Drug treatment


Effect of Adding Dexamethasone to Continued Ranibizumab Treatment in Patients With Persistent Diabetic Macular Edema: A DRCR Network Phase 2 Randomized Clinical Trial.


IMPORTANCE: Some eyes have persistent diabetic macular edema (DME) following anti-vascular endothelial growth factor (anti-VEGF) therapy for DME. Subsequently adding intravitreous corticosteroids to the treatment regimen might result in better outcomes than continued anti-VEGF therapy alone.

OBJECTIVE: To compare continued intravitreous ranibizumab alone with ranibizumab plus intravitreous dexamethasone implant in eyes with persistent DME.

DESIGN, SETTING, AND PARTICIPANTS: Phase 2 multicenter randomized clinical trial conducted at 40 US sites in 129 eyes from 116 adults with diabetes between February 2014 and December 2016. Eyes had persistent DME, with visual acuity of 20/32 to 20/320 after at least 3 anti-VEGF injections before a run-in phase, which included an additional 3 monthly 0.3-mg ranibizumab injections. Data analysis was according to intent to treat.

INTERVENTIONS: Following the run-in phase, study eyes that had persistent DME and were otherwise eligible were randomly assigned to receive 700 μg of dexamethasone (combination group, 65 eyes) or sham treatment (ranibizumab group, 64 eyes) in addition to continued 0.3-mg ranibizumab in both treatment arms as often as every 4 weeks based on a structured re-treatment protocol.

MAIN OUTCOMES AND MEASURES: The primary outcome was change in mean visual acuity letter score at 24 weeks as measured by the electronic Early Treatment Diabetic Retinopathy Study (E-ETDRS). The principal secondary outcome was change in mean central subfield thickness as measured with the use of optical coherence tomography.

RESULTS: Of the 116 randomized patients, median age was 65 years (interquartile range [IQR], 58-71 years); 50.9% were female and 60.3% were white. Mean (SD) improvement in visual acuity from randomization was 2.7 (9.8) letters in the combination group and 3.0 (7.1) letters in the ranibizumab group, with the adjusted treatment group difference (combination minus ranibizumab) of -0.5 letters (95% CI, -3.6 to 2.5; 2-sided P = .73). Mean (SD) change in central subfield thickness in the combination group was -110 (86) μm compared with -62 (97) μm for the ranibizumab group (adjusted difference, -52; 95% CI, -82 to -22; 2-sided P < .001). Nineteen eyes (29%) in the combination group experienced increased intraocular pressure or initiated treatment with antihypertensive eyedrops compared with 0 in the ranibizumab group (2-sided P < .001).
CONCLUSIONS AND RELEVANCE: Although its use is more likely to reduce retinal thickness and increase intraocular pressure, the addition of intravitreous dexamethasone to continued ranibizumab therapy does not improve visual acuity at 24 weeks more than continued ranibizumab therapy alone among eyes with persistent DME following anti-VEGF therapy.

PMID: 29127949


Geographic and Demographic Variation in Use of Ranibizumab Versus Bevacizumab for Neovascular Age-related Macular Degeneration in the United States.

Gower EW, Stein JD, Shekhawat NS, Mikkilineni S, Blachley TS, Pajewski NM.

PURPOSE: To examine demographic and geographic variation in the use of ranibizumab and bevacizumab for the treatment of neovascular age-related macular degeneration (AMD) among Medicare beneficiaries.

DESIGN: Retrospective cohort study.

METHODS: Using a 100% sample of Medicare claims data, we evaluated Medicare beneficiaries (N = 195,812) with an index claim for neovascular AMD between July 1, 2006, and June 30, 2009, to determine whether beneficiaries first received ranibizumab or bevacizumab following initial diagnosis.

RESULTS: The overall proportion of beneficiaries that first received ranibizumab for neovascular AMD was 35%, and varied significantly (0.9%-84.6%) across the 306 US hospital referral regions (median = 33%, interquartile range = 17%-49%). Based on hierarchical logistic regression models, the likelihood of receiving ranibizumab declined over time (adjusted odds ratio (aOR) comparing treatment in 2009 vs 2006 = 0.39, P < .001). After we controlled for year of treatment, black beneficiaries were 45% less likely to receive ranibizumab compared to non-blacks (P < .0001). Beneficiaries residing in urban areas (aOR vs isolated rural towns = 1.12, P < .001), in zip codes with higher median incomes, and in the New England and East South Central census regions (aOR vs Pacific census region = 5.57, P < .001; aOR = 3.58, P < .001, respectively) had increased odds of receiving ranibizumab.

CONCLUSIONS: The odds of receiving bevacizumab vs ranibizumab as initial therapy for neovascular AMD among US Medicare beneficiaries varied substantially across geographic and demographic groups. Relatively fewer patients received ranibizumab for initial neovascular AMD treatment in 2009 vs 2006. Future research should study the drivers of variation in utilization of these interventions, the extent this variation indicates differential access to these agents, and whether treatment choice impacts patient outcomes.

PMID: 29106914

Eye (Lond). 2017 Nov 3. [Epub ahead of print]

Efficacy and timing of adjunctive therapy in the anti-VEGF treatment regimen for macular oedema in retinal vein occlusion: 12-month real-world result.


Purpose: Various combination treatment regimens have been tried to improve the short-term efficacy of intravitreal monotherapy for the treatment of macular oedema (MO) secondary to retinal vein occlusion (RVO). Our study introduces the RandOL protocol (Ranibizumab and Ozurdex with Laser photocoagulation) of initial anti-VEGF therapy, controlling recurrent non-ischaemic MO with an intravitreal steroid and applying laser therapy to non-perfused retina. We describe our 12-month follow-up experience on timing for adjunctive therapy and real-world effectiveness and safety data.
Methods: A retrospective analysis was carried out on 66 consecutive treatment-naive RVO patients with MO who received our RandOL treatment regimen. Baseline visual acuity (VA) and central retinal thickness (CRT) were compared with 12-month result.

Results: At 12 months, 77% had significant VA improvement, 52% had ≥3-line improvement, and 15% were worse. Significant improvements in CRT were observed in 97% (baseline median CRT=531 μm (IQR 435-622) reduced to 245 μm (IQR 221-351, P<0.001) at 12 months); 76% achieved a dry fovea at 1 year. Mean number of total injections required was 5.5 (range 2-11) and 6% required ≥9 injections in 1 year. Although 70% received additional Ozurdex, 82% received ≥1 sessions of laser therapy. The BRVO subgroup achieved better VA and CRT improvement at 1 year, but small numbers limit definitive statistical conclusions.

Conclusions: Our real-world results using a combination treatment protocol for RVO-related MO achieved similar desirable anatomical and visual outcomes as with a single-agent therapy with less intravitreal re-treatment rates at first year. Randomised controlled studies are needed to evaluate the role of laser and the ideal timing of combination therapy.

PMID: 29099501


**Two-Year Outcome of Aflibercept in Patients with Pigment Epithelial Detachment due to Neovascular Age-Related Macular Degeneration (nAMD) Refractory to Ranibizumab.**

Tran THC, Dumas S, Coscas F.

**PURPOSE:** To evaluate the response of intravitreal aflibercept injection (IAI) in eyes with detachment of retinal pigment epithelium (DEP) secondary to nAMD refractory to monthly ranibizumab.

**PATIENTS AND METHODS:** This is a retrospective, multicenter study. All patients received 3 IAI then treated as needed every 4 weeks for 12 months. During the second year, the eyes were treated with a treat-and-extend regimen.

**RESULTS:** Forty-four eyes were included. Best-corrected visual acuity improved significantly after the loading phase (3.1 ± 6.4 letters) and at 6 months (2.8 ± 6.4 letters), but change was not significant at 1 year and 2 years. The height of the DEP was significantly decreased at 3 months and 6 months, but the difference did not reach statistical difference at 1 and 2 years. Rate of eyes with complete resolution of exudation was 59% after the loading phase and 34.3% at 2 years. Mean interval of anti-VEGF injection was extended from 31 ± 2.6 days to 61 ± 5 days after conversion.

**CONCLUSIONS:** Aflibercept intravitreal injection in patients with fibrovascular DEP due to nAMD who respond poorly to monthly ranibizumab led to short-term functional and anatomical improvement. Reduction of intravitreal injection frequency was obtained until 2 years of follow-up.

PMID: 29093970 PMCID: PMC5615945

**J Fr Ophtalmol. 2017 Nov 4. [Epub ahead of print]**

**Change in choroidal thickness after intravitreal injection for treatment of neovascular age-related macular degeneration: Ranibizumab versus aflibercept.**

Kaya F.

**PURPOSE:** To compare the changes in subfoveal choroidal thickness after intravitreal ranibizumab or
aflibercept injections for neovascular age-related macular degeneration (nAMD).

METHODS: In this retrospective study, 28 eyes with nAMD treated with 3 consecutive monthly injections of ranibizumab (IVR) and 24 eyes with nAMD treated with 3 consecutive monthly injections of aflibercept (IVA) between September 2012 and June 2016 were reviewed. The follow-up time was 6 months. Changes in two groups’ best-corrected visual acuity (BCVA) and subfoveal choroidal thickness by using enhanced depth imaging optical coherence tomography at 1st, 3rd and 6th months were recorded and compared.

RESULTS: Choroidal thickness decreased significantly in eyes treated with IVR (P=0.015, 0.01 and 0.01, respectively) or IVA (P=0.001, 0.001 and <0.001, respectively) at 1, 3 and 6 months examination but IVA treated eyes presented a significantly further reduction in choroidal thickness when compared with ranibizumab (P=0.03, 0.04 and 0.03, respectively). There was no significant difference between aflibercept and ranibizumab group when change in BCVA from baseline compared at 1, 3 and 6th months (P=0.54, 0.06 and 0.37, respectively). There was no correlation between change in choroidal thickness and the BCVA outcomes in either group.

CONCLUSIONS: Subfoveal choroidal thickness decreased significantly after both of IVR and IVA injections in patients with nAMD. In conclusion, intravitreal injections of ranibizumab or aflibercept affect not only neovascular lesion but also the underlying choroid.

PMID: 29113742


Effects of Aflibercept for Neovascular Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis of Observational Comparative Studies.

Zhang Y, Chioreso C, Schweizer ML, Abràmoff MD.

PURPOSES: To compare the effects of aflibercept and other anti-vascular endothelial growth factor (anti-VEGF) medications on both functional and anatomical outcomes for treatment-naïve neovascular age-related macular degeneration (nAMD) in the real world.

METHODS: A systematic review and meta-analysis of observational comparative studies.

RESULTS: A total of 18 studies remained after literature selection and quality assessment of 1697 studies. The most common aflibercept treatment regimen was three monthly injections followed by pro re nata (PRN). Aflibercept and ranibizumab had similar effects in 2-year treatment. At 3, 6, 12, and 24 months, the differences in the logarithm of minimum angle of resolution (logMAR) decrease in aflibercept and ranibizumab groups were 0.00 (95% confidence interval [CI]: -0.03 to 0.02); 0.01 (95% CI: -0.02 to 0.05); -0.03 (95% CI: -0.07 to 0.01); and -0.06 (95% CI: -0.30 to 0.17), respectively; the differences in decrease of central retinal thickness (CRT) were 3.25 μm (95% CI: -15.03 to 21.53); 7.89 μm (95% CI: -31.91 to 47.69); 2.89 μm (95% CI: -18.33 to 24.11); and -2.42 μm (95% CI: -77.87 to 73.03), respectively. However, aflibercept was significantly more effective in patients with initial reduced visual acuity (logMAR >0.6 or <55 letters; P = 0.001). In the first year, treatment frequency was not significantly different for aflibercept and ranibizumab, but aflibercept required fewer injections than ranibizumab with PRN regimen (mean -0.90; 95% CI: -1.80 to 0.00).

CONCLUSIONS: Aflibercept has comparable effects with ranibizumab for treatment-naïve nAMD in the real world, and may be more effective for patients with initial lower visual acuity.

PMID: 29094167 PMCID: PMC5667400
**Biomed Pharmacother. 2017 Oct 26;97:293-299. [Epub ahead of print]**

**Subthreshold diode micropulse laser versus conventional laser photocoagulation monotherapy or combined with anti-VEGF therapy for diabetic macular edema: A Bayesian network meta-analysis.**

Wu Y, Ai P, Ai Z, Xu G.

AIMS: To assess the effects of laser photocoagulation as monotherapy or adjuvant therapy for the treatment of DME.

METHODS: A search of the Cochrane Library, Pubmed, Embase, and the clinicaltrial.gov registry for randomized clinical trials comparing any two treatments of interest (SDMLP monotherapy, CLP monotherapy, CLP plus anti-VEGF therapy) was performed. Data were collected and pooled by Bayesian network meta-analyses which accounts for both direct and indirect comparisons. The primary outcome was the mean change in best-corrected visual acuity measured by the logarithm of the minimal angle of resolution units. The secondary outcome was the mean change in central macular thickness from baseline to month 12.

RESULTS: Ranibizumab therapy combined with CLP was more effective than SDMLP alone (MD, -0.396; 95% CrI, -0.746 to -0.062) and CLP alone (MD, -0.621; 95% CrI, -0.823 to -0.431). There was no apparent difference of efficacy between SDMLP alone and CLP alone (MD, -0.225; 95% CrI, -0.501 to 0.058). There was no apparent difference of efficacy between SDMLP alone and Bevacizumab therapy combined with CLP (MD, -0.003, 95% CrI, -0.815 to 0.805).

CONCLUSION: There was no apparent difference on improving vision between SDMLP monotherapy and CLP monotherapy. The most effective treatment in the network was ranibizumab therapy combined with CLP followed by SDMLP monotherapy, Bevacizumab therapy combined with CLP, and CLP monotherapy in rank order.

PMID: 29091878


**Detailed analysis of retinal morphology in patients with diabetic macular edema (DME) randomized to ranibizumab or triamcinolone treatment.**


PURPOSE: Our purpose was to compare the impact in diabetic macula edema (DME) of two intravitreal drugs (0.5 mg ranibizumab vs. 8 mg triamcinolone) on changes in retinal morphology in spectral-domain optical coherence tomography (SD OCT) images, color fundus photography (CF) and fluorescein angiography (FA) images during a 1-year follow-up.

METHODS: Post hoc analysis was conducted of morphologic characteristics in OCT, FA and CF images of eyes with a center involving DME that were included in a prospective double-masked randomized trial. Eligible patients were divided at random into two groups receiving either pro re nata treatment with 0.5 mg ranibizumab or 8 mg triamcinolone after a fixed loading dose. OCT and CF images were acquired at monthly visits and FA images every three months.

RESULTS: Twenty-five eyes of 25 patients (ranibizumab: n = 10; triamcinolone: n = 15) were included in this study. Patients treated with ranibizumab showed better visual acuity results after 12 months than patients receiving triamcinolone (p = 0.015) although edema reduction was similar (p = 0.426) in both groups. The initial effect on macular edema shedding after a single ranibizumab injection could be amplified with the following two injections of the loading dose. After a single injection of triamcinolone the beneficial initial effect on the macula edema faded within 3 months. Subretinal fluid and INL cystoid spaces diminished early in the course of treatment while fluid accumulation in the ONL seemed to be more
persistent in both treatment arms. In FA, the area of leakage diminished significantly in both treatment arms. After repeated injections the morphologic OCT and FA characteristics of the treatment arms converged.

CONCLUSIONS: Despite the higher dosage of triamcinolone, both therapies were safe and effective for treating diabetic macular edema. Fluid accumulation in the INL and subretinal space was more responsive to therapy than fluid accumulation in the ONL.

PMID: 29080915

The RELATION study: efficacy and safety of ranibizumab combined with laser photocoagulation treatment versus laser monotherapy in NPDR and PDR patients with diabetic macular oedema.
PURPOSE: To assess efficacy and safety of intravitreal ranibizumab 0.5 mg plus laser (COMBI) versus laser monotherapy (LASER) in patients with visual impairment due to diabetic macular oedema (DME) in either nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) and to analyse the relevance of inner versus outer retinal thickness.
METHODS: In this double-masked, multicentre phase IIIb study, patients (N = 128) were randomized (2:1) to receive COMBI (n = 85) versus LASER (n = 43). Patients received four initial monthly injections of ranibizumab 0.5 mg (COMBI) or sham (LASER) followed by pro re nata (PRN) injections. In both groups, patients received laser at baseline and additional laser at 3 monthly intervals, as needed. The study was started in 2010 and was prematurely terminated due to approval of ranibizumab for DME.
RESULTS: The least squares (LS) mean change in mean best-corrected visual acuity (BCVA) from baseline to month 12 was higher in the COMBI (6.5) versus LASER (2.3) group (LS mean difference: 4.2 [95% CI 0.9; 7.4] letters, p = 0.01, primary end-point). There was also a tendency in the same direction for the subgroup of 26 patients with PDR (LS mean difference 14.7, p = 0.11). Mean central retinal thickness decreased by 107.3 μm in the COMBI group and by 80.3 μm in the LASER group from baseline to month 12 (p = 0.28). Ranibizumab was well tolerated.
CONCLUSION: This study showed that ranibizumab plus laser is a valuable treatment option for the management of DME. Patients with DME in PDR might also benefit from combined therapy compared to laser alone.
PMID: 29090846

OCT-based deep learning algorithm for the evaluation of treatment indication with anti-vascular endothelial growth factor medications.
Prahs P, Radeck V, Mayer C, Cvetkov Y, Cvetkova N, Helbig H, Märker D.
PURPOSE: Intravitreal injections with anti-vascular endothelial growth factor (anti-VEGF) medications have become the standard of care for their respective indications. Optical coherence tomography (OCT) scans of the central retina provide detailed anatomical data and are widely used by clinicians in the decision-making process of anti-VEGF indication. In recent years, significant progress has been made in artificial intelligence and computer vision research. We trained a deep convolutional artificial neural network to predict treatment indication based on central retinal OCT scans without human intervention.
METHOD: A total of 183,402 retinal OCT B-scans acquired between 2008 and 2016 were exported from the institutional image archive of a university hospital. OCT images were cross-referenced with the electronic institutional intravitreal injection records. OCT images with a following intravitreal injection during the first 21 days after image acquisition were assigned into the 'injection' group, while the same amount of random OCT images without intravitreal injections was labeled as 'no injection'. After image preprocessing, OCT images were split in a 9:1 ratio to training and test datasets. We trained a GoogLeNet inception deep convolutional neural network and assessed its performance on the validation dataset. We calculated prediction accuracy, sensitivity, specificity, and receiver operating characteristics.

RESULTS: The deep convolutional neural network was successfully trained on the extracted clinical data. The trained neural network classifier reached a prediction accuracy of 95.5% on the images in the validation dataset. For single retinal B-scans in the validation dataset, a sensitivity of 90.1% and a specificity of 96.2% were achieved. The area under the receiver operating characteristic curve was 0.968 on a per B-scan image basis, and 0.988 by averaging over six B-scans per examination on the validation dataset.

CONCLUSION: Deep artificial neural networks show impressive performance on classification of retinal OCT scans. After training on historical clinical data, machine learning methods can offer the clinician support in the decision-making process. Care should be taken not to mistake neural network output as treatment recommendation and to ensure a final thorough evaluation by the treating physician.

PMID: 29127485


Radiation retinopathy treated successfully with aflibercept.

Pooprasert P, Young-Zvandasara T, Al-Bermani A.

Abstract: Aflibercept (aflibercept) is a novel anti-vascular endothelial growth factor drug indicated for wet age-related macular degeneration and macular oedema secondary to retinal vein occlusion and diabetic macular oedema. While only newly introduced on the market, it is growing in popularity and over 5.5 million doses have been prescribed worldwide. Due to its versatile mechanism, it is indicated for numerous eye pathologies, and in particular, has been adapted to treat various types of retinopathy. To our knowledge, this is the first case report of solely using aflibercept to treat cystoid macular oedema in radiation retinopathy.

PMID: 29127134


Evolving multidimensional pharmacological approaches to CNV therapy in AMD.

Ehrenberg M, Benny O.

PURPOSE: The leading cause of severe visual loss worldwide is age-related macular degeneration. Although anti-Vascular Endothelial Growth Factor agents have significantly led to the initial pharmacologic reversal of vision loss in many cases of exudative macular degeneration, there still has been recurrence of choroidal neovascularization, and/or the onset of chorioretinal atrophy with fibrosis.

MATERIALS AND METHODS: In this review we discuss the status of anti- Vascular Endothelial Growth Factor in age-related macular degeneration and describe different studies focused on new potential therapeutic targets beyond anti- Vascular Endothelial Growth Factor.

RESULTS: Further investigations have elicited that Vascular Endothelial Growth Factor is only one of many
angiogenic, and pro-inflammatory factors that bring about the growth and leakage of active choroidal neovascularization. Various new multifaceted strategies, including inhibitors to down-stream targets of endothelial cell division, such as TNP-470, may lead to a more permanent inactivation of choroidal neovascularization.

CONCLUSIONS: Based on the accumulated results in the treatment of age-related macular degeneration, it is hoped that the appropriate combination of anti-Vascular Endothelial Growth Factor agents with longer-acting and multidimensional pharmaceuticals, such as Methionine Aminopeptidase-2 inhibitors, will more effectively control choroidal neovascularization, prevent atrophy and fibrosis, and reduce the burden of frequent intraocular injections in age-related macular degeneration.

PMID: 29111834


Aflibercept in diabetic macular edema refractory to previous bevacizumab: outcomes and predictors of success.


PURPOSE: To evaluate functional and anatomical outcomes after aflibercept in patients with diabetic macular edema (DME) with poor response to bevacizumab.

METHODS: We retrospectively reviewed patients with DME recalcitrant to bevacizumab who were switched to aflibercept between January and December 2015. All patients had a minimal follow-up of three months before the conversion and underwent at least three injections of bevacizumab. Functional outcome consisted in best corrected visual acuity (VA). Anatomical outcomes were demonstrated through central macular thickness (CMT) measured by optical coherence tomography.

RESULTS: Forty-nine eyes of 34 subjects were reviewed. Mean VA improved from 0.55 ± 0.32 logMAR to 0.46 ± 0.33 logMAR (p = 0.038). Mean CMT decreased from 473 ± 146 μm to 349 ± 85 μm (p < 0.001). Twelve eyes (24%) demonstrated absence of macular edema after aflibercept. Previous bevacizumab exposure did not correlate with different outcomes. The variation of VA in response to aflibercept was significantly superior in the group with poorer VA before the switch (mean variation of -0.097 ± 0.21 logMAR) when compared to eyes with VA < 0.4 logMAR (mean variation of +0.019 ± 0.090 logMAR; p = 0.036). The same scenario was verified for anatomical outcomes as eyes with poor vision before the switch (≥0.4 logMAR) achieved superior reduction in CMT in response to aflibercept (mean CMT variation of -157 ± 171 μm versus -49.5 ± 39.9 μm; p = 0.01). Pre-switch CMT was a predictor of CMT reduction after switching (B = -0.945; confidence interval 95% -1.1; -0.76; p < 0.001).

CONCLUSIONS: Conversion to aflibercept for persistent DME resulted in functional and anatomical improvements and these outcomes were not influenced by previous bevacizumab exposure. Pre-switch CMT was a predictor of anatomical changes after aflibercept.

PMID: 29082448


The Finnish national guideline for diagnosis, treatment and follow-up of patients with wet age-related macular degeneration.

Tuuminen R, Tuulonen A, Kaarniranta K; Expert Panel co-ordinated by the Finnish Medical Society Duodecim, the Finnish Ophthalmological Society and all Departments of Ophthalmology of the University
and Central Hospitals in Finland.

PMID: 29110437

Inadvertent intralenticular dexamethasone implant: 1-year follow-up and management.
Caglar C.

Abstract: We report the case of a 72-year-old female who developed macular edema (ME) due to hemicentral retinal vein occlusion in her right eye. A dexamethasone implant was inadvertently injected into the crystalline lens. The patient was followed without repositioning of the dexamethasone implant during the 12 months. Besides, the posterior subcapsular cataract and ME had progressed significantly; hence, cataract extraction and intravitreal ranibizumab injection were performed in the same session. A three-piece intraocular lens was implanted in the sulcus with optic captured, and then intravitreal ranibizumab injection was performed. The patient had an uncomplicated postoperative recovery. At 2 months, best-corrected visual acuity was 0.7, and the macula was dry.

PMID: 29118503 PMCID: PMC5657170

Commentary: NHS patients should have a choice of drug for wet age-related macular degeneration, despite pressure from pharma.
Hambleton D.
PMID: 29089330

Are the odds shifting against pharma in the fight for cheaper treatment for macular degeneration?
Cohen D.
PMID: 29089312

Age-related macular degeneration foils drugmakers.
Dolgin E.
PMID: 29121027

Other treatment & diagnosis

Ophthalmology. 2017 Nov 2. [Epub ahead of print]
Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT:
Classification of Atrophy Report 3.


PURPOSE: To develop consensus terminology and criteria for defining atrophy based on OCT findings in the setting of age-related macular degeneration (AMD).

DESIGN: Consensus meeting.

PARTICIPANTS: Panel of retina specialists, image reading center experts, retinal histologists, and optics engineers.

METHODS: As part of the Classification of Atrophy Meetings (CAM) program, an international group of experts surveyed the existing literature, performed a masked analysis of longitudinal multimodal imaging for a series of eyes with AMD, and reviewed the results of this analysis to define areas of agreement and disagreement. Through consensus discussions at 3 meetings over 12 months, a classification system based on OCT was proposed for atrophy secondary to AMD. Specific criteria were defined to establish the presence of atrophy.

MAIN OUTCOME MEASURES: A consensus classification system for atrophy and OCT-based criteria to identify atrophy.

RESULTS: OCT was proposed as the reference standard or base imaging method to diagnose and stage atrophy. Other methods, including fundus autofluorescence, near-infrared reflectance, and color imaging, provided complementary and confirmatory information. Recognizing that photoreceptor atrophy can occur without retinal pigment epithelium (RPE) atrophy and that atrophy can undergo an evolution of different stages, 4 terms and histologic candidates were proposed: complete RPE and outer retinal atrophy (cRORA), incomplete RPE and outer retinal atrophy, complete outer retinal atrophy, and incomplete outer retinal atrophy. Specific OCT criteria to diagnose cRORA were proposed: (1) a region of hypertransmission of at least 250 μm in diameter, (2) a zone of attenuation or disruption of the RPE of at least 250 μm in diameter, (3) evidence of overlying photoreceptor degeneration, and (4) absence of scrolled RPE or other signs of an RPE tear.

CONCLUSIONS: A classification system and criteria for OCT-defined atrophy in the setting of AMD has been proposed based on an international consensus. This classification is a more complete representation of changes that occur in AMD than can be detected using color fundus photography alone. Longitudinal information is required to validate the implied risk of vision loss associated with these terms. This system will enable such future studies to be undertaken using consistent definitions.

PMID: 29103793

Retina. 2017 Nov 7. [Epub ahead of print]

REDUCED GANGLION CELL VOLUME ON OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH GEOGRAPHIC ATROPHY.

Ramkumar HL, Nguyen B, Bartsch DU, Saunders LJ, Muftuoglu IK, You Q, Freeman WR.

PURPOSE: Geographic atrophy (GA) is the sequelae of macular degeneration. Automated inner retinal analysis using optical coherence tomography is flawed because segmentation software is calibrated for normal eyes. The purpose of this study is to determine whether ganglion cell layer (GCL) volume is reduced in GA using manual analysis.
METHODS: Nineteen eyes with subfoveal GA and 22 controls were selected for morphometric analyses. Heidelberg scanning laser ophthalmoscope optical coherence tomography images of the optic nerve and macula were obtained, and the Viewing Module was used to manually calibrate retinal layer segmentation. Retinal layer volumes in the central 3-mm and surrounding 6-mm diameter were measured. Linear mixed models were used for statistics.

RESULTS: The GCL volume in the central 3 mm of the macula is less (P = 0.003), and the retinal nerve fiber layer volume is more (P = 0.02) in patients with GA when compared with controls. Ganglion cell layer volume positively correlated with outer nuclear layer volume (P = 0.020).

CONCLUSION: The patients with geographic atrophy have a small significant loss of the GCL. Ganglion cell death may precede axonal loss, and increased macular retinal nerve fiber layer volumes are not indicative of GCL volume. Residual ganglion cell stimulation by interneurons may enable vision in patients with GA.

PMID: 29117065


Computer-aided diagnosis based on enhancement of degraded fundus photographs.


PURPOSE: Retinal imaging is an important and effective tool for detecting retinal diseases. However, degraded images caused by the aberrations of the eye can disguise lesions, so that a diseased eye can be mistakenly diagnosed as normal. In this work, we propose a new image enhancement method to improve the quality of degraded images.

METHODS: A new method is used to enhance degraded-quality fundus images. In this method, the image is converted from the input RGB colour space to LAB colour space and then each normalized component is enhanced using contrast-limited adaptive histogram equalization. Human visual system (HVS)-based fundus image quality assessment, combined with diagnosis by experts, is used to evaluate the enhancement.

RESULTS: The study included 191 degraded-quality fundus photographs of 143 subjects with optic media opacity. Objective quality assessment of image enhancement (range: 0-1) indicated that our method improved colour retinal image quality from an average of 0.0773 (variance 0.0801) to an average of 0.3973 (variance 0.0756). Following enhancement, area under curves (AUC) were 0.996 for the glaucoma classifier, 0.989 for the diabetic retinopathy (DR) classifier, 0.975 for the age-related macular degeneration (AMD) classifier and 0.979 for the other retinal diseases classifier.

CONCLUSION: The relatively simple method for enhancing degraded-quality fundus images achieves superior image enhancement, as demonstrated in a qualitative HVS-based image quality assessment. This retinal image enhancement may, therefore, be employed to assist ophthalmologists in more efficient screening of retinal diseases and the development of computer-aided diagnosis.

PMID: 29090844


Challenges and advantages in wide-field optical coherence tomography angiography imaging of the human retinal and choroidal vasculature at 1.7-MHz A-scan rate.

Poddar R, Migacz JV, Schwartz DM, Werner JS, Gorczynska I.
Abstract: We present noninvasive, three-dimensional, depth-resolved imaging of human retinal and choroidal blood circulation with a swept-source optical coherence tomography (OCT) system at 1065-nm center wavelength. Motion contrast OCT imaging was performed with the phase-variance OCT angiography method. A Fourier-domain mode-locked light source was used to enable an imaging rate of 1.7 MHz. We experimentally demonstrate the challenges and advantages of wide-field OCT angiography (OCTA). In the discussion, we consider acquisition time, scanning area, scanning density, and their influence on visualization of selected features of the retinal and choroidal vascular networks. The OCTA imaging was performed with a field of view of 16 deg (5 mm×5 mm) and 30 deg (9 mm×9 mm). Data were presented in en face projections generated from single volumes and en face projection mosaics generated from up to 4 datasets. OCTA imaging at 1.7 MHz A-scan rate was compared with results obtained from a commercial OCTA instrument and with conventional ophthalmic diagnostic methods: fundus photography, fluorescein, and indocyanine green angiography. Comparison of images obtained from all methods is demonstrated using the same eye of a healthy volunteer. For example, imaging of retinal pathology is presented in three cases of advanced age-related macular degeneration.

PMID: 29090534


Advanced quantitative analysis of the sub-retinal pigment epithelial space in recurrent neovascular age-related macular degeneration.


Abstract: To quantitatively evaluate changes in the sub-retinal pigment epithelial (RPE) space and determine the association with recurrent neovascular age-related macular degeneration (AMD). Twenty-two eyes treated with intravitreal aflibercept for treatment-naive neovascular AMD were studied retrospectively. The sub-RPE area, volume, and central retinal thickness (CRT) were evaluated 1 and 2 months after the loading phase using spectral-domain optical coherence tomography. Recurrence was defined as newly detected neovascular activity during the 6 months after the loading phase. In eyes with recurrent AMD, the sub-RPE area increased significantly (P = 0.036) from 1 to 2 months after the loading phase and the sub-RPE volume increased marginally (P = 0.06). Subgroup analysis showed significant (P = 0.008 and P = 0.016, respectively) increases in the sub-RPE area and volume in typical AMD. In eyes with no recurrence, no significant changes occurred in the two parameters. No significant CRT changes occurred in eyes with or without a recurrence. A quantitative analysis demonstrated an increased likelihood of the sub-RPE space shortly after the loading phase in eyes with recurrent AMD; no changes occurred in eyes without a recurrence. These early changes in the sub-RPE space could indicate disease activity and are valuable for predicting recurrences of neovascular AMD.

PMID: 29095879


The Impact of Epiretinal Membrane in Neovascular Age-Related Macular Degeneration Treatment: A Spectral-Domain Optical Coherence Tomography Study.

Chatziralli I, Stavrakas P, Theodossiadis G, Ananikas K, Dimitriou E, Theodossiadis P.

PURPOSE: The purpose of this prospective study was to evaluate the impact of epiretinal membrane (ERM) on anatomical and functional results in patients with wet age-related macular degeneration (AMD) treated with intravitreal anti-vascular endothelial growth (anti-VEGF) injections.

METHODS: Participants in the study were 48 patients with either wet AMD alone (AMD group, n = 27) or AMD and ERM (AMD/ERM group, n = 21). All patients received intravitreal anti-VEGF injections (three
monthly injections and PRN thereafter) and were followed up for at least 12 months. All participants had best-corrected visual acuity (BCVA) measurement and spectral domain-optical coherence tomography (SD-OCT) at each visit, while fluorescein angiography was performed at baseline and then at the discretion of the physician.

RESULTS: There was a statistically significant improvement in BCVA at month 12 compared to baseline in each group (p < 0.001 for both groups), while the two groups did not differ significantly regarding BCVA at the end of the follow-up (p = 0.056). Additionally, there was a statistically significant reduction in CRT in both groups at month 12 (p < 0.001 for AMD group and p = 0.004 for AMD/ERM group) with no statistically significant difference between the groups (p = 0.183). Patients in the AMD group had a lower percentage of subretinal fluid (25.9%) than patients in the AMD/ERM group (52.4%) at the end of the follow-up, while ellipsoid zone disruption was found to be more profound in the AMD/ERM group (38.1%) than in the AMD group (18.5%). Patients in the AMD/ERM group needed more injections (7.1 ± 2.0 injections) than patients in the AMD group (4.8 ± 1.7 injections).

CONCLUSIONS: Patients in the AMD/ERM group had a higher percentage of subretinal and intraretinal fluid and ellipsoid zone interruption during the follow-up period. Anti-VEGF treatment appeared to have a beneficial effect in both groups, although the AMD/ERM group needed more injections compared to the AMD group.

PMID: 29115893

Retina. 2017 Oct 30. [Epub ahead of print]

MINIMAL OPTICAL COHERENCE TOMOGRAPHY B-SCAN DENSITY FOR RELIABLE DETECTION OF INTRARETINAL AND SUBRETINAL FLUID IN MACULAR DISEASES.

Fang PP, Domdei N, Herrmann P, Schmitz-Valckenberg S, Holz FG, Harmening WM, Krohne TU.

PURPOSE: To determine the minimal optical coherence tomography B-scan density for reliable detection of intraretinal and subretinal fluid.

METHODS: Spectral domain optical coherence tomography raster scanning (Spectralis; Heidelberg Engineering, Heidelberg, Germany) using a scan field of 20° × 20° of 97 B-scans with an interscan distance (ISD) of 60 μm was performed in 150 eyes of 150 consecutive patients at monitoring visits for intravitreal anti-vascular endothelial growth factor therapy. Using custom software, every other B-scan was repeatedly deleted to generate additional data sets with an ISD of 120 μm (49 B-scans), 240 μm (25 B-scans), and 480 μm (13 B-scans). Two independent reviewers evaluated the data sets for the presence of cystoid spaces of intraretinal fluid and subretinal fluid.

RESULTS: Treatment diagnoses were neovascular age-related macular degeneration (68.0%), macular edema secondary to retinal vein occlusion (20.7%), diabetic macular edema (10.7%), and other retinal diseases (4.0%). Using the source data sets with an ISD of 60 μm, intraretinal fluid was detected in 56.0%, subretinal fluid in 19.3%, and either/both in 68.7%. Compared with these results, the sensitivity of detection of intraretinal fluid and/or subretinal fluid using an ISD of 120 μm, 240 μm, and 480 μm was 99.0% (95% confidence interval, 94.7-100.0; P = 0.5), 97.1% (91.7-99.4; P = 0.1), and 87.4% (79.4-93.1; P = 0.0001), respectively.

CONCLUSION: An increase of ISD up to 240 μm does not significantly impair the detection of treatment-relevant exudative retinal changes in monitoring during intravitreal therapy of macular diseases. These findings are relevant for the choice of optical coherence tomography B-scan density in both routine clinical care and interventional clinical studies.

PMID: 29095359
Ophthalmologe. 2017 Nov 6. [Epub ahead of print]

[Who visits an ophthalmologist and how often? Results of the German nationwide adult health survey (DEGS1)]. [Article in German]

Schuster AK, Wolfram C, Bertram B, Pfeiffer N.

BACKGROUND: The prevalence of eye diseases increases in the second half of life, especially cataract, glaucoma and age-related macular degeneration. In this study we examined the influencing factors for visiting an ophthalmologist in the last 12 months.

METHODS: Visits to an ophthalmologist's practice in the last 12 months and the frequency were surveyed in the German nationwide adult health survey wave 1 (DEGS1) study (baseline examination from 2008 to 2011, N = 7987, 52.6% women, age 18-79 years). Data on utilization were processed by taking the complex study design into consideration. Multivariable logistic regression analysis was used to determine associated factors including age, sex, socioeconomic status, place of residence, type of health insurance (e.g. statutory or private) and diabetes.

RESULTS: Between the ages of 18 and 79 years, 29.3% of survey participants in Germany visited an ophthalmologist in the last year, while after the age of 60 years this was only 50.4%. Multivariable logistic regression analysis showed an association with female sex (odds ratio OR = 1.51, p < 0.001), older age, type of health insurance (private vs. statutory: OR = 0.77, p = 0.006) and diabetes (OR = 3.84, p < 0.001), but no association with socioeconomic status (p = 0.29) or place of residence (p = 0.06).

CONCLUSION: Approximately one third of the German population visit an ophthalmologist at least once a year. Especially diabetics showed a high utilization of ophthalmological consultations, which could be based on the interdisciplinary guidelines for early detection of diabetic eye complications.

PMID: 29110124


Multi-categorical deep learning neural network to classify retinal images: A pilot study employing small database.

Choi JY, Yoo TK, Seo JG, Kwak J, Um TT, Rim TH.

Abstract: Deep learning emerges as a powerful tool for analyzing medical images. Retinal disease detection by using computer-aided diagnosis from fundus image has emerged as a new method. We applied deep learning convolutional neural network by using MatConvNet for an automated detection of multiple retinal diseases with fundus photographs involved in STructured Analysis of the REtina (STARE) database. Dataset was built by expanding data on 10 categories, including normal retina and nine retinal diseases. The optimal outcomes were acquired by using a random forest transfer learning based on VGG-19 architecture. The classification results depended greatly on the number of categories. As the number of categories increased, the performance of deep learning models was diminished. When all 10 categories were included, we obtained results with an accuracy of 30.5%, relative classifier information (RCI) of 0.052, and Cohen's kappa of 0.224. Considering three integrated normal, background diabetic retinopathy, and dry age-related macular degeneration, the multi-categorical classifier showed accuracy of 72.8%, 0.283 RCI, and 0.577 kappa. In addition, several ensemble classifiers enhanced the multi-categorical classification performance. The transfer learning incorporated with ensemble classifier of clustering and voting approach presented the best performance with accuracy of 36.7%, 0.053 RCI, and 0.225 kappa in the 10 retinal diseases classification problem. First, due to the small size of datasets, the deep learning techniques in this study were ineffective to be applied in clinics where numerous patients suffering from various types of retinal disorders visit for diagnosis and treatment. Second, we found that the transfer learning incorporated with ensemble classifiers can improve the classification performance in order to detect multi-categorical
retinal diseases. Further studies should confirm the effectiveness of algorithms with large datasets obtained from hospitals.

PMID: 29095872


In Vivo Multimodal Imaging of Drusenoid Lesions in Rhesus Macaques.


Abstract: Nonhuman primates are the only mammals to possess a true macula similar to humans, and spontaneously develop drusenoid lesions which are hallmarks of age-related macular degeneration (AMD). Prior studies demonstrated similarities between human and nonhuman primate drusen based on clinical appearance and histopathology. Here, we employed fundus photography, spectral domain optical coherence tomography (SD-OCT), fundus autofluorescence (FAF), and infrared reflectance (IR) to characterize drusenoid lesions in aged rhesus macaques. Of 65 animals evaluated, we identified lesions in 20 animals (30.7%). Using the Age-Related Eye Disease Study 2 (AREDS2) grading system and multimodal imaging, we identified two distinct drusen phenotypes - 1) soft drusen that are larger and appear as hyperreflective deposits between the retinal pigment epithelium (RPE) and Bruch's membrane on SD-OCT, and 2) hard, punctate lesions that are smaller and undetectable on SD-OCT. Both exhibit variable FAF intensities and are poorly visualized on IR. Eyes with drusen exhibited a slightly thicker RPE compared with control eyes (+3.4 μm, P=0.012). Genetic polymorphisms associated with drusenoid lesions in rhesus monkeys in ARMS2 and HTRA1 were similar in frequency between the two phenotypes. These results refine our understanding of drusen development, and provide insight into the absence of advanced AMD in nonhuman primates.

PMID: 29101353


Use of a Neural Net to Model the Impact of Optical Coherence Tomography Abnormalities on Vision in Age-Related Macular Degeneration.

Aslam TM, Zaki HR, Mahmood S, Ali ZC, Ahmad NA, Thorell MR, Balaskas K.

PURPOSE: To develop a neural network for the estimation of visual acuity from optical coherence tomography (OCT) images of patients with neovascular age related macular degeneration and to demonstrate its use to model the impact of specific controlled OCT changes on vision.

DESIGN: Artificial Intelligence (neural network) study.

METHODS: We assessed 1400 OCT scans of patients with neovascular age related macular degeneration (AMD). 15 physical features for each eligible OCT as well as patient age were used as input data and corresponding recorded visual acuity as the target data to train, validate and test a supervised neural network. We then applied this network to model the impact on acuity of defined OCT changes in subretinal fluid, subretinal hyperreflective material and loss of external limiting membrane integrity.

RESULTS: 1,210 eligible OCT scans were analysed resulting in 1210 data points which were each 16 dimensional. A ten layer feed-forward neural network with one hidden layer of 10 neurons was trained to predict acuity and demonstrated a root mean square error of 8.2 letters for predicted compared to actual visual acuity and a mean regression coefficient of 0.85. A virtual model using this network demonstrated the relationship of visual acuity to specific, programmed changes in OCT characteristics. When external limiting membrane (ELM) is intact, there is a shallow decline in acuity with increasing sub-retinal fluid but a much
steeper decline with equivalent increasing sub-retinal hyperreflective material. When ELM is not intact, all visual acuities are reduced. Increasing subretinal hyperreflective material or subretinal fluid in this circumstance reduces vision further still, but with a smaller gradient than when ELM is intact.

CONCLUSIONS: The supervised machine learning neural network developed is able to generate an estimated visual acuity value from OCT images in a population of patients with AMD. These findings should be of clinical and research interest in macular degeneration, for example in estimating visual prognosis or highlighting the importance of developing treatments targeting more visually destructive pathologies.

PMID: 29101008

Ophthalmology. 2017 Oct 27. [Epub ahead of print]

The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration.


Abstract: Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) that leads to progressive and irreversible loss of visual function. Geographic atrophy is defined by the presence of sharply demarcated atrophic lesions of the outer retina, resulting from loss of photoreceptors, retinal pigment epithelium (RPE), and underlying choriocapillaris. These lesions typically appear first in the perifoveal macula, initially sparing the foveal center, and over time often expand and coalesce to include the fovea. Although the kinetics of GA progression are highly variable among individual patients, a growing body of evidence suggests that specific characteristics may be important in predicting disease progression and outcomes. This review synthesizes current understanding of GA progression in AMD and the factors known or postulated to be relevant to GA lesion enlargement, including both affected and fellow eye characteristics. In addition, the roles of genetic, environmental, and demographic factors in GA lesion enlargement are discussed. Overall, GA progression rates reported in the literature for total study populations range from 0.53 to 2.6 mm2/year (median, ∼1.78 mm2/year), assessed primarily by color fundus photography or fundus autofluorescence (FAF) imaging. Several factors that could inform an individual's disease prognosis have been replicated in multiple cohorts: baseline lesion size, lesion location, multifocality, FAF patterns, and fellow eye status. Because best-corrected visual acuity does not correspond directly to GA lesion enlargement due to possible foveal sparing, alternative assessments are being explored to capture the relationship between anatomic progression and visual function decline, including microperimetry, low-luminance visual acuity, reading speed assessments, and patient-reported outcomes. Understanding GA progression and its individual variability is critical in the design of clinical studies, in the interpretation and application of clinical trial results, and for counseling patients on how disease progression may affect their individual prognosis.

PMID: 29110945


A biolayer interferometry-based enzyme-linked aptamer sorbent assay for real-time and highly sensitive detection of PDGF-BB.

Gao S, Zheng X, Wu J.

Abstract: Accurate, fast and sensitive detection of disease-specific protein biomarkers, especially in blood, urine, or other bodily fluids, is an important approach to achieve early disease diagnosis. Platelet-derived growth factor-BB (PDGF-BB), a widely used biomarker, is involved in a substantial number of serious diseases, such as hepatic fibrosis, atherosclerosis, age-related macular degeneration and diabetic eye disease and is often over-expressed in human malignant tumors. Therefore, the development of sensitive and specific detection methods for PDGF-BB is of great importance for the early diagnosis of disease and
assessments of patient recovery. In the current study, a biolayer interferometry-based enzyme-linked aptamer sorbent assay (BLI-ELASA) was successfully established for rapid (20-25min), high-throughput (8 or 16 samples) and real-time monitoring of PDGF-BB in clinical samples. The method exhibited a broad detection range from 0.5 to 1000ng/mL of PDGF-BB (good linear range from 0.5 to 10ng/mL), with a low detection limit of 0.08ng/mL. Moreover, BLI-ELASA was applied to the detection of PDGF-BB in spiked serum and urine samples and showed a high degree of selectivity for PDGF-BB, good reproducibility, and stability. We believe that the methodology in this work can be easily adapted to detect other biomolecules in clinical samples, including viruses, pathogens and toxins, in a rapid, sensitive, high-throughput and real-time manner.

PMID: 29125972

Pathogenesis


The Role of Mitochondria in AMD: Current Knowledge and Future Applications.

Riazi-Esfahani M, Kuppermann BD, Kenney MC.

Abstract: Mitochondria are organelles which comprise the main respiratory machinery in the eukaryotic cells. In addition to their crucial role in energy production, they have profound effects on apoptosis and retrograde signaling to nucleus. Mitochondria have their own DNA, which codes for different proteins mostly involved in oxidative phosphorylation. Significant changes in the mitochondria of retinal pigment epithelium have been reported in age-related macular degeneration (AMD), which is correlated with the severity of the disease. Cybrid cell lines that have identical nuclei but mitochondria from different individuals can provide a unique means for studying the relationship between mitochondria and AMD. Different approaches for protection of mitochondria have been introduced which can be considered as potential future treatments for AMD and other age-related disorders.

PMID: 29090054 PMCID: PMC5644411


Human retinal pigment epithelial cell proliferation by the combined stimulation of hydroquinone and advanced glycation end-products via up-regulation of VEGF gene.


Abstract: Although recent research showed that advanced glycation endproduct (AGE) and hydroquinone (HQ) are related to the pathogenesis of age-related macular degeneration (AMD), the mechanism how AGE and HQ induce or accelerate AMD remains elusive. In the present study, we examined the effects of AGE and HQ on changes of human retinal pigment epithelial (RPE) cell numbers and found that the viable cell numbers were markedly reduced by HQ by apoptosis and that AGE prevented the decreases of HQ-treated cell numbers by increased replicative DNA synthesis of RPE cells without changing apoptosis. Real-time RT-PCR revealed that vascular endothelial growth factor (VEGF)-A mRNA was increased by HQ treatment and the addition of HQ+AGE resulted in a further increment. The increase of VEGF secretion was confirmed by ELISA, and inhibition of VEGF signaling by chemical inhibitors and small interfering RNA decreased the HQ+AGE-induced increases in RPE cell numbers. The deletion analysis demonstrated that -102 to -43 region was essential for the VEGF-A promoter activation. Site-directed mutations of specificity protein 1 (SP1) binding sequences in the VEGF-A promoter and RNA interference of SP1 revealed that SP1 is an essential transcription factor for VEGF-A expression. These results indicate that HQ induces
RPE cell apoptosis, leading to dry AMD, and suggest that AGE stimulation in addition to HQ enhances VEGF-A transcription via the AGE-receptor for AGE pathway in HQ-damaged cells. As a result, the secreted VEGF acts as an autocrine/paracrine growth factor for RPE and/or adjacent vascular cells, causing wet AMD.

PMID: 29124153 PMCID: PMC5668646

**Mol Pharm. 2017 Nov 9. [Epub ahead of print]**

**Acid-Induced Intracellular Dissociation of β-Cyclodextrin-Threaded Polyrotaxanes Directed toward Attenuating Phototoxicity of Bisretinoids through Promoting Excretion.**

Tamura A, Ohashi M, Nishida K, Yui N.

Abstract: In the retinal pigment epithelium of patients with age-related macular degeneration (AMD), excess N-retinylidene-N-retinylethanolamine (A2E), a dimer of all-trans-retinal, accumulates to induce inflammatory cytokine secretion and phototoxic effects. Therefore, the reduction of intracellular A2E is a promising approach for the prevention and treatment of AMD. In this study, acid-labile β-cyclodextrin (β-CD)-threaded polyrotaxanes (PRXs) were synthesized and investigated their effects on the removal of A2E accumulated in retinal pigment epithelium cells (ARPE-19) in comparison to nonlabile PRXs and 2-hydroxypropyl β-CD (HP-β-CD) were examined. GC-MS and HPLC studies strongly suggest that the acid-labile PRXs dissociated into their constituent molecules in cells by lysosomal acidification and threaded β-CDs were considered to be released from the PRXs. The released β-CDs formed an inclusion complex with A2E, which promoted the excretion of A2E. Indeed, the acid-labile PRXs effectively reduced intracellular A2E level at approximately a 10-fold lower concentration than HP-β-CD. Accompanied with A2E removal, the toxicity and phototoxicity of A2E were attenuated by treatment with acid-labile PRXs. Because the nonlabile PRX failed to reduce intracellular A2E level and attenuate phototoxicity, intracellular release of threaded β-CDs from the acid-labile PRX might contribute to reducing intracellular A2E. We conclude that acid-labile PRXs are promising candidates for the treatment of macular diseases through the removal of toxic metabolites.

PMID: 29120644


**Isorhamnetin prevents H2O2-induced oxidative stress in human retinal pigment epithelial cells.**

Wang J, Gong HM, Zou HH, Liang L, Wu XY.

Abstract: Isorhamnetin, a 3-O-methylated metabolite of quercetin, exhibits antioxidant effects. However, to the best of our knowledge, no study to date has focused on the effects of isorhamnetin on retinal pigment epithelium (RPE) cells, and its underlying molecular mechanisms. Therefore, the present study aimed to examine the potential protective effect of isorhamnetin against oxidative stress in human RPE cells. The results demonstrated that pretreatment of RPE cells with isorhamnetin significantly protected cell viability against oxidative stress. In addition, isorhamnetin pretreatment inhibited hydrogen peroxide (H2O2) -induced reactive oxygen species (ROS) production and caspase-3 activation in RPE cells. Furthermore, isorhamnetin pretreatment significantly increased the phosphorylation of phosphoinositide 3-kinase (PI3K) and AKT serine/threonine kinase 1 (Akt) in RPE cells exposed to H2O2, compared with cells treated with H2O2 alone. Taken together, the present results demonstrated that isorhamnetin protected human RPE cells from oxidative stress-induced cell death, and this effect was associated with activation of the PI3K/Akt signaling pathway. Thus, isorhamnetin may be considered as a potential antioxidant useful for the prevention of age-related macular degeneration.

PMID: 29115489
**Curr Mol Med. 2017 Nov 5. [Epub ahead of print]**

**bmp3 is required for integrity of blood brain barrier by promoting pericyte coverage in zebrafish embryos.**

Lei D, Jin X, Wen L, Dai H, Ye Z, Wang G.

**BACKGROUND:** The compromise of blood brain barrier (BBB) integrity is often associated with human hemorrhage stroke and neurodegeneration diseases, including retina diseases, such as age-related macular degeneration and diabetic retinopathy. Brain pericytes play pivotal roles in regulation and maintenance of BBB integrity. However, the mechanisms underlying brain pericyte development to establish BBB integrity remain unclear.

**METHODS:** Zebrafish transgenic lines Tg(flk1:GFP; gata1:dsRed), Tg(flk1:GFP), Tg(fli1:GFP) and Tg(BRE:GFP) were used in this work. The functional studies of bmp3 were performed by mopholino oligonucleotide (MO) injection, dye-based permeability assay, RT-PCR, in vivo imaging, immunofluorescence staining and statics analysis.

**RESULTS:** Here we report that bmp3 regulates BBB integrity in zebrafish brain by promoting pericyte development. Knockdown of bmp3 with injection of bmp3-MO causes intracerebral hemorrhage in zebrafish embryos. Meanwhile, disruption of bmp3 function by bmp3-MO injection impairs cerebral pericyte coverage in zebrafish embryos. Mechanistically, knockdown of bmp3 disrupts the pattern and activities of BMP signaling in zebrafish brain, thus probably disrupting the balance of TGFβ/BMP signaling in zebrafish embryos.

**CONCLUSION:** In summary, our data shows that bmp3 regulates BBB integrity potentially by promoting pericyte development.

PMID: 29110609

**Oxid Med Cell Longev. 2017;2017:6210694. Epub 2017 Sep 1.**

**Salvianolic Acid A Inhibits OX-LDL Effects on Exacerbating Choroidal Neovascularization via Downregulating CYLD.**

Mao K, Shu W, Liu L, Gu Q, Qiu Q, Wu X.

**BACKGROUNDS:** Age-related macular degeneration is closely related to lipid oxidation, while relationship between OX-LDL and choroidal neovascularization is unclear. Recently, cylindromatosis is proved to regulate angiogenesis. However, its role in CNV progression remained unclear. Salvianolic acid A is widely used in vascular diseases. We investigated the relationship between OX-LDL and CNV and explore antineovascularization mechanism of Sal A.

**METHODS:** C57BL6/J mice were randomized into four groups and injected with PBS or OX-LDL, together with Sal A for one week. CNV was induced by laser; CNV severity was analyzed by fundus fluorescein angiography, H&E staining, and choroid flat mount after 1 week. In in vitro experiments, ARPE-19 and HUVECs were cultured with OX-LDL (with or without Sal A) for 48 hours. Angiogenic proteins, cell junction integrity, and tube formation were measured. CYLD siRNA and specific inhibitors were used to explore mechanisms of CYLD in promoting OX-LDL-induced CNV progression.

**RESULTS:** OX-LDL promoted laser-induced CNV volume by increasing VEGF, PDGF, and CYLD levels. Sal A antagonized OX-LDL effects and restrained CNV progression by decreasing VEGF/PDGF/CYLD, increasing antiangiostatin levels, and promoting P62-CYLTD-TRAF6 interaction.

**CONCLUSIONS:** We demonstrated oxidation damage exacerbates CNV progression, and Sal A could be a clinical therapeutic reagent to exudative AMD.

PMID: 29081889 PMCID: PMC5610829
Cell Biochem Biophys. 2017 Nov 2. [Epub ahead of print]

Oxidation-Induced Increase In Photoreactivity of Bovine Retinal Lipid Extract.

Koscielniak A, Serafin M, Duda M, Oles T, Zadlo A, Broniec A, Berdeaux O, Gregoire S, Bretillon L, Sarna T, Pawlak A.

Abstract: The mammalian retina contains a high level of polyunsaturated fatty acids, including docosahexaenoic acid (22:6) (DHA), which are highly susceptible to oxidation. It has been shown that one of the products of DHA oxidation-carboxyethylpyrrole (CEP) generated in situ, causes modifications of retinal proteins and induces inflammation response in the outer retina. These contributing factors may play a role in the development of age-related macular degeneration (AMD). It is also possible that some of the lipid oxidation products are photoreactive, and upon irradiation with blue light may generate reactive oxygen species. Therefore, in this work we analysed oxidation-induced changes in photoreactivity of lipids extracted from bovine neural retinas. Lipid composition of bovine neural retinas closely resembles that of human retinas making the bovine tissue a convenient model for studying the photoreactivity and potential phototoxicity of oxidized human retinal lipids. Lipid composition of bovine neural retinas Folch’ extracts (BRex) was determined by gas chromatography (GC) and liquid chromatography coupled to an electrospray ionization source-mass spectrometer (LC-ESI-MS) analysis. Liposomes prepared from BRex, equilibrated with air, were oxidized in the dark at 37 °C for up to 400 h. The photoreactivity of BRex at different stages of oxidation was studied by EPR-oximetry and EPR-spin trapping. Photogeneration of singlet oxygen (1O2, 1Δg) by BRex was measured using time-resolved detection of the characteristic phosphorescence at 1270 nm. To establish contribution of lipid components to the analysed photoreactivity of Folch’ extract of bovine retinas, a mixture of selected synthetic lipids in percent by weight (w/w %) ratio resembling that of the BRex has been also studied. Folch’s extraction of bovine neural retinas was very susceptible to oxidation despite the presence of powerful endogenous antioxidants such as α-tocopherol and zeaxanthin. Non-oxidized and oxidized BRex photogenerated singlet oxygen with moderate quantum yield. Blue-light induced generation of superoxide anion by Folch’ extract of bovine neural retinas strongly depended on the oxidation time. The observed photoreactivity of the studied extract gradually increased during its in vitro oxidation.

PMID: 29098642


Serum starvation of ARPE-19 changes the cellular distribution of cholesterol and Fibulin3 in patterns reminiscent of age-related macular degeneration.

Rajapakse D, Peterson K, Mishra S, Wistow G.

Abstract: Retinal pigment epithelium (RPE) has been implicated as key source of cholesterol-rich deposits at Bruch’s membrane (BrM) and in drusen in aging human eye. We have shown that serum-deprivation of confluent RPE cells is associated with upregulation of cholesterol synthesis and accumulation of unesterified cholesterol (UC). Here we investigate the cellular processes involved in this response. We compared the distribution and localization of UC and esterified cholesterol (EC); the age-related macular degeneration (AMD) associated EFEMP1/Fibulin3 (Fib3); and levels of acyl-coenzyme A (CoA): cholesterol acyltransferases (ACAT) ACAT1, ACAT2 and Apolipoprotein B (ApoB) in ARPE-19 cells cultured in serum-supplemented and serum-free media. The results were compared with distributions of these lipids and proteins in human donor eyes with AMD. Serum deprivation of ARPE-19 was associated with increased formation of FM dye-positive membrane vesicles, many of which co-labeled for UC. Additionally, UC colocalized with Fib3 in distinct granules. By day 5, serum-deprived cells grown on transwells secreted Fib3 basally into the matrix. While mRNA and protein levels of ACTA1 were constant over several days of serum-deprivation, ACAT2 levels increased significantly after serum-deprivation, suggesting increased formation of EC. The lower levels of intracellular EC observed under serum-deprivation were associated with
increased formation and secretion of ApoB. The responses to serum-deprivation in RPE-derived cells: accumulation and secretion of lipids, lipoproteins, and Fib3 are very similar to patterns seen in human donor eyes with AMD and suggest that this model mimics processes relevant to disease progression.

PMID: 29097185

**BMC Ophthalmol. 2017 Nov 2;17(1):198.**

**Blue-light filtering alters angiogenic signaling in human retinal pigmented epithelial cells culture model.**


**BACKGROUND:** Light exposure and more specifically the spectrum of blue light contribute to the oxidative stress in Age-related macular degeneration (AMD). The purpose of the study was to establish whether blue light filtering could modify proangiogenic signaling produced by retinal pigmented epithelial (RPE) cells under different conditions simulating risk factors for AMD.

**METHODS:** Three experiments were carried out in order to expose ARPE-19 cells to white light for 48 h with and without blue light-blocking filters (BLF) in different conditions. In each experiment one group was exposed to light with no BLF protection, a second group was exposed to light with BLF protection, and a control group was not exposed to light. The ARPE-19 cells used in each experiment prior to light exposure were cultured for 24 h as follows: Experiment 1) Normoxia, Experiment 2) Hypoxia, and Experiment 3) Lutein supplemented media in normoxia. The media of all groups was harvested after light exposure for sandwich ELISA-based assays to quantify 10 pro-angiogenic cytokines.

**RESULTS:** A significant decrease in angiogenin secretion levels and a significant increase in bFGF were observed following light exposure, compared to dark conditions, in both normoxia and hypoxia conditions. With the addition of a blue light-blocking filter in normoxia, a significant increase in angiogenin levels was observed. Although statistical significance was not achieved, blue light filters reduce light-induced secretion of bFGF and VEGF to near normal levels. This trend is also observed when ARPE-19 cells are grown under hypoxic conditions and when pre-treated with lutein prior to exposure to experimental conditions.

**CONCLUSIONS:** Following light exposure, there is a decrease in angiogenin secretion by ARPE-19 cells, which was abrogated with a blue light - blocking filter. Our findings support the position that blue light filtering affects the secretion of angiogenic factors by retinal pigmented epithelial cells under normoxic, hypoxic, and lutein-pretreated conditions in a similar manner.

PMID: 29096624 PMCID: PMC5667496


**Changes in extracellular matrix cause RPE cells to make basal deposits and activate the alternative complement pathway.**

Fernandez-Godino R, Bujakowska KM, Pierce EA.

**Abstract:** The design of efficient therapies for age-related macular degeneration (AMD) is limited by our understanding of the pathogenesis of basal deposits, which form between retinal pigment epithelium (RPE) and Bruch's membrane (BrM) early in disease, and involve activation of the complement system. To investigate the roles of BrM, RPE and complement in AMD, we generated abnormal extracellular matrix (ECM) using CRISPR-edited ARPE-19 cells. We introduced to these cells the p.R345W mutation in EFEMP1, which causes early-onset macular degeneration. The abnormal ECM binds active complement C3 and causes the formation of basal deposits by normal human fetal (hf)RPE cells. hfRPE cells grown on
abnormal ECM or BrM explants from AMD donors show chronic activation of the alternative complement pathway by excessive deposition of C3b. This process is exacerbated by impaired ECM turnover via increased matrix metalloproteinase-2 (MMP-2) activity. The local cleavage of C3 via convertase-independent mechanisms can be a new therapeutic target for early AMD.

PMID: 29095988


Age-Related Macular Degeneration: A Connection between Human Herpes Virus-6A-Induced CD46 Downregulation and Complement Activation?
Fierz W.

Abstract: Viruses are able to interfere with the immune system by docking to receptors on host cells that are important for proper functioning of the immune system. A well-known example is the human immunodeficiency virus that uses CD4 cell surface molecules to enter host lymphocytes and thereby deleteriously destroying the helper cell population of the immune system. A more complicated mechanism is seen in multiple sclerosis (MS) where human herpes virus-6A (HHV-6A) infects astrocytes by docking to the CD46 surface receptor. Such HHV-6A infection in the brain of MS patients has recently been postulated to enable Epstein-Barr virus (EBV) to transform latently infected B-lymphocytes in brain lesions leading to the well-known phenomenon of oligoclonal immunoglobulin production that is widely used in the diagnosis of MS. The cellular immune response to HHV-6A and EBV is one part of the pathogenic mechanisms in MS. A more subtle pathogenic mechanism can be seen in the downregulation of CD46 on astrocytes by the infecting HHV-6A. Since CD46 is central in regulating the complement system, a lack of CD46 can lead to hyperactivation of the complement system. In fact, activation of the complement system in brain lesions is a well-known pathogenic mechanism in MS. In this review, it is postulated that a similar mechanism is central in the development of age-related macular degeneration (AMD). One of the earliest changes in the retina of AMD patients is the loss of CD46 expression in the retinal pigment epithelial (RPE) cells in the course of geographic atrophy. Furthermore, CD46 deficient mice spontaneously develop dry-type AMD-like changes in their retina. It is also well known that certain genetic polymorphisms in the complement-inhibiting pathways correlate with higher risks of AMD development. The tenet is that HHV-6A infection of the retina leads to downregulation of CD46 and consequently to hyperactivation of the complement system in the eyes of susceptible individuals.

PMID: 29093709 PMCID: PMC5651521


HtrA1 activation is driven by an allosteric mechanism of inter-monomer communication.

Abstract: The human protease family HtrA is responsible for preventing protein misfolding and mislocalization, and a key player in several cellular processes. Among these, HtrA1 is implicated in several cancers, cerebrovascular disease and age-related macular degeneration. Currently, HtrA1 activation is not fully characterized and relevant for drug-targeting this protease. Our work provides a mechanistic step-by-step description of HtrA1 activation and regulation. We report that the HtrA1 trimer is regulated by an allosteric mechanism by which monomers relay the activation signal to each other, in a PDZ-domain independent fashion. Notably, we show that inhibitor binding is precluded if HtrA1 monomers cannot communicate with each other. Our study establishes how HtrA1 trimerization plays a fundamental role in proteolytic activity. Moreover, it offers a structural explanation for HtrA1-defective pathologies as well as
mechanistic insights into the degradation of complex extracellular fibrils such as tubulin, amyloid beta and tau that belong to the repertoire of HtrA1.

PMID: 29093542 PMCID: PMC5666011


Current Anti-Integrin Therapy for Ocular Disease.


Abstract: The integrin family of cell adhesion molecules mediates homeostasis, signal transduction, and various other interactions between the cell and the extracellular matrix. Integrins are type-1 transmembrane glycoproteins located on the cell surface, widely expressed in leukocytes, which play an important role in the inflammatory pathway. The purpose of this review is to summarize the current state of anti-integrin therapy and to assess ongoing clinical trials in ocular disease. We performed a search on PubMed, CINAHL, and Embase for the published literature available using the MeSH terms: "integrin therapy" and "αLβ2," "α4β1" and/or "ophthalmology," and "clinical trials." We used no language restrictions. We generated searches to account for synonyms of these keywords and MESH headings as follows: (1) "integrin," "therapy," or "treatment"; (2) "clinical trials," "ophthalmology," or "ocular." In addition, the analysis included phase 2 and phase 3 clinical trials with a minimal follow-up of six months. Integrin antagonists have shown their capacity to improve signs and symptoms of patients with dry eye disease, age-related macular degeneration, diabetic macular edema, and vitreomacular traction.

PMID: 29087767


Tenascins in Retinal and Optic Nerve Neurodegeneration.

Reinhard J, Roll L, Faissner A.

Abstract: Tenascins represent key constituents of the extracellular matrix (ECM) with major impact on central nervous system (CNS) development. In this regard, several studies indicate that they play a crucial role in axonal growth and guidance, synaptogenesis and boundary formation. These functions are not only important during development, but also for regeneration under several pathological conditions. Additionally, tenascin-C (Tnc) represents a key modulator of the immune system and inflammatory processes. In the present review article, we focus on the function of Tnc and tenascin-R (Tnr) in the diseased CNS, specifically after retinal and optic nerve damage and degeneration. We summarize the current view on both tenascins in diseases such as glaucoma, retinal ischemia, age-related macular degeneration (AMD) or diabetic retinopathy. In this context, we discuss their expression profile, possible functional relevance, remodeling of the interacting matrisome and tenascin receptors, especially under pathological conditions.

PMID: 29109681 PMCID: PMC5660115

Epidemiology


Multiple Deprivation, Vision Loss, and Ophthalmic Disease in Adults: Global Perspectives.

Lane M, Lane V, Abbott J, Braithwaite T, Shah P, Denniston AK.
Abstract: The association between socio-economic position and morbidity and mortality has long been recognised. We evaluate the evidence for an association between multiple aspects of deprivation and ocular health in a global context. This is a systematic review of studies that evaluated deprivation in the adult population in the context of the major acquired causes of visual loss such as cataract, diabetic eye disease, glaucoma, age-related macular degeneration, and ocular trauma. The search strategy identified relevant studies reported between 1946 to August 2016, with randomized control trials, case control, cohort and cross-sectional study designs being selected for inclusion. The studies identified in this review from across the world demonstrate the extent to which common themes such as low educational attainment and low income may be associated with increased incidence of various sight-threatening conditions and may adversely affect access to specialist assessment and delivery of treatment. Health inequality may always persist, but an increased recognition of the importance of the various impacts of deprivation may empower policy makers to target limited resources to the most vulnerable groups in order to deliver the greatest benefit.

PMID: 29100897

Dan Med J. 2017 Nov;64(11).

Prevalence of neovascular age-related macular degeneration and geographic atrophy in Denmark.
Sedeh FB, Scott DAR, Subhi Y, Sørensen TL.

INTRODUCTION: In Denmark, age-related macular degeneration (AMD) is the most common cause of blindness. To better understand current and future challenges, we estimated and projected the annual number of patients with neovascular AMD and geographic atrophy in Denmark from 2016 to 2060.

METHODS: Detailed age- and gender-stratified prevalence estimates of neovascular AMD and geographic atrophy in a Scandinavian population were identified and applied to age- and gender-stratified population numbers provided by Statistics Denmark. Prevalence estimates were calculated for each year from 2016 to 2060. Future forecasts were provided by Statistics Denmark and based on calculations by the Danish Institute for Economic Modelling and Forecasting.

RESULTS: We estimated that there are currently ~30,000 patients with neovascular AMD and ~21,000 patients with geographic atrophy in Denmark. The majority of these patients are persons aged ≥ 85 years. For neovascular AMD, the number of patients will grow to ~33,000 in 2020, ~58,000 in 2040 and ~72,000 in 2060. For geographic atrophy, the number of patients will grow to ~23,000 in 2020, ~41,000 in 2040, and ~50,000 in 2060.

CONCLUSIONS: We expect a steady growth in the prevalence of neovascular AMD and geographic atrophy in Denmark due to an ageing population. These numbers emphasise the importance of disease prevention, careful planning of health service activities and continuing research.

PMID: 29115208


Comment on: Vitreomacular Adhesion and Its Association With Age-Related Macular Degeneration in a Population-Based Setting: The Alienor Study.
Maggio E, Polito A, Pertile G.

PMID: 29101406
Genetics & gene therapy

Eye (Lond). 2017 Nov 10. [Epub ahead of print]

Genetics and genetic testing for age-related macular degeneration.

Warwick A, Lotery A.

Abstract: Considerable advances have been made in our understanding of age-related macular degeneration (AMD) genetics over the past decade. The genetic associations discovered to date are estimated to account for approximately half of AMD heritability, and functional studies of these variants have revealed new insights into disease pathogenesis, leading to the development of potential novel therapies. There is furthermore growing interest in genetic testing for predicting an individual's risk of AMD and offering personalised preventive or therapeutic treatments. We review the progress made so far in AMD genetics and discuss the possible applications for genetic testing.

PMID: 29125146


Genetic variations in Bestrophin-1 and associated clinical findings in two Chinese patients with juvenile-onset and adult-onset best vitelliform macular dystrophy.


Abstract: Best vitelliform macular dystrophy (BVMD) is a hereditary retinal disease characterized by the bilateral accumulation of large egg yolk-like lesions in the sub-retinal and sub-retinal pigment epithelium spaces. Macular degeneration in BVMD can begin in childhood or adulthood. The variation in the age of onset is not clearly understood. The present study characterized the clinical characteristics of two Chinese patients with either juvenile-onset BVMD or adult-onset BVMD and investigated the underlying genetic variations. A 16-year-old male (Patient 1) was diagnosed with juvenile-onset BVMD and a 43-year-old female (Patient 2) was diagnosed with adult-onset BVMD. Comprehensive ophthalmic examinations were performed, including best-corrected visual acuity, intraocular pressure, slit-lamp examination, fundus photography, optical coherence tomography, fundus fluorescein angiography imaging and Espion electrophysiology. Genomic DNA was extracted from peripheral blood leukocytes collected from these patients, their family members, and 200 unrelated subjects within the same population. The 11 exons of the bestrophin-1 (BEST1) gene were amplified by polymerase chain reaction and directly sequenced. Both patients presented lesions in the macular area. In Patient 1, a heterozygous mutation c.903T>G (p.D301E) in exon 8 of the BEST1 gene was identified. This mutation was not present in any of the unaffected family members or the normal controls. Polymorphism phenotyping and the sorting intolerant from tolerant algorithm predicted that the amino acid substitution D301E in bestrophin-1 protein was damaging. In Patient 2, a single nucleotide polymorphism c.1608C>T (p.T536T) in exon 10 of the BEST1 gene was identified. These findings expand the spectrum of BEST1 genetic variation and will be valuable for genetic counseling and the development of therapeutic interventions for patients with BVMD.

PMID: 29115605


Identification of IncRNAs involved in biological regulation in early age-related macular degeneration.

Zhu W, Meng YF, Xing Q, Tao JJ, Lu J, Wu Y.
BACKGROUND: Age-related macular degeneration (AMD) is one of the most common causes of adult blindness in developed countries. However, the role of long noncoding RNAs (lncRNAs) in the development and progression of early AMD is unclear.

METHODS: We established the lncRNA profile of early AMD by reannotation of microarrays from the gene expression omnibus database. Quantitative real-time polymerase chain reaction was used to determine the expression of selected lncRNAs.

RESULTS: The expression profiles of 9 cases of AMD and 7 controls were studied. A total of 266 differentially expressed genes (DEGs) were detected (94 upregulated and 172 downregulated). Among all the DEGs, 64 were lncRNAs. Advanced bioinformatics analyses demonstrated that differentially expressed lncRNAs could play significant roles in visual perception, sensory perception of light stimulus, and cognition. The pathway analyses showed that the two most significantly influenced Kyoto Encyclopedia of Genes and Genomes pathways were those of phototransduction and purine metabolism. By the analyses of the key lncRNAs, it was found that RP11-234O6.2 was downregulated in the aging retinal pigment epithelium (RPE) cellular model. Exogenous RP11-234O6.2 treatment led to increased cell viability and improved apoptosis but it did not affect the cell migration ability of aging RPE cells.

CONCLUSION: This study indicated that lncRNAs are differentially expressed in early AMD and may produce important regulatory effects. An lncRNA, RP11-234O6.2, might be involved in the biological regulation of early AMD and have therapeutic potential.

PMID: 29089757 PMCID: PMC5655033


A Deep Phenotype Association Study Reveals Specific Phenotype Associations with Genetic Variants in Age-related Macular Degeneration: Age-Related Eye Disease Study 2 (AREDS2) Report No. 14.


PURPOSE: Age-related macular degeneration (AMD), a multifactorial disease with variable phenotypic presentation, was associated with 52 single nucleotide polymorphisms (SNPs) at 34 loci in a genome-wide association study (GWAS). These genetic variants could modulate different biological pathways involved in AMD, contributing to phenotypic variability. To better understand the effects of these SNPs, we performed a deep phenotype association study (DeePAS) in the Age-Related Eye Disease Study 2 (AREDS2), followed by replication using AREDS participants, to identify genotype associations with AMD and non-AMD ocular and systemic phenotypes.

DESIGN: Cohort study.

PARTICIPANTS: AREDS and AREDS2 participants.

METHODS: AREDS2 participants (discovery cohort) had detailed phenotyping for AMD; other eye conditions; cardiovascular, neurologic, gastrointestinal, and endocrine disease; cognitive function; serum nutrient levels; and others (total of 139 AMD and non-AMD phenotypes). Genotypes of the 52 GWAS SNPs were obtained. The DeePAS was performed by correlating the 52 SNPs to all phenotypes using logistic and linear regression models. Associations that reached Bonferroni-corrected statistical significance were replicated in AREDS.

MAIN OUTCOME MEASURES: Genotype-phenotype associations.

RESULTS: A total of 1776 AREDS2 participants had 5 years follow-up; 1435 AREDS participants had 10 years. The DeePAS revealed a significant association of the rs3750846 SNP at the ARMS2/HTRA1 locus.
with subretinal/sub-retinal pigment epithelial (RPE) hemorrhage related to neovascular AMD (odds ratio 1.55 [95% confidence interval 1.31-1.84], P = 2.67 \times 10^{-7}). This novel association remained significant after conditioning on participants with neovascular AMD (P = 2.42 \times 10^{-4}). Carriers of rs3750846 had poorer visual acuity during follow-up (P = 6.82 \times 10^{-7}) and were more likely to have a first-degree relative with AMD (P = 5.38 \times 10^{-6}). Two SNPs at the CFH locus, rs10922109 and rs570618, were associated with the drusen area in the Early Treatment Diabetic Retinopathy Study Report (ETDRS) grid (P = 2.29 \times 10^{-11} and P = 3.20 \times 10^{-9}, respectively) and the center subfield (P = 1.24 \times 10^{-9} and P = 6.68 \times 10^{-8}, respectively). SNP rs570618 was additionally associated with the presence of calcified drusen (P = 5.38 \times 10^{-6}). Except for positive family history of AMD with rs3750846, all genotype-phenotype associations were significantly replicated in AREDS. No pleiotropic associations were identified.

CONCLUSIONS: The association of the SNP at the ARMS2/HTRA1 locus with subretinal/sub-RPE hemorrhage and poorer visual acuity and of SNPs at the CFH locus with drusen area may provide new insights in pathophysiological pathways underlying different stages of AMD.

PMID: 29096998


**Interactions among different genetic loci in age-related macular degeneration.**

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

PURPOSE: To evaluate the possible synergistic effect of at risk genotypes of ARMS2/LOC387715 (A69S), DNA repair SMUG1 rs3087404, CCL2-2518, C3 (R102G), CFH Y402H, complement factor B (L9H), and complement factor I (CFI) (G119R) in advanced age-related macular degeneration compared to those of healthy controls. Elucidation of synergistic effects between different genetic loci may clarify their pathogenetic pathways.

METHODS: We calculated relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S) to estimate the additive or supra-additive effects of the mentioned genotypes.

RESULTS: ARMS2-CFH [RERI = 4.78 (95% CI 2.17-10.61), AP = 0.65 (95% CI 0.33-0.83), S = 4.11 (95% CI 1.40-12.06)], and CFH-C3 combinations [RERI = 2.71 (95% CI 0.04-7.01) AP = 0.47 (95% CI -0.03-0.7) S = 2.30 (95%CI 0.97-5.45)] have the most significant levels of synergism and C3-CFI combination [RERI = -1.65 (95%CI -4.34-0.06), AP = -0.92(95%CI -3.09 - -0.09), S = 0.32 (95%CI 0.09 = 1.20)] has the most significant level of antagonism.

CONCLUSION: Among different genotype combinations ARMS2-CFH and CFH-C3 combinations have the most significant levels of synergism and C3-CFI combination has the most significant level of antagonism in AMD patients.

PMID: 29087762

**Nat Genet. 2017 Oct 30. [Epub ahead of print]**

**Exome-wide association study of plasma lipids in >300,000 individuals.**

Liu DJ, Peloso GM, Yu H, et al

Abstract: We screened variants on an exome-focused genotyping array in >300,000 participants (replication in >280,000 participants) and identified 444 independent variants in 250 loci significantly associated with total cholesterol (TC), high-density-lipoprotein cholesterol (HDL-C), low-density-lipoprotein cholesterol (LDL-C), and/or triglycerides (TG). At two loci (JAK2 and A1CF), experimental analysis in mice showed lipid
changes consistent with the human data. We also found that: (i) beta-thalassemia trait carriers displayed lower TC and were protected from coronary artery disease (CAD); (ii) excluding the CETP locus, there was not a predictable relationship between plasma HDL-C and risk for age-related macular degeneration; (iii) only some mechanisms of lowering LDL-C appeared to increase risk for type 2 diabetes (T2D); and (iv) TG-lowering alleles involved in hepatic production of TG-rich lipoproteins (TM6SF2 and PNPLA3) tracked with higher liver fat, higher risk for T2D, and lower risk for CAD, whereas TG-lowering alleles involved in peripheral lipolysis (LPL and ANGPTL4) had no effect on liver fat but decreased risks for both T2D and CAD.

PMID: 29083408

**Stem cells**


Human stem cell-derived retinal epithelial cells activate complement via collectin 11 in response to stress.


Abstract: Age-related macular degeneration (AMD) is a major cause of blindness and is associated with complement dysregulation. The disease is a potential target for stem cell therapy but success is likely to be limited by the inflammatory response. We investigated the innate immune properties of human induced-pluripotent stem cell (iPSC)-derived RPE cells, particularly with regard to the complement pathway. We focused on collectin-11 (CL-11), a pattern recognition molecule that can trigger complement activation in renal epithelial tissue. We found evidence of constitutive and hypoxia-induced expression of CL-11 in iPSC-RPE cells, and in the extracellular fluid. Complement activation on the cell surface occurred in conjunction with CL-11 binding. CL-11 has been shown to activate inflammatory responses through recognition of L-fucose, which we confirmed by showing that fucosidase-treated cells, largely, failed to activate complement. The presence of CL-11 in healthy murine and human retinal tissues confirmed the biological relevance of CL-11. Our data describe a new trigger mechanism of complement activation that could be important in disease pathogenesis and therapeutic interventions.

PMID: 29116192


Perspectives of Stem Cell-Based Therapy for Age-Related Retinal Degenerative Diseases.

Holan V, Hermankova B, Kossl J.

Abstract: Retinal degenerative diseases, which include age-related macular degeneration, retinitis pigmentosa, diabetic retinopathy, and glaucoma, mostly affect the elderly population and are the most common cause of decreased quality of vision or even blindness. So far, there is no satisfactory treatment protocol to prevent, stop, or cure these disorders. A great hope and promise for patients suffering from retinal diseases is represented by stem cell-based therapy that could replace diseased or missing retinal cells and support regeneration. In this respect, mesenchymal stem cells (MSCs) that can be obtained from the particular patient and used as autologous cells have turned out to be a promising stem cell type for treatment. Here we show that MSCs can differentiate into cells expressing markers of retinal cells, inhibit production of pro-inflammatory cytokines by retinal tissue, and produce a number of growth and neuroprotective factors for retinal regeneration. All of these properties make MSCs a prospective cell type for cell-based therapy of age-related retinal degenerative diseases.

PMID: 29113466
Development of a new tissue injector for subretinal transplantation of human embryonic stem cell derived retinal pigmented epithelium.


BACKGROUND: Subretinal cell transplantation is a challenging surgical maneuver. This paper describes the preliminary findings of a new tissue injector for subretinal implantation of an ultrathin non-absorbable substrate seeded with human embryonic stem cell-derived retinal pigment epithelium (hESC-RPE).

METHODS: Ultrathin Parylene-C substrates measuring 3.5 mm × 6.0 mm seeded with hESC-RPE (implant referred to as CPCB-RPE1) were implanted into the subretinal space of 12 Yucatan minipigs. Animals were euthanized immediately after the procedure and underwent spectral domain optical coherence tomography (SD-OCT) and histological analysis to assess the subretinal placement of the implant. Evaluation of the hESC-RPE cells seeded on the substrate was carried out before and after implantation using standard cell counting techniques.

RESULTS: The tissue injector delivered the CPCB-RPE1 implant through a 1.5 mm sclerotomy and a 1.0-1.5 mm retinectomy. SD-OCT scans and histological examination revealed that substrates were precisely placed in the subretinal space, and that the hESC-RPE cell monolayer continued to cover the surface of the substrate after the surgical procedure.

CONCLUSION: This innovative tissue injector was able to efficiently deliver the implant in the subretinal space of Yucatan minipigs, preventing significant hESC-RPE cell loss, minimizing tissue trauma, surgical complications and postoperative inflammation.

PMID: 29093829 PMCID: PMC5662097