

Issue 152

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

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Drug treatment

Am J Ophthalmol. 2013 Oct 7. pii: S0002-9394(13)00550-3. doi: 10.1016/j.ajo.2013.08.013. [Epub ahead of print]

Randomized Controlled Trial of Intravitreal Ranibizumab Versus Standard Grid Laser for Macular Edema Following Branch Retinal Vein Occlusion.

Tan MH, McAllister IL, Gillies ME, Verma N, Banerjee G, Smithies LA, Wong WL, Wong TY.

Centre for Ophthalmology and Visual Science, Lions Eye Institute, The University of Western Australia, Perth, Australia; Department of Ophthalmology, Royal Perth Hospital, Perth, Australia.

PURPOSE: To assess the efficacy of intravitreal 0.5 mg ranibizumab for the treatment of center-involving macular edema secondary to branch retinal vein occlusion (BRVO) over 1 year compared with standard-of-care grid laser.

DESIGN: A prospective randomized controlled clinical trial.

METHODS: A total of 36 patients with vision loss in 1 eye attributable to macular edema following BRVO were recruited from 5 institutions. Patients were randomized 1:1 to a treatment group that received 6 monthly injections of 0.5 mg ranibizumab and thereafter monthly as needed based on best-corrected visual acuity (BCVA) and central foveal thickness (CFT) assessments on optical coherence tomography scans, or a standard-of-care group that received monthly sham injections for the 1-year duration of the study. Grid laser was administered at 13 and 25 weeks in both groups if criteria for laser treatment were met. Main outcome measures included mean change in BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores from baseline to month 12. Secondary outcomes included anatomic outcomes and the percentage of patients requiring grid laser in both groups.

RESULTS: Mean BCVA change from baseline was significantly greater in the treatment compared with the standard-of-care group at 12 months (12.5 ETDRS letters vs -1.6 ETDRS letters, $P = .032$). The mean CFT was significantly reduced in the treatment compared with standard-of-care group (361.7 μm vs 175.6 μm , $P = .025$). At 13 and 25 weeks, more patients in the standard-of-care group (68.4%, 50.0%) received grid laser than in the treatment group (6.7%, 8.3%). No new ocular or systemic adverse events were observed.

CONCLUSIONS: Compared with standard grid laser, intravitreal ranibizumab provided significant and sustained benefits in visual acuity gain and anatomic improvement in eyes with macular edema secondary to BRVO.

PMID: 24112635 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2013 Oct 10. doi: 10.1001/jamaophthalmol.2013.5002. [Epub ahead of print]

Initial Exploration of Oral Pazopanib in Healthy Participants and Patients With Age-Related Macular Degeneration.

McLaughlin MM, Paglione MG, Slakter J, Tolentino M, Ye L, Xu CF, Suttle AB, Kim RY.

GlaxoSmithKline, King of Prussia, Pennsylvania.

IMPORTANCE: Neovascular age-related macular degeneration (AMD) is managed with intravitreal anti-vascular endothelial growth factor therapy; however, the burden of care is high and alternate approaches could be beneficial.

OBJECTIVE To identify an acceptable dose of oral pazopanib for investigation in AMD.

DESIGN, SETTING, AND PARTICIPANTS Fourteen-day, placebo-controlled, dose-rising study in 72 healthy participants and 28-day phase 2a open-label study in 15 patients with subfoveal choroidal neovascularization secondary to AMD at a clinical unit for healthy participants and outpatient for patients with AMD.

INTERVENTION Oral pazopanib tablets, 5 to 30 mg daily (healthy participants) and 15 mg daily (patients with AMD).

MAIN OUTCOMES AND MEASURES Safety, pharmacokinetics, best-corrected visual acuity, central retinal lesion thickness, and central retinal thickness at day 29.

RESULTS Oral pazopanib up to 30 mg daily in healthy participants and 15 mg daily in patients with AMD was well tolerated. Six of 15 patients received rescue therapy before day 29; all had the CFH Y402H CC "high-risk" genotype for AMD. Nine patients completed the study without rescue with improvements from baseline in best-corrected visual acuity (8 Early Treatment Diabetic Retinopathy Study letters), central retinal lesion thickness ($-50.94\ \mu\text{m}$), and central retinal thickness ($-50.28\ \mu\text{m}$). There was a trend for association between the CFH Y402H T allele ("low risk" for AMD, $n = 6$) and improvement.

CONCLUSIONS AND RELEVANCE Oral pazopanib (15 mg daily) was well tolerated and resulted in improvements in mean best-corrected visual acuity, central retinal lesion thickness, and central retinal thickness at day 29 in a per-protocol, nonrescued AMD population ($n = 9$). It is postulated that CFH Y402H genotype may help predict which patients respond to pazopanib. The size and length limitations of this study warrant further investigation to determine if oral pazopanib may be an appropriate treatment for a subset of neovascular patients with AMD or as an adjunct to standard of care.

PMID: 24113783 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2013 Sep;61(9):490-496.

Intravitreal anti-VEGF monotherapy for thick submacular hemorrhage of less than 1 week duration secondary to neovascular age-related macular degeneration.

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Department of Surgery, University of Illinois College of Medicine, Peoria Campus; Illinois Retina Institute, Peoria, IL, USA.

Aim: To investigate the role of anti-VEGF monotherapy in patients with thick submacular hemorrhage (SMH) of ≤ 1 week duration secondary to neovascular age-related macular degeneration (N-AMD).

Materials and Methods: A retrospective chart review of 14 eyes of 14 patients presenting with acute decrease in central vision of ≤ 1 week duration secondary to a thick SMH measuring ≥ 2 MPS disk areas

from N-AMD was performed. Intravitreal injections of bevacizumab 1.25 mg (13 eyes) or ranibizumab 0.5 mg (1 eye) were given monthly until resolution of SMH and less frequently thereafter, based on treat-and-extend approach utilizing spectral domain optical coherence tomography (SDOCT). Patients with follow-up of ≥ 6 months were included.

Results: Patients presented after a median of 4 (range 1-7) days from the onset of SMH. Mean lesion size was 27.9 mm² (range 5.47-100, median 15), with blood comprising 77-98% of the lesion. Presenting visual acuity (VA) ranged from 20/60 to hand motions (median 20/200). Patients received a mean of 11.4 (range 5-20) injections over 18.4 (range 7-50) months. SMH resolved in all eyes in a mean of 4.8 (range 2-8) months. At 6 months follow-up, mean VA gain was -0.54 logMAR (range: -1.5 to +1, Snellen range 20/25-20/400, median 20/100, $P = 0.0037$), with 11 gaining ≥ 0.2 logMAR. Mean change in VA from baseline at final follow-up was -0.58 logMAR (range -1.6 to +1, Snellen range 20/30-20/400, median 20/60; $P = 0.0022$).

Conclusion: A good anatomical and visual outcome can be accomplished in patients with thick SMH secondary to N-AMD treated with anti-VEGF monotherapy within 1 week.

PMID: 24104707 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2013 Sep;61(9):475-478.

Anti-vascular endothelial growth factor in age-related macular degeneration: Puzzle or a silent beginning!

Natarajan S.

PMID: 24104704 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2013 Sep;61(9):528-530.

One day wonder: Fast resolution of macular edema following intravitreal ranibizumab in retinal venous occlusions.

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Department of Vitreo-Retina, Centre for Sight, Safdarjung Enclave, New Delhi, India.

Abstract: Macular edema is a significant cause of vision loss in patients with central retinal vein occlusions and branch retinal vein occlusions. Vascular endothelial growth factor (VEGF) appears to be a key factor in the pathogenesis of this disease. Anti-VEGF therapy, such as intravitreal ranibizumab provides an effective treatment against vision-threatening macular edema. We report three patients of retinal vein occlusion with macular edema who demonstrated overnight resolution of macular edema following treatment with intravitreal ranibizumab (0.5 mg). 3D optical coherence tomography (Optovue) was used as a tool for comparison of the macular thickness before and after treatment. The significant reductions in the central foveal thickness demonstrated in these patients one night after intravitreal injections could have significant influence on modifying current treatment protocols. Early treatment of macular edema related to retinal venous occlusive disease with anti-VEGF injections could result in faster visual rehabilitation in these patients.

PMID: 24104718 [PubMed - as supplied by publisher]

Colloids Surf B Biointerfaces. 2013 Jul 26;112C:474-482. doi: 10.1016/j.colsurfb.2013.07.039. [Epub ahead of print]

Synthesis, characterization and in vitro studies of celecoxib-loaded poly(ortho ester) nanoparticles targeted for intraocular drug delivery.

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Abstract: The present investigation is aimed at improving the ocular bioavailability of a poorly water soluble drug, celecoxib, to offer new options in the treatment of chronic eye diseases, such as age-related macular degeneration and diabetic retinopathy. To do so, we developed a novel formulation of drug-loaded poly (ortho ester) nanoparticles (NPs). We characterized the NPs in terms of size, morphology, controlled-release, degradation and cytocompatibility. Stable and transparent NP emulsions were prepared following a double emulsion solvent diffusion method employing poloxamer 188 as a stabilizer. Physical properties showed a narrow range size distribution of 151-164nm with spherical morphology, negative zeta potentials and remarkably high celecoxib encapsulation efficiency (98%) and loading (64%) of poly(ortho ester) NPs. Drug release followed a zero-order release by a surface erosion-controlled mechanism without any burst effect. Degradation of poly(ortho ester) NPs was observed by measuring the concentration of initial degradation product such as, lactic acid. MTT studies revealed minimal toxicity of NPs (up to 1mg/ml) toward HEK 293 cells. Poly(ortho ester) NPs were not internalized by either Müller or HEK 293 cells, which is highly desirable for a drug carrier to deliver the drugs for prolonged periods to the back of eye. These features have the potential to decrease the number of intraocular injections required to treat chronic eye diseases.

PMID: 24103464 [PubMed - as supplied by publisher]

Can J Diabetes. 2013 Oct;37S4:S48. doi: 10.1016/j.jcjd.2013.08.140.

A Canadian 12-month, PhIIIb study of Ranibizumab Combination or Monotherapy in Visual Impairment due to Diabetic Macular Edema: Preliminary Analysis ("RESPOND").

Berger A, Sheidow T, Li R, Rehel B, Takacs FD, Courseau AS.

Toronto, ON; London, ON; Basle, Switzerland; Markham, ON; Dorval, QC.

PMID: 24095431 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Conf Proc IEEE Eng Med Biol Soc. 2013 Jul;2013:7392-7395.

Drusen quantification for early identification of age related macular degeneration (AMD) using color fundus imaging.

Bhuiyan A, Karmakar C, Xiao D, Ramamohanarao K, Kanagasingam Y.

Abstract: Age-related macular degeneration (AMD) is a major cause of visual impairment in the elderly and identifying people with the early stages of AMD is important when considering the design and implementation of preventative strategies for late AMD. Quantification of drusen size and total area covered by drusen is an important risk factor for progression. In this paper, we propose a method to detect drusen and quantify drusen size along with the area covered with drusen in macular region from standard color retinal images. We used combined local intensity distribution, adaptive intensity thresholding and edge

information to detect potential drusen areas. The proposed method detected the presence of any drusen with 100% accuracy (50/50 images). For drusen detection accuracy (DDA), the segmentations produced by the automated method on individual images achieved mean sensitivity and specificity values of 74.94% and 81.17%, respectively.

PMID: 24111453 [PubMed - as supplied by publisher]

Conf Proc IEEE Eng Med Biol Soc. 2013 Jul;2013:7388-7391.

Automatic detection of subretinal fluid and sub-retinal pigment epithelium fluid in optical coherence tomography images.

Ding W, Young M, Bourgault S, Lee S, Albani DA, Kirker AW, Forooghian F, Sarunic MV, Merkur AB, Beg MF.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. Subretinal fluid (SRF) and sub-retinal pigment epithelium (sub-RPE) fluid are signs of AMD and can be detected in optical coherence tomography images. However, manual detection and segmentation of SRFs and sub-RPE fluids are laborious and time consuming. In this paper, a novel pipeline is proposed for automatic detection of SRFs and sub-RPE fluids. First, top and bottom layers of retina are segmented using a graph cut method. Then, a Split Bregman-based segmentation method is used to segment dark regions between layers. These segmented regions are considered as potential fluid candidates, on which a set of features are generated. After that, a random forest classifier is trained to distinguish between the true fluid regions from the falsely detected fluid regions. This method shows reasonable performance in a leave-one-out evaluation using a dataset from 21 patients.

PMID: 24111452 [PubMed - as supplied by publisher]

Ophthalmologe. 2013 Oct 3. [Epub ahead of print]

[Reticular drusen over time with SD-OCT.][Article in German]

Auge J, Steinberg JS, Fleckenstein M, Holz FG, Schmitz-Valckenberg S.

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AIM: The aim of the study was the analysis of reticular drusen (RDR) in patients with age-related macular degeneration using simultaneous confocal scanning laser ophthalmoscopy (cSLO) and spectral domain optical coherence tomography (SD-OCT) at different time points.

METHODS: Included in this retrospective analysis were 47 eyes from 32 patients (median age 80.1 years, range 66-89 years) with RDR at baseline and at least one follow-up visit. Registration of the cSLO near-infrared reflectance image and the SD-OCT B-scan (Spectralis HRA + OCT, Heidelberg Engineering, Heidelberg) at different time points was carried out using the AutoRescan tool.

RESULTS: While either no alterations or increase in the RDR area (n = 19 eyes) or RDR density (n = 15) were seen by cSLO imaging, the analysis of the SD-OCT B-scans at different time points revealed a more complex picture. An increase in two well visible lesions at the baseline visit was detected in 8 eyes at the first follow-up and in 3 eyes at the second follow-up examination. A regression was seen in 5 eyes at the first follow-up and in 3 eyes at the second follow-up visit. In most eyes (n = 23), an increase of one with a parallel decrease of the second RDR lesion in the identical B-scan was identified at the first follow-up visit, whereas individual RDR showed an increase at the second follow-up examination that had initially shown a decrease in size at the first follow-up visit.

CONCLUSIONS: The results indicate underlying dynamic processes in the development and changes of

RDR over time. For a more accurate analysis, the exact registration of SD-OCT B-scans at different time points and the use of high-resolution very dense volume scans would be helpful in order to assess such discrete changes of miniscule intraretinal lesions over time.

PMID: 24114561 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Oct 10. pii: iovs.12-11073v1. doi: 10.1167/iovs.12-11073. [Epub ahead of print]

Association between Geographic Atrophy Progression and Reticular Pseudodrusen in Eyes with Dry Age-Related Macular Degeneration.

Marsiglia M, Boddu S, Bearely S, Xu L, Breaux BE Jr, Freund KB, Yannuzzi LA, Smith RT.

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Purpose: To evaluate geographic atrophy (GA) progression in eyes with dry age-related macular degeneration (AMD) and to determine factors related to GA expansion, notably reticular pseudodrusen (RPD), also known as subretinal drusenoid deposits (SDD) or reticular macular disease (RMD).

Methods: This was a retrospective cohort study of patients with dry AMD who were diagnosed with GA in at least 1 eye and were imaged with sequential fundus autofluorescence (FAF) and/or near infrared reflectance (NIR-R) imaging. Images were analyzed for the presence of GA within the macular region. GA progression was measured in the fields of a modified Wisconsin grid and spatially correlated with RPD. Factors also evaluated for association with GA progression included initial GA size and pattern.

Results: The study sample included 126 eyes of 92 patients, with an average follow-up of 20.4 months (SD=11.7). At baseline, 93.6% of eyes had RPD, and the average GA area was 2.8 mm² (SD=2.9). The average GA progression rate was 0.8 mm²/year (SD=0.6), with a statistically significant difference between the unilobular and multilobular phenotype groups (0.3 mm²/year vs. 0.9 mm²/year, p=0.02). Patients in the lower 50th percentile of initial GA area had a lower progression rate than patients in the upper 50th percentile (0.6 mm²/year vs. 1.1 mm²/year, p<0.001). GA progression was more frequent in fields with RPD than in those without RPD (74.2% vs. 41.7%, p<0.001).

Conclusions: The high correlation between the presence of RPD (also known as SDD or RMD) and the presence of GA and the expansion of GA into areas with these lesions suggest that they are an early manifestation of the process leading to GA.

PMID: 24114542 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Oct 2. [Epub ahead of print]

Relationship between Visual Acuity and Spectral Domain Optical Coherence Tomography Retinal Parameters in Neovascular Age-Related Macular Degeneration.

Ristau T, Keane PA, Walsh AC, Engin A, Mokwa N, Kirchhof B, Sadda SR, Liakopoulos S.

Cologne Image Reading Center, Department of Ophthalmology, University Hospital of Cologne, Cologne, Germany.

Purpose: Relationship between spectral domain optical coherence tomography (SD-OCT) and visual acuity (VA) in neovascular age-related macular degeneration (NVAMD).

Procedures: VA and SD-OCTs of 64 treatment-naïve eyes with NVAMD were retrospectively collected at baseline and 1 year ($n = 30$). Retinal and subretinal spaces were manually analyzed. Volume and thickness measurements were correlated with VA.

Results: At baseline, lower VA correlated with increased volume of subretinal hyperreflective material ($R = 0.4$, $p < 0.001$) and with decreased volume of the photoreceptor layer (PRL, $R = -0.4$, $p < 0.01$). At 1 year, lower VA correlated with decreased volume of the retina ($R = -0.7$, $p < 0.001$), outer nuclear layer ($R = -0.6$, $p < 0.05$) and PRL ($R = -0.7$, $p < 0.001$). Decrease in VA after 1 year correlated with a decrease in PRL ($R = 0.4$, $p < 0.05$).

Conclusions: Quantitative analysis of SD-OCT revealed correlations between VA and retinal and subretinal morphological changes in NVAMD. **Message:** Atrophy of the outer retina is an important correlate for lower VA in NVAMD. © 2013 S. Karger AG, Basel.

PMID: 24107542 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Oct;48(5):431-437. doi: 10.1016/j.jcjo.2013.07.013.

Biofeedback stimulation in patients with age-related macular degeneration: comparison between 2 different methods.

Amore FM, Paliotta S, Silvestri V, Piscopo P, Turco S, Reibaldi A.

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OBJECTIVE: To evaluate changes in patient's visual performance after rehabilitation training with 2 different biofeedback training programs offered by the MP-1 microperimeter. Spontaneous retinal location of preferred retinal loci (PRLs) and fixation stability are not always optimal for best visual performances. MP-1 microperimeter biofeedback techniques have been suggested as modalities for training for better fixation stability and to find a better location of the new PRL in a more useful area of the retina in nonoptimal cases. The MP-1 microperimeter offers different biofeedback strategies, such as acoustic biofeedback and structured light stimulus plus acoustic biofeedback.

DESIGN: Retrospective study.

PARTICIPANTS: Thirty subjects affected by age-related macular degeneration with absolute central scotoma.

METHODS: A standard protocol of examination before and after visual rehabilitation training was performed on all study subjects. Assessment included demographics data, visual acuity, fixation stability, retinal sensitivity, and reading speed. Rehabilitation training was performed with standard and structured stimulus biofeedback. The whole sample was divided into 2 groups of 15 patients attending the 2 different stimulation training biofeedback.

RESULTS: Mean reading speed was found to be significantly increased for both groups ($p < 0.05$ and $p < 0.01$). Also, a statistically significant improvement of fixation stability was registered for both groups ($p < 0.01$). Only patients trained with the flickering pattern biofeedback stimulation increased retinal sensitivity ($p < 0.01$).

CONCLUSIONS: Both regular biofeedback and flickering pattern biofeedback training seem to improve visual functions. More benefits seem to be accrued, however, with flickering pattern biofeedback training.

PMID: 24093192 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Oct;48(5):427-430. doi: 10.1016/j.jcjo.2013.03.001. Epub 2013 Sep 2.

Use of prisms for vision rehabilitation after macular function loss may impact oculomotor control.

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OBJECTIVE: To determine the effect from using prisms for image relocation on fixation stability estimates in low-vision (LV) patients with age-related macular degeneration (AMD).

METHODS: The study was designed as a prospective, nonrandomized, observational case series. Inclusion criteria included documented AMD, LV with best corrected visual acuity of 20/50 to 20/400 in the better eye, and cases wearing distance glasses with prisms for image relocation incorporated in the glasses. Preferred retinal locus (PRL) and fixation stability were assessed using the Nidek MP1 and MAIA microperimeters. A control group was used to compare results.

RESULTS: We recruited 14 study subjects with AMD and 10 with no retinal pathology serving as a control group. On average, 6 (SD 2) prisms diopters were prescribed to all in distant viewing glasses. Fixation stability was better at 3-month interval from baseline ($p = 0.021$) in the AMD group and stayed the same for the following 9 months. No change in fixation stability was noticed in the control group. There was no statistically significant difference in PRL eccentricity between the 3- and 12-month intervals in the AMD group ($p = 0.39$). However, there was a positive correlation between PRL eccentricity and baseline bivariate contour ellipse area in the AMD group ($p = 0.052$).

CONCLUSIONS: Patients with LV with AMD who are using prisms for image relocation toward the peripheral retina exhibit better fixation stability than those who are not using prisms. Better fixation stability may impact on other visual outcomes. Use of prisms should be considered in any LV rehabilitation attempt and used in conjunction with other modern interventions in LV rehabilitation.

PMID: 24093191 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Oct;48(5):420-426. doi: 10.1016/j.jcjo.2013.07.012.

Rehabilitative approach in patients with ring scotoma.

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OBJECTIVE: To investigate the rehabilitative approach in patients with ring scotoma. A central scotoma is characteristic for patients with age-related macular degeneration (AMD). Sometimes patients with AMD maintain a residual central vision area within the scotoma (ring scotoma).

DESIGN: Prospective, nonrandomized case series.

PARTICIPANTS: Twenty-four patients with AMD.

METHODS: A formal low-vision assessment was performed for all study patients. The assessment included best corrected visual acuity (BCVA), contrast sensitivity, reading speed, and microperimetry. All patients were provided a low-vision assessment to satisfy patients' needs. Devices were prescribed accordingly.

RESULTS: The BCVA found was 0.4 logMAR (SD 0.1). All had central and stable fixation. Residual central retinal area size and sensitivity measured 2.4° (SD 0.8) and 3.1 dB (SD 0.8), respectively. Twenty patients

achieved better vision with optical magnification in the eye with ring scotoma. Mean reading speed achieved was 50.2 words/min (SD 20.9). A linear correlation was found for reading speed with both central area sensitivity ($r^2 = 0.5$, $p < 0.05$) and contrast sensitivity ($r^2 = 0.3$, $p < 0.05$).

CONCLUSIONS: In patients with AMD with ring scotoma, moderate amounts of magnification seem to provide satisfactory rehabilitation outcomes. Central retinal spared area sensitivity may predict reading speed outcomes, whereas residual central area size is likely to be useful in determining magnification.

PMID: 24093190 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Oct;48(5):394-399. doi: 10.1016/j.jcjo.2013.04.006.

Fixation stability measurements in patients with neovascular age-related macular degeneration treated with ranibizumab.

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OBJECTIVE: To evaluate which of 2 measuring units (bivariate contour ellipse area [BCEA] vs Fujii) yields more accurate measurements of fixation stability, obtained using the MP-1 device, in patients with neovascular age-related macular degeneration (nAMD) treated with intravitreal injections of ranibizumab, during a 12-month follow-up period.

DESIGN: Small retrospective, noncomparative, interventional case series.

PARTICIPANTS: A total of 25 eyes in 25 patients (13 males, 12 females; mean age 71.72 ± 7.98 years).

METHODS: All participants were older than 50 years, diagnosed with active subfoveal choroidal neovascularization, had best corrected visual acuity (BCVA) values above 20/100, and all lesion types were included. All patients underwent a loading phase with 3 consecutive intravitreal injections of 0.05 mg ranibizumab at monthly intervals. Patients were retreated after the third injection if they exhibited a 100- μ m increase in macular thickness or evidence of intraretinal and/or subretinal fluid and new subretinal hemorrhage, observed with spectral-domain optical coherence tomography and fluorescein angiography. The data collected included BCVA and mean macular sensitivities, BCEA, and fixation patterns, performed at baseline and at months 4 and 12, using the MP-1 device.

RESULTS: The mean total injection number was 5.92 ± 1.18 (minimum 3, maximum 8). Mean BCVA at baseline was 0.55 ± 0.28 logMAR and increased significantly to 0.50 ± 0.33 logMAR. Mean macular sensitivity at baseline was 7.06 ± 4.59 dB and increased significantly to 8.40 ± 4.82 . Mean BCEA was 2.19 ± 1.38 deg² and decreased significantly to 1.68 ± 1.43 deg². Fixation stability patterns, according to the protocol set out by Fujii, did not change significantly during follow-up.

CONCLUSIONS: Compared with Fujii fixation stability patterns, BCEA correlated better with variations in macular sensitivity and BCVA. BCEA can be added to the traditional parameters used to evaluate the efficacy of intravitreal injections in patients with nAMD.

PMID: 24093186 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Oct;48(5):386-393. doi: 10.1016/j.jcjo.2013.03.022.

Microperimetry, fundus autofluorescence, and retinal layer changes in progressing geographic atrophy.

Pilotto E, Benetti E, Convento E, Guidolin F, Longhin E, Parrozzani R, Midena E.

Department of Ophthalmology, University of Padova, Padova.

OBJECTIVE: To analyze correlation among microperimetry, inner and outer retinal layers, and fundus autofluorescence (FAF) changes in eyes with progressing geographic atrophy (GA) secondary to age-related macular degeneration.

METHODS: Microperimetry, spectral-domain optical coherence tomography (SD-OCT), standard short-wavelength FAF (SW-FAF), and near-infrared-wavelength FAF (NIR-FAF) were performed for all patients at both baseline and follow-up visits. FAF pattern, integrity of photoreceptor inner segment/outer segment (IS/OS) junction, total retinal thickness (RT), inner retinal layers (IRL), and outer retinal layers (ORL) thickness changes of every microperimetry extrafoveal tested point were analyzed.

RESULTS: A total of 366 microperimetry tested points were analyzed (6 patients, 7 eyes). Mean retinal sensitivity significantly decreased ($p = 0.0149$), and the percentage of dense scotomas significantly increased ($p = 0.0125$). Mean RT and mean ORL thickness significantly decreased (both $p < 0.0001$). Mean IRL thickness significantly increased ($p = 0.0001$). The decrease of ORL thickness was inversely correlated to the IRL thinning ($\rho = -0.710$). FAF pattern at baseline was correlated to RT and ORL thickness (both $p < 0.0001$) and was significantly correlated to the risk to evolve to dense scotoma during follow-up ($p = 0.0001$ at SW-FAF, $p < 0.0001$ at NIR-FAF). Tested points showing at baseline the loss of photoreceptor IS/OS junction had a greater risk for evolving to dense scotoma compared with those with intact photoreceptor IS/OS junction (odds ratio 3.56, 95% CI 2.41-5.27).

CONCLUSIONS: Retinal sensitivity changes are correlated to IRL and ORL thickness changes, and to photoreceptor IS/OS junction integrity. FAF patterns remain a relevant factor in predicting GA evolution. Microperimetry, SW-FAF and NIR-FAF, and SD-OCT should be combined to obtain adequate morphologic and functional prospective information.

PMID: 24093185 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Oct;48(5):381-385. doi: 10.1016/j.jcjo.2013.04.004. Epub 2013 Sep 2.

The worse eye is not as bad as it seems to be in AMD cases.

Podbielski DW, Reyes SV, Markowitz SN.

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OBJECTIVE: It is the aim of this study to review residual vision in the less used eye of patients with age-related macular degeneration (AMD) using modern concepts for residual visual functions in addition to traditional methods for assessing visual acuity.

DESIGN: The study was designed as a retrospective, nonrandomized, observational case series.

PARTICIPANTS: Consecutive cases tested with microperimetry instruments were identified from archives. Included were cases with diagnosed AMD of all age groups and all visual acuity levels.

METHODS: In all cases, microperimetric technology was used to assess residual visual function. Outcome measures selected for analysis were visual acuity, preferred retinal loci (PRL) topography, fixation stability, and PRL span.

RESULTS: Data were collected and analyzed for both eyes from 51 patients with AMD low vision. There were 23 males and 28 females whose mean age was 84 (± 7) years. Within the group the difference in visual acuity estimates between the better seeing and the less used eye was statistically significant ($p = 0.001$). Similar positive statistical significant differences were noticed at all spatial frequencies (except at 6

cycles/degree) when testing contrast sensitivity. All other measurements were not statistically different between the better seeing and the poorer eye. This applies to the fixation stability and PRL span estimates. Almost half (49%) of the cases showed retinal noncorrespondence of PRLs between the 2 eyes.

CONCLUSIONS: Visual acuity estimates are not a reliable measure for residual vision. The less used eye in AMD cases has much better residual vision than thought before according to modern outcome measures. This new concept should be taken into account by all practitioners and be applied during all low vision rehabilitation interventions.

PMID: 24093184 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Oct;48(5):375-380. doi: 10.1016/j.jcjo.2013.05.021.

Static and dynamic retinal fixation stability in microperimetry.

Longhin E, Convento E, Pilotto E, Bonin G, Vujosevic S, Kotsafti O, Midena E.

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OBJECTIVE: To compare static (during a pure fixation task) versus dynamic (during microperimetry) quantification of fixation stability using microperimetry in normal and pathologic eyes, by means of 2 available (clinical and bivariate contour ellipse area [BCEA]) classification methods.

DESIGN: Prospective comparative observational study.

PARTICIPANTS: One hundred and forty-nine eyes (110 patients) with different macular diseases and 171 normal eyes (109 subjects).

METHODS: In all eyes studied, fixation stability was acquired during an isolated fixation task (static fixation) and during microperimetry (dynamic fixation). All fixation data were analyzed and compared by means of a clinical classification and by means of BCEA quantification.

RESULTS: Pathologic eyes were classified as follows: 41 eyes with diabetic macular edema (DME group), 13 eyes with vitreoretinal interface disease, 60 eyes with age-related macular degeneration (AMD group), and 35 eyes with primary open-angle glaucoma. Fixation stability was not uniform among groups according to clinical classification in both static and dynamic modalities ($p < 0.0001$). AMD group showed larger BCEA areas compared with all other groups ($p < 0.0001$). All pathologic groups showed more unstable fixation in dynamic fashion according to both clinical and BCEA methods ($p < 0.0001$). The variation of fixation stability of control group in dynamic task was highlighted only by BCEA analysis ($p < 0.0001$). A deterioration of retinal fixation according to clinical method matches a significant increase in BCEA areas ($p < 0.0001$).

CONCLUSIONS: The detection of clinical fixation stability changes improves when acquired in the dynamic modality. BCEA analysis provides more accurate evaluation of fixation stability and may detect minimal quantitative changes of the fixation area. However, a standard clinical classification can also detect changes in fixation stability in pathologic eyes. Both methods are useful tools in the evaluation of fixation stability.

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Preferred retinal locus profile during prolonged fixation attempts.

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OBJECTIVE: The retinal area or location used during any fixation attempt defines the preferred retinal locus (PRL). It is presumed that during prolonged fixation attempts there may be various representative reference points within the PRL area. This study aims to clarify this presumption.

DESIGN: Prospective, nonrandomized, observational case series.

PARTICIPANTS: Sixty-five eyes of 41 patients from the University of Nottingham, Queen's Medical Centre Retina and Low Vision Clinics.

METHODS: A total of 65 eyes of 41 patients from the University of Nottingham, Queen's Medical Centre Retina and Low Vision Clinics were assessed for PRL using the Macular Integrity Assessment (MAIA) microperimetry equipment (CenterVue, Padova, Italy). The MAIA allows automatic calculation for 2 points named PRL_initial (PRLi), which is calculated after the first 10 seconds of fixation, and PRL_final (PRLf), which is calculated after the completion of all fixation attempts during the microperimetry test.

RESULTS: Estimates of PRLi and PRLf were produced for all patients. Forty-six (71%) eyes were classified as having stable fixation; 40 of the 46 eyes (87%) had both PRLs location over the fovea centralis. Nineteen of 65 eyes (29%) were classified as having unstable or relatively unstable fixation; different PRLi and PRLf locations were found in 18 (95%) of the 19 eyes, including 13 (68%) with central geographic atrophy secondary to dry age-related macular degeneration. The mean rate of change was 5.3 units in fixation per unit change in distance in both PRLi and PRLf.

CONCLUSIONS: The representative points during prolonged fixation attempts may vary at different stages of fixation. This is reflected in the characteristics of fixation stability of the patients and presents a possible association with main pathology responsible for low vision.

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Can J Ophthalmol. 2013 Oct;48(5):358-363. doi: 10.1016/j.jcjo.2013.03.021. Epub 2013 Sep 2.

Fundus-driven perimetry (microperimetry) compared to conventional static automated perimetry: similarities, differences, and clinical applications.

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Abstract: Fundus-driven perimetry, commonly known as microperimetry, is a technique for measuring visual field sensitivity, whilst simultaneously viewing the fundus. In this article, we review the technique, focusing on the MP-1 microperimeter (Nidek Instruments, Inc, Padua, Italy); we compare it with conventional static automated perimetry, emphasizing the importance of understanding the effects of the different stimulus conditions and data analyses on the interpretation of microperimetry data. The clinical applications of the technique, in the evaluation of functional and structural changes that accompany retinal diseases, are illustrated by its use in patients with age-related macular degeneration, Stargardt disease, and retinitis pigmentosa. In addition, the advantages and limitations of the technique are summarized.

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Indian J Ophthalmol. 2013 Sep;61(9):507-510.

Foveal slope measurements in subjects with high-risk of age-related macular degeneration.

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Background: Recent reports indicated that the slope of the foveal depression influences the macular pigment (MP) spatial profile. MP has been shown to confer possible protection against age-related macular degeneration (ARMD) because of its antioxidant properties.

Aims: To study the configuration of foveal slope and the foveal thickness in fellow eyes of subjects with unilateral neovascular ARMD.

Settings and design: Case-control series.

Materials and Methods: The study population consisted of 30 cases aged >50, who had unilateral choroidal neovascular membrane (CNVM) or disciform scar in the fellow eye and 29 controls aged >50, who had no sign of ARMD in the either eye. Using spectral-domain optical coherence tomography, foveal thickness at different locations including the central subfield foveal thickness (CSFT) was noted. The foveal slopes were calculated in the six radial scans (between 0.25° and 1° retinal eccentricity) as well as the 3D scan.

Results: Cases had a significantly higher CSFT when compared to controls ($215.1 \pm 36.19 \mu$ vs. $193.0 \pm 17.38 \mu$, $P = 0.004$). On the 3D scan, the cases had shallower superior (cases 1.32 ± 0.32 vs. controls 1.45 ± 0.13 , $P = 0.04$) and temporal slopes (cases 1.27 ± 0.21 vs. controls 1.39 ± 0.12 , $P = 0.01$) in comparison to the controls.

Conclusions: We noted a shallower superior and temporal foveal slope and a higher CSFT in the fellow eyes of subjects with a unilateral neovascular ARMD. Prospective studies observing the development of CNVM in subjects with altered foveal slope might provide more information on this optical coherence tomography finding.

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Pathogenesis

Proc Natl Acad Sci U S A. 2013 Oct 8. [Epub ahead of print]

Aryl hydrocarbon receptor deficiency causes dysregulated cellular matrix metabolism and age-related macular degeneration-like pathology.

Hu P, Herrmann R, Bednar A, Saloupis P, Dwyer MA, Yang P, Qi X, Thomas RS, Jaffe GJ, Boulton ME, McDonnell DP, Malek G.

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Abstract: The aryl hydrocarbon receptor (AhR) is a nuclear receptor that regulates xenobiotic metabolism and detoxification. Herein, we report a previously undescribed role for the AhR signaling pathway as an essential defense mechanism in the pathogenesis of early dry age-related macular degeneration (AMD), the leading cause of vision loss in the elderly. We found that AhR activity and protein levels in human retinal pigment epithelial (RPE) cells, cells vulnerable in AMD, decrease with age. This finding is significant given that age is the most established risk factor for development of AMD. Moreover, AhR^{-/-} mice exhibit decreased visual function and develop dry AMD-like pathology, including disrupted RPE cell tight junctions, accumulation of RPE cell lipofuscin, basal laminar and linear-like deposit material, Bruch's membrane thickening, and progressive RPE and choroidal atrophy. High-serum low-density lipoprotein levels were also observed in AhR^{-/-} mice. In its oxidized form, this lipoprotein can stimulate increased secretion of extracellular matrix molecules commonly found in deposits from RPE cells, in an AhR-dependent manner.

This study demonstrates the importance of cellular clearance via the AhR signaling pathway in dry AMD pathogenesis, implicating AhR as a potential target, and the mouse model as a useful platform for validating future therapies.

PMID: 24106308 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Oct 8. pii: iovs.13-12923v1. doi: 10.1167/iov.13-12923. [Epub ahead of print]

Aurintricarboxylic Acid Inhibits Complement Activation, Membrane Attack Complex and Choroidal Neovascularization in a Model of Macular Degeneration.

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Purpose: Immunocytochemical and genetic data implicate a significant role for the activation of complement in the pathology of age-related macular degeneration (AMD). Individuals homozygous for a Y402H polymorphism in Factor H have elevated levels of membrane attack complex (MAC) in their choroidal blood vessels and retinal pigment epithelium (RPE) relative to individuals homozygous for the wild type allele. An R95X polymorphism in C9, a protein necessary for the final assembly of MAC, is partially protective against the formation of choroidal neovascularization (CNV) in AMD patients. Aurintricarboxylic Acid (ATA) is a small molecule inhibitor of MAC. Our hypothesis was that attenuation of the formation of MAC on ocular tissues by ATA may protect mice against laser induced CNV.

Methods: The ability of ATA to inhibit human complement mediated cell lysis, inhibit formation of human MAC and inhibit formation of tubes by endothelial cells was examined in vitro. Subsequently, the Bruch's membrane of adult mice was damaged using an argon laser, followed by intravitreal injection of ATA. One week later, choroidal flat mounts from these mice were stained for the presence of MAC, endothelial cells and macrophages.

Results: ATA protects cells from human complement mediated lysis, attenuates assembly of the membrane attack complex and inhibits tube formation by endothelial cells in vitro. ATA also attenuates CNV, MAC deposition and macrophage infiltration in a murine model of exudative AMD.

Conclusions: ATA warrants further study as a potential drug for the treatment of exudative and non exudative AMD.

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Invest Ophthalmol Vis Sci. 2013 Oct 8. pii: iovs.13-12730v1. doi: 10.1167/iov.13-12730. [Epub ahead of print]

Comparative Analysis of Aqueous Humor Cytokine Levels Between Patients With Exudative Age-related Macular Degeneration and Normal Controls.

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Purpose: To investigate the cytokine markers associated with exudative age-related macular degeneration (AMD) present in aqueous humor. This goal was achieved by comparing the concentrations of more than 500 molecules in aqueous humor, between exudative AMD patients and controls.

Methods: Aqueous humor samples were acquired from 20 patients with exudative AMD and 20 control

subjects. Raybio® human antibody array technology was used to simultaneously screen for any difference in the expression of any of 507 molecules. To validate the antibody array result, concentrations of insulin-like growth factor binding protein 2 (IGFBP-2), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) were measured by enzyme-linked immunosorbent assay (ELISA).

Results: Twenty molecules studied exhibited inter-group differences. Twelve molecules including IGFBP-2, IGFBP-6, IGFBP-7, and glucocorticoid-induced tumor necrosis factor receptor family related gene (GTR) ligand, were detected in high densities in exudative AMD patients. Eight other molecules were present at higher concentrations in control patients. ELISA confirmed that IGFBP-2 levels were higher in patients with exudative AMD (7.47 ± 6.19 ng/mL) in comparison to control subjects (3.07 ± 3.34 ng/mL, $P = 0.008$). IGF-1 and VEGF levels were also increased in the former group (2.20 ± 0.26 versus 1.99 ± 0.35 ng/mL, $P = 0.040$; 122.25 ± 63.24 versus 86.98 ± 44.41 pg/mL, $P = 0.048$, respectively).

Conclusions: The pattern of cytokine expression in the aqueous humor of exudative AMD patients varies from that of normal control subjects. The increased levels of IGFBP-2 and IGF-1 in exudative AMD eyes indicate that the altered expression of IGF-related molecules may be involved in disease pathogenesis and suggests potential biomarkers for exudative AMD.

PMID: 24106111 [PubMed - as supplied by publisher]

J Pathol. 2013 Sep 19. doi: 10.1002/path.4266. [Epub ahead of print]

Mechanisms of Age Related Macular Degeneration and Therapeutic Opportunities.

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Abstract: As the population ages in many nations increase, age-related degenerative diseases pose significant socioeconomic challenges. One of the key degenerative diseases that compromise quality of life is Age Related Macular Degeneration (AMD, or ARAMD). AMD is a multi-faceted condition that affects the central retina, which ultimately leads to blindness in millions of people worldwide. The pathophysiology and risk factors for AMD are complex, and the symptoms manifest in multiple related but distinct forms. The ability to develop effective treatments for AMD will depend on a thorough understanding of the underlying pathophysiology, risk factors, and driver molecular pathways, as well as the ability to develop useful animal models. This review provides an overview of the aforementioned aspects in AMD.

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Conf Proc IEEE Eng Med Biol Soc. 2013 Jul;2013:69-72.

Multicompartment retinal ganglion cells response to high frequency bi-phasic pulse train stimulation: Simulation results.

Maturana MI, Grayden DB, Burkitt AN, Meffin H, Kameneva T.

Abstract: Retinal ganglion cells (RGCs) are the sole output neurons of the retina that carry information about a visual scene to the brain. By stimulating RGCs with electrical stimulation, it is possible to elicit a sensation of light for people with macular degeneration or retinitis pigmentosa. To investigate the responses of RGCs to high frequency bi-phasic pulse train stimulation, we use previously constrained models of multi-compartment OFF RGCs. The morphologies of mouse RGCs are taken from the Chalupa set of the NeuroMorpho database. The cell models are divided into compartments representing the dendrites, soma and axon that vary between the cells. A total of 132 cells are simulated in the NEURON environment. Results show that the cell morphology plays an important role in the response characteristics

of the cell to high frequency bi-phasic pulse train stimulation.

PMID: 24109626 [PubMed - as supplied by publisher]

PLoS One. 2013 Sep 30;8(9):e75964.

Expression Analysis of an Evolutionarily Conserved Alternative Splicing Factor, Sfrs10, in Age-Related Macular Degeneration.

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Abstract: Age-related macular degeneration (AMD) is the most common cause of blindness in the elderly population. Hypoxic stress created in the micro-environment of the photoreceptors is thought to be the underlying cause that results in the pathophysiology of AMD. However, association of AMD with alternative splicing mediated gene regulation is not well explored. Alternative Splicing is one of the primary mechanisms in humans by which fewer protein coding genes are able to generate a vast proteome. Here, we investigated the expression of a known stress response gene and an alternative splicing factor called Serine-Arginine rich splicing factor 10 (Sfrs10). Sfrs10 is a member of the serine-arginine (SR) rich protein family and is 100% identical at the amino acid level in most mammals. Immunoblot analysis on retinal extracts from mouse, rat, and chicken showed a single immunoreactive band. Further, immunohistochemistry on adult mouse, rat and chicken retinæ showed pan-retinal expression. However, SFRS10 was not detected in normal human retina but was observed as distinct nuclear speckles in AMD retinæ. This is in agreement with previous reports that show Sfrs10 to be a stress response gene, which is upregulated under hypoxia. The difference in the expression of Sfrs10 between humans and lower mammals and the upregulation of SFRS10 in AMD is further reflected in the divergence of the promoter sequence between these species. Finally, SFRS10+ speckles were independent of the SC35+ SR protein speckles or the HSF1+ stress granules. In all, our data suggests that SFRS10 is upregulated and forms distinct stress-induced speckles and might be involved in AS of stress response genes in AMD.

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PLoS One. 2013 Oct 1;8(10):e76325.

CEP Biomarkers as Potential Tools for Monitoring Therapeutics.

Renganathan K, Gu J, Rayborn ME, Crabb JS, Salomon RG, Collier RJ, Kapin MA, Romano C, Hollyfield JG, Crabb JW.

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BACKGROUND: Carboxyethylpyrrole (CEP) adducts are oxidative modifications derived from docosahexaenoate-containing lipids that are elevated in ocular tissues and plasma in age-related macular degeneration (AMD) and in rodents exposed to intense light. The goal of this study was to determine whether light-induced CEP adducts and autoantibodies are modulated by pretreatment with AL-8309A under conditions that prevent photo-oxidative damage of rat retina. AL-8309A is a serotonin 5-HT1A receptor agonist.

METHODS: Albino rats were dark adapted prior to blue light exposure. Control rats were maintained in normal cyclic light. Rats were injected subcutaneously 3x with 10 mg/kg AL-8309A (2 days, 1 day and 0 hours) before light exposure for 6 h (3.1 mW/cm², λ=450 nm). Animals were sacrificed immediately

following light exposure and eyes, retinas and plasma were collected. CEP adducts and autoantibodies were quantified by Western analysis or ELISA.

RESULTS: ANOVA supported significant differences in mean amounts of CEP adducts and autoantibodies among the light + vehicle, light + drug and dark control groups from both retina and plasma. Light-induced CEP adducts in retina were reduced ~20% following pretreatment with AL-8309A ($n = 62$ rats, $p = 0.006$) and retinal CEP immunoreactivity was less intense by immunohistochemistry. Plasma levels of light-induced CEP adducts were reduced at least 30% ($n = 15$ rats, $p = 0.004$) by drug pretreatment. Following drug treatment, average CEP autoantibody titer in light exposed rats ($n = 22$) was unchanged from dark control levels, and ~20% ($p = 0.046$) lower than in vehicle-treated rats.

CONCLUSIONS: Light-induced CEP adducts in rat retina and plasma were significantly decreased by pretreatment with AL-8309A. These results are consistent with and extend previous studies showing AL-8309A reduces light-induced retinal lesions in rats and support CEP biomarkers as possible tools for monitoring the efficacy of select therapeutics.

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Epidemiology

Front Aging Neurosci. 2013 Oct 2;5:56.

Co-morbidity of depression and anxiety in common age-related eye diseases: a population-based study of 662 adults.

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Abstract: This study examined the prevalence of co-morbid age-related eye disease and symptoms of depression and anxiety in late life, and the relative roles of visual function and disease in explaining symptoms of depression and anxiety. A community-based sample of 662 individuals aged over 70 years was recruited through the electoral roll. Vision was measured using a battery of tests including high and low contrast visual acuity, contrast sensitivity, motion sensitivity, stereoacuity, Useful Field of View, and visual fields. Depression and anxiety symptoms were measured using the Goldberg scales. The prevalence of self-reported eye disease [cataract, glaucoma, or age-related macular degeneration (AMD)] in the sample was 43.4%, with 7.7% reporting more than one form of ocular pathology. Of those with no eye disease, 3.7% had clinically significant depressive symptoms. This rate was 6.7% among cataract patients, 4.3% among those with glaucoma, and 10.5% for AMD. Generalized linear models adjusting for demographics, general health, treatment, and disability examined self-reported eye disease and visual function as correlates of depression and anxiety. Depressive symptoms were associated with cataract only, AMD, comorbid eye diseases and reduced low contrast visual acuity. Anxiety was significantly associated with self-reported cataract, and reduced low contrast visual acuity, motion sensitivity and contrast sensitivity. We found no evidence for elevated rates of depressive or anxiety symptoms associated with self-reported glaucoma. The results support previous findings of high rates of depression and anxiety in cataract and AMD, and in addition show that mood and anxiety are associated with objective measures of visual function independently of self-reported eye disease. The findings have implications for the assessment and treatment of mental health in the context of late-life visual impairment.

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Retina. 2013 Oct 4. [Epub ahead of print]

INCIDENCE AND CHARACTERISTICS OF NEOVASCULARIZATION IN FELLOW EYES OF JAPANESE PATIENTS WITH UNILATERAL RETINAL ANGIOMATOUS PROLIFERATION.

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PURPOSE: To describe the incidence and characteristics of neovascularization in fellow eyes of Japanese patients with unilateral retinal angiomatous proliferation (RAP).

METHODS: We retrospectively studied patients with unilateral RAP in one center between 2003 and 2010. The minimal follow-up time was 2 years. The prevalence rates of soft drusen and reticular pseudodrusen in the fellow eyes at the first visit were examined in color fundus photographs and optical coherence tomography images. Stepwise analysis was performed to identify a correlation between the incidence of RAP in the fellow eyes and age, gender, follow-up time, soft drusen, and reticular pseudodrusen.

RESULTS: Twenty eyes were included in this study. The mean follow-up time was 49 months (range, 24-108 months). At the first visit, soft drusen was seen in 19 eyes (95%) and reticular pseudodrusen in 11 eyes (55%). Neovascular age-related macular degeneration developed in 10 eyes, including RAP in 9 eyes (45%) and polypoidal choroidal vasculopathy in 1 eye (5%). Stepwise analysis showed that reticular pseudodrusen and longer follow-up time were correlated significantly ($P = 0.0384$ and $P = 0.0341$, respectively) with the incidence of RAP.

CONCLUSION: Bilateral RAP developed in almost half of the eyes initially diagnosed with unilateral RAP and the incidence increased with time. Reticular pseudodrusen is a risk factor for bilateral RAP.

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Genetics

Genome Med. 2013 Oct 11;5(9):84. [Epub ahead of print]

Genetic architecture of retinal and macular degenerative diseases: the promise and challenges of next-generation sequencing.

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Abstract: Inherited retinal degenerative diseases (RDDs) display wide variation in their mode of inheritance, underlying genetic defects, age of onset, and phenotypic severity. Molecular mechanisms have not been delineated for many retinal diseases, and treatment options are limited. In most instances, genotype-phenotype correlations have not been elucidated because of extensive clinical and genetic heterogeneity. Next-generation sequencing (NGS) methods, including exome, genome, transcriptome and epigenome sequencing, provide novel avenues towards achieving comprehensive understanding of the genetic architecture of RDDs. Whole-exome sequencing (WES) has already revealed several new RDD genes, whereas RNA-Seq and ChIP-Seq analyses are expected to uncover novel aspects of gene regulation and biological networks that are involved in retinal development, aging and disease. In this review, we focus on the genetic characterization of retinal and macular degeneration using NGS technology and discuss the basic framework for further investigations. We also examine the challenges of NGS application in clinical diagnosis and management.

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Clin Experiment Ophthalmol. 2013 Sep 30. doi: 10.1111/ceo.12235. [Epub ahead of print]

How genetic studies have advanced our understanding of Age-related Macular Degeneration and their impact on patient care: a review.

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Abstract: The last 10 years has seen an unprecedented explosion in our knowledge regarding the genomic basis of age related macular degeneration (AMD). This has come about through major advances in computing power, microfabrication of large numbers of molecular markers on chips and improved statistical algorithms for analysis. In tandem, it has become clear that AMD appears to be a multifactorial disease with influences from genetic and structural variants as well as epigenetic involvement. The combination of these factors with known environmental determinants indicates the highly complex nature of this disease but at the same time also offers insights into risk prediction and disease stratification through genotype profiling.

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Diet & lifestyle

Nutrition. 2013 November - December;29(11-12):1412-1417. doi: 10.1016/j.nut.2013.05.012.

Age-related macular degeneration: Effects of a short-term intervention with an oleaginous kale extract-a pilot study.

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OBJECTIVE: Age-related macular degeneration (AMD) is a multifactorial degenerative disease of the retina, which accounts for slowly progressive visual impairment in the elderly. An increased dietary intake of xanthophylls is suggested to be inversely related to the risk of macular disease.

METHODS: The present study was designed as a randomized, double-blind, placebo-controlled, parallel trial examining the influence of a short-term intervention with an oleaginous extract of *Brassica oleracea* var. *sabellica* L. (kale) on plasma xanthophyll concentrations and the optical density of the macular pigment xanthophylls (MPOD). Twenty patients with non-exudative AMD were recruited for a 10-wk study period (2-wk run-in, 4-wk intervention, 4-wk washout). All participants received 50 mL of a beverage containing either an oleaginous extract of kale (kale) or refined rapeseed oil (placebo). The verum product provides 10 mg lutein and 3 mg zeaxanthin per day.

RESULTS: The concentrations of the xanthophylls in plasma and the MPOD increased significantly in the kale group after 4 wk of intervention. The successive washout period resulted in a significant decline of the values in plasma and macula. The values at the end of the study were still significantly higher than the initial values. Nevertheless, the improvements did not persist over 4 wk of washout.

CONCLUSION: The distribution of the xanthophylls in the macula seems to be more dynamic than originally assumed.

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