abstract: Since the discovery of induced pluripotent stem cells (iPSCs) generation, much progress has been made in the fields of medical and pharmaceutical research, such as cell transplantation therapy. We have generated retinal cells and tissues, including retinal pigment epithelia (RPE), from human iPSCs. The ability to produce iPSCs from patients allows for autologous transplantation without causing immune rejection. The autologous transplantation of iPSC-derived retinal pigment epithelial sheets to a patient with age-related macular degeneration was carried out in Japan in 2014 as a first-in-human clinical study. Biotechnology has enabled the development of a wide range of drugs, including cell-based drugs. We are currently developing iPSC-derived RPE sheets as next-generation cell-based drugs aimed at allogeneic transplantation utilizing iPSC banks of homozygotes of human leukocyte antigen at 3 loci. Regulatory science concerning cellular and tissue-based products is a vital matter associated with the realization of regenerative medicine. Here we review the most recent progress in retinal regeneration and drug development, as well as its future prospects.

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Grafted c-kit+/SSEA1- eye-wall progenitor cells delay retinal degeneration in mice by regulating neural plasticity and forming new graft-to-host synapses.

Chen X, Chen Z, Li Z, Zhao C, Zeng Y, Zou T, Fu C, Liu X, Xu H, Yin ZQ.

BACKGROUND: Despite diverse pathogenesis, the common pathological change observed in age-related macular degeneration and in most hereditary retinal degeneration (RD) diseases is photoreceptor loss. Photoreceptor replacement by cell transplantation may be a feasible treatment for RD. The major obstacles to clinical translation of stem cell-based cell therapy in RD remain the difficulty of obtaining sufficient

quantities of appropriate and safe donor cells and the poor integration of grafted stem cell-derived photoreceptors into the remaining retinal circuitry.

METHODS: Eye-wall c-kit+/stage-specific embryonic antigen 1 (SSEA1)- cells were isolated via fluorescence-activated cell sorting, and their self-renewal and differentiation potential were detected by immunochemistry and flow cytometry in vitro. After labeling with quantum nanocrystal dots and transplantation into the subretinal space of rd1 RD mice, differentiation and synapse formation by daughter cells of the eye-wall c-kit+/SSEA1- cells were evaluated by immunochemistry and western blotting. Morphological changes of the inner retina of rd1 mice after cell transplantation were demonstrated by immunochemistry. Retinal function of rd1 mice that received cell grafts was tested via flash electroretinograms and the light/dark transition test.

RESULTS: Eye-wall c-kit+/SSEA1- cells were self-renewing and clonogenic, and they retained their proliferative potential through more than 20 passages. Additionally, eye-wall c-kit+/SSEA1- cells were capable of differentiating into multiple retinal cell types including photoreceptors, bipolar cells, horizontal cells, amacrine cells, Müller cells, and retinal pigment epithelium cells and of transdifferentiating into smooth muscle cells and endothelial cells in vitro. The levels of synaptophysin and postsynaptic density-95 in the retinas of eye-wall c-kit+/SSEA1- cell-transplanted rd1 mice were significantly increased at 4 weeks post transplantation. The c-kit+/SSEA1- cells were capable of differentiating into functional photoreceptors that formed new synaptic connections with recipient retinas in rd1 mice. Transplantation also partially corrected the abnormalities of inner retina of rd1 mice. At 4 and 8 weeks post transplantation, the rd1 mice that received c-kit+/SSEA1- cells showed significant increases in a-wave and b-wave amplitude and the percentage of time spent in the dark area.

CONCLUSIONS: Grafted c-kit+/SSEA1- cells restored the retinal function of rd1 mice via regulating neural plasticity and forming new graft-to-host synapses.

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diet, lifestyle and low vision

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Associations between Serum Vitamin D and Genetic Variants in Vitamin D Pathways and Age-Related Macular Degeneration in the European Eye Study.

McKay GJ, Young IS, McGinty A, Bentham GC, Chakravarthy U, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Vioque J, de Jong PT, Fletcher AE.

PURPOSE: To study associations between early and late age-related macular degeneration (AMD) and neovascular AMD (nvAMD) with serum 25-hydroxy vitamin D (25(OH)D) and genetic variants in vitamin D pathway genes.

DESIGN: Population-based, cross-sectional study in a random sample aged 65 years or older from 7 European countries.

PARTICIPANTS: Of 4753 participants, 4496 (2028 men and 2468 women), with a mean age of 73 years, provided a blood sample; 2137 had no signs of AMD, 2209 had early AMD, and 150 had late AMD, of whom 104 had nvAMD.

METHODS: Participants were interviewed to determine smoking and alcohol use, sunlight exposure, and diet; underwent fundus photography. Fundus images were graded using the International Classification System for Age-Related Maculopathy. The 25(OH)D was measured by liquid chromatography-tandem mass spectrometry and categorized as deficient (<30 nmol/l), insufficient (30-50 nmol/l), or adequate (≥50 nmol/l). Genotyping was performed on a subsample of 1284 AMD cases and controls for 93 single nucleotide polymorphisms (SNPs) from 7 genes. Associations were investigated by linear or logistic regression adjusted for potential confounders.

MAIN OUTCOME MEASURES: Adjusted odds ratio (OR) for 3 outcomes (early AMD, late AMD, nvAMD).

RESULTS: No linear association was found with 25(OH)D and early or late AMD or nvAMD. There was no association between insufficient or deficient status with early or late AMD. Deficient status was associated with nvAMD (adjusted OR, 1.27; 95% confidence interval, 1.1-1.45; $P < 0.0001$). Significant ($P < 0.05$) associations with 25(OH)D were found for SNPs in genes GC, VDR, CYP2R1, and CYP27B1. Two SNPs (VDR) were associated with early AMD, 4 SNPs (RXRA) and 1 SNP (VDR) were associated with nvAMD, and 1 SNP (RXRA), 2 SNPs (VDR), and 1 SNP (CYP2R1) were associated with late AMD. After Bonferroni correction, no SNPs were associated with early AMD, late AMD, or nvAMD.

CONCLUSIONS: Deficiency in 25(OH)D was associated with nvAMD, but the adjusted OR was small, and we cannot exclude residual confounding. The hypothesis of a causal association of vitamin D with AMD is not supported by clear evidence for an association of vitamin D SNPs with early AMD, late AMD, or nvAMD.

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Increased fall risk in patients with neovascular age-related macular degeneration: a three-year follow-up study.

Chung SD, Hu CC, Lin HC, Kao LT, Huang CC.

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Middle East Afr J Ophthalmol. 2016 Oct-Dec;23(4):302-306.

The Evaluation of Reading Performance with Minnesota Low Vision Reading Charts in Patients with Age-related Macular Degeneration.

Altinbay D, Adibelli FM, Taskin I, Tekin A.

PURPOSE: To evaluate the reading performance using the Minnesota low vision reading (MNREAD) charts, of patients with age-related macular degeneration (AMD) who use low vision aid (LVA) devices.

MATERIALS AND METHODS: This prospective study enrolled 27 patients with AMD. Distance visual acuity (VA) was evaluated with a distance chart designed for patients with low vision. Near vision and reading performance were evaluated with the Turkish version of the MNREAD charts. Unaided vision and vision with LVA devices and high spherical add near glasses was measured. $P < 0.05$ was considered statistically significant.

RESULTS: The mean unaided near VA was 1.05 ± 0.27 log of the minimum angle of resolution (LogMAR). The mean VA with the LVA devices was 0.71 ± 0.41 LogMAR. Reading acuity ranged between 1.15 and 0.21 LogMAR, critical print size was between - 1.2 and 0.2 LogMAR. Maximum reading speeds were between 0 and 103 words/min. The cases are divided into groups in terms of reading speed according to age, gender, diagnosis, and education. Reading speed was negatively correlated to increasing age.

CONCLUSION: MNREAD reading charts can be used to evaluate reading performance in patients with AMD with low vision. The outcomes of the present study indicate that optical correction is adequate for near VA requirements in this patient population. However, optical correction was inadequate for improving reading performance. Appropriate rehabilitation programs can be used to increase reading speed.

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Polyphenol-enriched *Vaccinium uliginosum* L. fractions reduce retinal damage induced by blue light in A2E-laden ARPE19 cell cultures and mice.

Lee BL, Kang JH, Kim HM, Jeong SH, Jang DS, Jang YP, Choung SY.

Abstract: Polyphenols exert beneficial effects on vision. We hypothesized that polyphenol components of *Vaccinium uliginosum* L. (V.U.) extract protect retinal pigment epithelial (RPE) cells against blue light-induced damage. Our aim was to test extracts containing polyphenol components to ascertain effects to reduce damage against blue light in RPEs. We measured the activity in fractions eluted from water, ethanol, and HP20 resin (FH), and found that the FH fraction had the highest beneficial activity. We isolated the individual active compounds from the FH fraction using chromatographic techniques, and found that FH contained flavonoids, anthocyanins, phenyl propanoids, and iridoids. Cell cultures of A2E-laden ARPE-19 exposed to blue light after treatment with V.U. extract fractions and their individual constituents indicated improvement. V. uliginosum L extract fractions and constituent compounds significantly reduced A2E photo-oxidation-induced RPE cell death and inhibited intracellular A2E accumulation. Furthermore, Balb/c male mice were exposed to blue light at 10000 lux for 1 h/d for 2 weeks to induce retinal damage. One week after the final blue light exposure, retinal damage evaluated revealed that the outer nuclear layer thickness and nuclei count were improved. Histologic examination of murine photoreceptor cells demonstrated that FH, rich in polyphenols, inhibited the loss of outer nuclear layer thickness and nuclei. Our findings suggest that V.U. extract and eluted fractions are a potential source of bioactive compounds that potentially serve a therapeutic approach for age-related macular degeneration.

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Intake of dietary salt and drinking water: Implications for the development of age-related macular degeneration.

Bringmann A, Hollborn M, Kohen L, Wiedemann P.

PURPOSE: Systemic hypertension is a risk factor of age-related retinal diseases such as diabetic retinopathy and age-related macular degeneration. High intake of dietary salt and low intake of water increase extracellular osmolality resulting in hypertension, in particular in salt-sensitive individuals. This review summarizes the present knowledge regarding the impact of salt and water intake on the regulation of blood pressure, retinal function, and the development of age-related retinal diseases.

METHODS: A literature search of the Medline database and a summary of recent studies that used human RPE cells.

RESULTS: The salt sensitivity of the blood pressure and plasma osmolality increase with age, and body water deficits are common in older individuals. High plasma osmolality has adverse effects in the retina. In RPE cells, high osmolality induces expression and secretion of angiogenic factors, such as vascular endothelial growth factor (VEGF), placental growth factor, and basic fibroblast growth factor, and expression of aquaporin-5, a water channel implicated in transepithelial water transport. The transcriptional activities of hypoxia-inducible factor-1 (HIF-1) and nuclear factor of activated T cell 5 (NFAT5) are critical for the production of VEGF in response to salt-induced osmotic stress. Salt-induced osmotic stress also induces priming of the NLRP3 inflammasome and activates inflammatory enzymes in RPE cells.

CONCLUSIONS: Raised plasma osmolality may aggravate age-related retinal diseases by stimulation of local inflammation and angiogenic factor production in the RPE. Alterations in salt and water consumption, and of minerals that stimulate renal salt excretion, may offer nutritional approaches to prevent age-related retinal disorders, in particular in salt-sensitive individuals and individuals who show signs of body dehydration.

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Monocular and Binocular Smooth Pursuit in Central Field Loss.

Shanidze N, Heinen S, Verghese P.

Abstract: Macular degeneration results in heterogeneous central field loss (CFL) and often has asymmetrical effects in the two eyes. As such, it is not clear to what degree the movements of the two eyes are coordinated. To address this issue, we examined smooth pursuit quantitatively in CFL participants during binocular viewing and compared it to the monocular viewing case. We also examined coordination of the two eyes during smooth pursuit and how this coordination was affected by interocular ratios of acuity and contrast, as well as CFL-specific interocular differences, such as scotoma sizes and degree of binocular overlap. We hypothesized that the coordination of eye movements would depend on the binocularity of the two eyes. To test our hypotheses, we used a modified step-ramp paradigm, and measured pursuit in both eyes while viewing was binocular, or monocular with the dominant or non-dominant eye. Data for CFL participants and age-matched controls were examined at the group, within-group, and individual levels. We found that CFL participants had a broader range of smooth pursuit gains and a significantly lower correlation between the two eyes, as compared to controls. Across both CFL and control groups, smooth pursuit gain and correlation between the eyes are best predicted by the ratio of contrast sensitivity between the eyes. For the subgroup of participants with measurable stereopsis, both smooth pursuit gain and correlation are best predicted by stereoacuity. Therefore, our results suggest that coordination between the eyes during smooth pursuit depends on binocular cooperation between the eyes.

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Scotoma Visibility and Reading Rate with Bilateral Central Scotomas.

Pratt JD, Stevenson SB, Bedell HE.

PURPOSE: In this experiment, we tested whether perceptually delineating the scotoma location and border with a gaze contingent polygon overlay improves reading speed and reading eye movements in patients with bilateral central scotomas.

METHODS: Eight patients with age-related macular degeneration and bilateral central scotomas read aloud MNRead style sentences with their preferred eye. Eye movement signals from an EyeLink II eyetracker were used to create a gaze contingent display in which a polygon overlay delineating the area of the patient's scotoma was superimposed on the text during 18 of the 42 trials. Blocks of six trials with the superimposed polygon were alternated with blocks of six trials without the polygon. Reading speed and reading eye movements were assessed before and after the subjects practiced reading with the polygon overlay.

RESULTS: All of the subjects but one showed an increase in reading speed. A paired-samples t-test for the group as a whole revealed a statistically significant increase in reading speed of 0.075 ± 0.060 (SD) log wpm after reading with the superimposed polygon. Individual subjects demonstrated significant changes in reading eye movements, with the greatest number of subjects demonstrating a shift in the average vertical fixation locus. Across subjects, there was no significant difference between the initial and final reading eye movements in terms of saccades per second, average fixation duration, average amplitude of saccades, or proportion of non-horizontal saccades.

CONCLUSIONS: The improvement in reading speed (0.075 log wpm or 19%) over the short experimental session for the majority of subjects indicates that making the scotoma location more visible is potentially beneficial for improving reading speed in patients with bilateral central scotomas. Additional research to examine the efficacy of more extended training with this paradigm is warranted.

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Training eye movements for visual search in individuals with macular degeneration.

Janssen CP, Verghese P.

Abstract: We report a method to train individuals with central field loss due to macular degeneration to improve the efficiency of visual search. Our method requires participants to make a same/different judgment on two simple silhouettes. One silhouette is presented in an area that falls within the binocular scotoma while they are fixating the center of the screen with their preferred retinal locus (PRL); the other silhouette is presented diametrically opposite within the intact visual field. Over the course of 480 trials (approximately 6 hr), we gradually reduced the amount of time that participants have to make a saccade and judge the similarity of stimuli. This requires that they direct their PRL first toward the stimulus that is initially hidden behind the scotoma. Results from nine participants show that all participants could complete the task faster with training without sacrificing accuracy on the same/different judgment task. Although a majority of participants were able to direct their PRL toward the initially hidden stimulus, the ability to do so varied between participants. Specifically, six of nine participants made faster saccades with training. A smaller set (four of nine) made accurate saccades inside or close to the target area and retained this strategy 2 to 3 months after training. Subjective reports suggest that training increased awareness of the scotoma location for some individuals. However, training did not transfer to a different visual search task. Nevertheless, our study suggests that increasing scotoma awareness and training participants to look toward their scotoma may help them acquire missing information.

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