Drug treatment


Diabetic macular oedema treated with intravitreal anti-vascular endothelial growth factor - 2-4 years follow-up of visual acuity and retinal thickness in 566 patients following Danish national guidelines.

Hodzic-Hadzibegovic D, Sander BA, Monberg TJ, Larsen M, Lund-Andersen H.

PURPOSE: To investigate long-term functional and anatomical outcomes, discontinuation patterns, drug switching and rates of nonimprovement in patients treated with ranibizumab pro re nata (PRN) regimen for diabetic macular oedema (DME) according to the Danish national guidelines.

METHODS: Retrospective cohort study of 566 eyes in 566 patients with centre-involved DME who started intravitreal treatment with ranibizumab between January 2011 and December 2013 in the Greater Copenhagen region. Data were retrieved from a database and patient records between January 2011 and March 2016 and analysed using mixed-model statistics.

RESULTS: At the conclusion of follow-up, 24.6% were in active ranibizumab follow-up, 25.4% had switched to other intravitreal pharmacotherapy, 31.6% had been discontinued because of disease stability, 13.8% had been lost to follow-up, 1.4% had been discontinued because of low visual acuity (VA), and 3.2% had died. At baseline, mean best-corrected visual acuity (BCVA) and mean central subfield thickness (CST) were 64.9 (±15.0) letters and 400.2 (±120.3) μm. Mean change in BCVA and mean change in CST from baseline to 3, 12, 24, 36 and 48 months of follow-up were +3.9, +3.5, +2.7, +1.8, +2.3 letters and -97.4, -102.6, -105.9, -106.9, -131.6 μm, respectively. Mean number of injections was 6.1 in year 1 and 1.8 in year 4. In 93 patients, drug switching to aflibercept showed no difference between the two drugs on BCVA or CST. In 79 patients, CST decreased <10% compared to baseline during the first year.

CONCLUSION: In a single-centre clinical setting, 566 patients treated for DME with ranibizumab according to the Danish national guidelines were followed for up to 4 years. Best-corrected visual acuity (BCVA) outcomes are in the low end of clinical studies, but studied on a wider population and achieved with fewer injections.

PMID: 29240306

Diabetic macular edema, innovative technologies and economic impact: New opportunities for the Lombardy Region healthcare system?


PURPOSE: Diabetic macular edema (DME) is a leading cause of vision loss and blindness. The aim of this study was to evaluate the economic benefits of introducing additional alternative technologies (Dexamethasone intravitreal implant - DEX - and Aflibercept injections), compared with the historical scenario of Ranibizumab intravitreal injections.

METHODS: A 3-year budget impact model was developed, taking into consideration the perspective of the Lombardy Region Healthcare Service (LRHS). Total administration costs (real-life data retrieved from clinical practice at three Departments of Ophthalmology) as well as costs related to the management of potential adverse events (information collected from the literature) were analysed.

RESULTS: Over a 36-month horizon, the results showed that a higher consumption of DEX could lead to significant economic savings for the Regional Healthcare Service, ranging from a minimum of -4.35% (if DEX were used only in the second-line of treatment) to a maximum of -12.97% (if DEX were used in both the first-line and second-line), including the potential impact of adverse events. Therapy costs with Aflibercept and Ranibizumab were similar.

CONCLUSIONS: This study demonstrates that concentrating all eligible patients within the Ranibizumab regimen is unlikely to represent a cost-effective strategy. Indeed, significant economic advantages would be achieved by introducing the other licensed alternatives, Dexamethasone implant and Aflibercept, thus optimising DME Italian healthcare expenditure. The results demonstrate DEX as an advantageous technological alternative for the target population affected by DME, both as a first- and second-line treatment option, reducing the economic burden of the pathology for the Regional/National Health Service.

PMID: 29240298


Aflibercept in macular edema secondary to retinal vein occlusion: A real life study.

Ozkaya A, Tulu B, Garip R.

PURPOSE: To evaluate the real life outcomes of intravitreal aflibercept (IVAfl) treatment in patients with macular edema (ME) secondary to retinal vein occlusion (RVO) during the first year of treatment.

METHODS: Retrospective case series. Newly diagnosed or persistent ME patients secondary to RVO who were treated with IVAfl and had a follow-up period of at least 12 months were included. Twenty-two patients (54.8%) received 3 loading month loading doses IVAfl initially, whereas 20 patients (45.2%) did not receive. Then the patients were treated on an as-needed treatment regimen. Primary outcome measures of this study included the change in best corrected visual acuity (BCVA) and central retinal thickness (CRT). Secondary outcome measures were the number of visits and injections.

RESULTS: Forty-two eyes of 42 patients were included. Fourteen patients (33.3%) had central RVO, and 28 (66.7%) had branch RVO. Mean BCVA at baseline and month 12 was 0.98 ± 0.58 and 0.82 ± 0.65 LogMAR, respectively (p = 0.04). Mean CRT at baseline and month 12 was 511 ± 141 and 304 ± 95 μm, respectively (p < 0.0001). Mean number of visits was 5.9 ± 2.1 (range 3-11) and injections was 3.2 ± 1.7 (range 1-8) at month 12.

CONCLUSION: In conclusion, IVAfl treatment seemed to be effective in patients with ME secondary to
RVO with respect to visual and anatomical outcomes in real life. In this study the number of visits and injections was lower than randomized controlled trials, but the functional and anatomical outcomes are probably still acceptable.

PMID: 29234221 PMCID: PMC5717494


[Time Course of Changes in Visual Acuity After a Single Injection of Aflibercept or Ranibizumab in Neovascular Age-related Macular Degeneration - Analysis of Aggregated Real Life Data]. [Article in German]

Wilke RGH, Finger RP, Sachs HG.

Abstract: Background Treatment of neovascular age-related macular degeneration (nvAMD) under real life conditions may differ from controlled prospective trials with respect to the number of injections and long term preservation of visual acuity. In many instances, intervals for controls and re-injection cannot be maintained as frequently as required. This case series examines actual intervals for control and re-injection visits, in order to estimate how prolonged intervals have an impact on momentary visual acuity and how long term visual outcome is affected. Patients/Material and Methods Retrospective case series of 1,324 eyes with nvAMD, treated with a total of 8,150 ranibizumab injections (according to the PRN regimen) or 1,725 aflibercept injections (according to a fixed regimen), during the observation period of up to 3 years. The evaluation covered the time interval between visits, impact of this on the course of visual acuity, as well as the number of injections throughout treatment. Results Planned intervals of 4 or 8 weeks between visits were more often exceeded in the PRN regimen than with the fixed regimen. Visual acuity does not peak after 4 weeks, but only between 6 and 8 weeks. No statistically significant difference between aflibercept and ranibizumab was found. If the mean interval for re-injection was maintained at 4-6 weeks, this gave the greatest gains in visual acuity at end of years 1 and 2, respectively. Any prolongation of these intervals was accompanied by worse long term visual acuity. The fixed regimen is associated with consistently briefer re-treatment intervals during years 2 and 3, than with the PRN regimen. Conclusion Our data point to the importance of frequent controls accompanied by timely retreatment, as these have a major impact on visual outcome. It therefore appears to be more important to choose a treatment plan that facilitates frequent re-injections than to select either of the two compounds.

PMID: 29232758


[Real-life Data on the Treatment of Diabetic Macular Oedema in Germany]. [Article in German]

Wilke RGH, Finger RP, Sachs HG.

Background: Controlled prospective clinical trials on the treatment of diabetic macular oedema (DME) using anti-VEGF compounds show very good results in visual acuity gain over several years. To date, only limited data are available from comparable studies under real-life settings in clinical routine. However, real-life data from other indications for anti-VEGF treatment suggest that, in clinical routine, gain in visual acuity is less pronounced and cannot be maintained over a longer period of time, which is related to the significantly lower number of injections administered in clinical routine. Here we report a case series from our clinical routine of patients treated with ranibizumab for visual significant DME.

Patients/Material and Methods: Retrospective case series of 335 cases with follow-up of up to 3 years. All cases in our clinic treated for visual significant DME with at least one injection of ranibizumab were evaluated for the course of visual acuity gain and number of injections received.
Results: A mean gain in visual acuity (VA) of +5.6 and +3.7 letters was found in years one and two, respectively, with a median VA of logMAR 0.52 (decimal 0.3) at baseline. The steepest increase in VA is found during the first 4 months, with a less pronounced increase up to month 16. The mean number of injections was 5.7, 3.2 and 1.1 for years one, two, and three, respectively.

Conclusions: Results of real life treatment in clinical routine are found to fall behind controlled, prospective trials, as found to the findings in other anti-VEGF indications: mean gain in VA is lower than in prospective trials, and the initial gain cannot be fully maintained over a prolonged time period. Similarly, the number of injections received is markedly lower than in controlled trials. This can partially be explained by differences in study populations and a negative selection bias in longer term results. However, additional barriers that hamper timely treatment tailored to disease activity requirements must be identified and circumvented where possible.

PMID: 29232757

Retina. 2017 Dec 11. [Epub ahead of print]

INTRAVITREAL ZIV-AFLIBERCEPT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: 52-Week Results.


PURPOSE: To evaluate the 52-week safety and efficacy of intravitreal ziv-aflibercept in patients with neovascular age-related macular degeneration.

METHODS: All patients received three monthly intravitreal injections of 0.05 mL of ziv-aflibercept (1.25 mg) followed by a pro re nata regimen. The best-corrected visual acuity and spectral domain optical coherence tomography were obtained at baseline and monthly. Full-field and multifocal electroretinograms were obtained at baseline and 4, 13, 26, and 52 weeks. For some full-field electroretinography parameters, we calculated the differences between baseline and 52 weeks and then compared those differences between treated and untreated fellow eyes.

RESULTS: Fifteen patients were included and 14 completed the 52-week follow-up. The mean best-corrected visual acuity improved from 0.95 ± 0.41 (20/200) at baseline to 0.75 ± 0.51 (20/125) logarithm of the minimum angle of resolution at 52 weeks (P = 0.0066). The baseline central retinal thickness decreased from 478.21 ± 153.48 μm to 304.43 ± 98.59 μm (P = 0.0004) at 52 weeks. Full-field electroretinography parameters used to assess retinal toxicity after intravitreal injections (rod response and oscillatory potentials) remained unchanged during follow-up. The average multifocal electroretinography macular response in 5° showed increased N1-P1 amplitude and decreased P1 implicit time (P < 0.05). One patient presented with intraocular inflammation after the seventh intravitreal procedure.

CONCLUSION: The results suggested that intravitreal ziv-aflibercept might be safe and effective for treating neovascular age-related macular degeneration. More patients and a longer follow-up are needed to confirm the long-term outcomes of intravitreal ziv-aflibercept.

PMID: 29232334


Investigation of time to first presentation and extrahospital factors in the treatment of neovascular age-related macular degeneration: a retrospective cross-sectional study.

Sim PY, Gajree S, Dhillon B, Borooah S.
OBJECTIVES: To assess the time from symptom onset to treatment for neovascular age-related macular degeneration (nvAMD) and to measure the awareness of AMD in Southeast Scotland.

DESIGN: Retrospective cross-sectional study.

SETTING: Secondary care, Southeast of Scotland.

METHODS: Patients treated with intravitreal therapy (IVT) for nvAMD in Southeast Scotland between 2013 and 2015 were identified using a treatment register. Notes were retrospectively reviewed. We measured time from: (A) symptom onset to first presentation at primary care, (B) referral to ophthalmic clinic appointment and (C) ophthalmic clinic appointment to first IVT treatment. To investigate AMD awareness, we performed a cluster random sample survey of patients visiting non-AMD ophthalmic clinics using a previously validated 12-item questionnaire.

RESULTS: 195 patients (mean age 78 years) were included in the study. The mean delays between the different stages A, B and C were 54.2 (95% CI ±13), 28.2 (95% CI ±4.0) and 31.5 (95% CI ±3.6) days, respectively. There was an additional mean delay of 7.5 (95% CI ±1.6) days when patients were indirectly referred by optometrists via general practitioners (P<0.05). 140 patients (mean age 78) participated in the awareness survey; 62.1% reported being ‘aware’ of AMD but only 37.3% described AMD symptoms correctly.

CONCLUSIONS: There was a significant delay at every step of the nvAMD care pathway. The causes for this were multifactorial and included delays in first presentation to a healthcare provider, referral from primary care and initiation of secondary care treatment. Our data are likely to underestimate prehospital delays as a large number of cases are likely to have undefined symptoms and onset. We also identified suboptimal awareness of AMD which could account for a substantial delay in presentation from symptom onset. These findings highlight the need to address AMD awareness and the need for urgent treatment to prevent avoidable vision loss resulting from nvAMD.

PMID: 29229653


SEVERE IMMUNE-MEDIATED THROMBOCYTOPENIA AFTER INTRAVITREAL BEVACIZUMAB INJECTION.

Li T, Witteman DT, Weber ED, Alexander WL, Schaber JD.

PURPOSE: To report a case of severe immune-mediated thrombocytopenia after intravitreal bevacizumab administration.

METHODS: A 77-year-old man with right-sided macular degeneration received intravitreal bevacizumab. After his third treatment dose, he was hospitalized for symptomatic thrombocytopenia (platelet count of 3 k/μL) and underwent testing to determine the etiology.

RESULTS: Initial platelet counts on admission were 3 k/μL, down from 238 k/μL 3 months before. A peripheral smear, coagulation studies, and an abdominal CT were unremarkable. A bone marrow biopsy revealed hypercellular marrow with megakaryocytic hyperplasia. Serum antiplatelet antibody testing identified antibodies against glycoprotein IV and human leukocyte antigens. A total of 13 units of platelets were administered and resulted in no significant response. Treatment with rituximab, romiplostim, and human leukocyte antigen-matched platelets resulted in slow recovery and normalization of platelet counts.

CONCLUSION: The case presented shows apparent severe immune-mediated thrombocytopenia after intravitreal bevacizumab administration.

PMID: 29227349


PURPOSE: In this study (AMD2000), we aimed to determine the visual prognosis of Japanese patients with age-related macular degeneration (AMD).

METHODS: This was a multicenter prospective observational cohort study. In total, 460 patients with AMD were recruited from April 2006 to March 2009 from 18 clinical trial sites in Japan. They were followed up for 5 years, as they continued to receive medical treatment.

RESULTS: Of the 409 study eyes followed up for at least 1 year, 243 eyes (59.4%) were treated with photodynamic therapy (PDT) using verteporfin, and 58 eyes (14.2%) were treated with intravitreal injections of antivascular endothelial growth factor agents as the initial treatment. The mean best-corrected visual acuities (BCVA) for typical AMD (tAMD; 0.688 ± 0.498) and polypoidal choroidal vasculopathy (PCV; 0.451 ± 0.395) were significantly less at 2 years (tAMD, 0.779 ± 0.632, P < 0.05; PCV, 0.534 ± 0.618, P < 0.05) and at 5 years (AMD, 0.873 ± 0.718, P < 0.05; PCV, 0.635 ± 0.668, P < 0.05) than at baseline. In eyes with tAMD, absence of blocked fluorescence was associated with 5-year maintenance of the baseline BCVA. Regarding PCV, the presence of polypoidal lesions and cystoid macular edema as well as the lesion size was associated with 5-year maintenance of the baseline BCVA. In some patients, the diagnosis changed: of the 192 eyes initially diagnosed with typical AMD, 19 were newly diagnosed with PCV during follow-up.

CONCLUSION: Maintaining the baseline BCVA over the long term is difficult in Japanese eyes with wet AMD.

PMID: 29224056

Other treatment & diagnosis

JAMA. 2017 Dec 12;318(22):2211-2223.

Development and Validation of a Deep Learning System for Diabetic Retinopathy and Related Eye Diseases Using Retinal Images From Multiethnic Populations With Diabetes.

Ting DSW, Cheung CY, Lim G, Wong TY et al.

IMPORTANCE: A deep learning system (DLS) is a machine learning technology with potential for screening diabetic retinopathy and related eye diseases.

OBJECTIVE: To evaluate the performance of a DLS in detecting referable diabetic retinopathy, vision-threatening diabetic retinopathy, possible glaucoma, and age-related macular degeneration (AMD) in community and clinic-based multiethnic populations with diabetes.

DESIGN, SETTING, AND PARTICIPANTS: Diagnostic performance of a DLS for diabetic retinopathy and related eye diseases was evaluated using 494 661 retinal images. A DLS was trained for detecting diabetic retinopathy (using 76 370 images), possible glaucoma (125 189 images), and AMD (72 610 images), and performance of DLS was evaluated for detecting diabetic retinopathy (using 112 648 images), possible glaucoma (71 896 images), and AMD (35 948 images). Training of the DLS was completed in May 2016, and validation of the DLS was completed in May 2017 for detection of referable diabetic retinopathy (moderate nonproliferative diabetic retinopathy or worse) and vision-threatening diabetic retinopathy (severe nonproliferative diabetic retinopathy or worse) using a primary validation data set in the Singapore
National Diabetic Retinopathy Screening Program and 10 multiethnic cohorts with diabetes.

EXPOSURES: Use of a deep learning system.

MAIN OUTCOMES AND MEASURES: Area under the receiver operating characteristic curve (AUC) and sensitivity and specificity of the DLS with professional graders (retinal specialists, general ophthalmologists, trained graders, or optometrists) as the reference standard.

RESULTS: In the primary validation dataset (n = 14,880 patients; 71,896 images; mean [SD] age, 60.2 [2.2] years; 54.6% men), the prevalence of referable diabetic retinopathy was 3.0%; vision-threatening diabetic retinopathy, 0.6%; possible glaucoma, 0.1%; and AMD, 2.5%. The AUC of the DLS for referable diabetic retinopathy was 0.936 (95% CI, 0.925–0.943), sensitivity was 90.5% (95% CI, 87.3%–93.0%), and specificity was 91.6% (95% CI, 91.0%–92.2%). For vision-threatening diabetic retinopathy, AUC was 0.958 (95% CI, 0.956–0.961), sensitivity was 100% (95% CI, 94.1%–100.0%), and specificity was 91.1% (95% CI, 90.7%–91.4%). For possible glaucoma, AUC was 0.942 (95% CI, 0.929–0.954), sensitivity was 96.4% (95% CI, 81.7%–99.9%), and specificity was 87.2% (95% CI, 86.8%–87.5%). For AMD, AUC was 0.931 (95% CI, 0.928–0.935), sensitivity was 93.2% (95% CI, 91.1%–99.8%), and specificity was 88.7% (95% CI, 88.3%–89.0%). For referable diabetic retinopathy in the 10 additional datasets, AUC range was 0.889 to 0.983 (n = 40,752 images).

CONCLUSIONS AND RELEVANCE: In this evaluation of retinal images from multiethnic cohorts of patients with diabetes, the DLS had high sensitivity and specificity for identifying diabetic retinopathy and related eye diseases. Further research is necessary to evaluate the applicability of the DLS in health care settings and the utility of the DLS to improve vision outcomes.

PMID: 29234807


Windsor MA, Sun SJJ, Frick KD, Swanson EA, Rosenfeld PJ, Huang D.

PURPOSE: To compare patient and Medicare savings from the use of optical coherence tomography (OCT) in guiding therapy for neovascular age-related macular degeneration (nvAMD) to the research investments made in developing OCT by the National Institutes of Health (NIH) and the National Science Foundation (NSF).

DESIGN: Observational cohort study.

METHODS: Main outcome measures were spending by Medicare as tracked by Current Procedural Terminology codes on intravitreal injections (67028), retinal OCT imaging (92134), and anti-vascular endothelial growth factor (anti-VEGF) treatment-specific J-codes (J0178, J2778, J9035, J3490, and J3590). These claims were identified from the Medicare Provider Utilization and Payment Data from the Centers for Medicare and Medicaid Services among fee-for-service (FFS) Medicare beneficiaries from 2012 to 2015; 2008 claims were acquired from the 100% FFS Part B Medicare Claims File. OCT research costs were determined by searching for grants awarded by NIH and NSF from inception to 2015. All costs and savings were discounted by 3% annually and adjusted for inflation to 2015 dollars.

RESULTS: From 2008 to 2015, the United States government and nvAMD patients have accrued an estimated savings of $9.0 billion and $2.2 billion, respectively, from the use of OCT to guide personalized anti-VEGF treatment. The $9.0 billion represents a 21-fold return on government investment into developing the technology through NIH and NSF grants.

CONCLUSIONS: Although an overall cost-benefit ratio of government-sponsored research is difficult to
estimate because the benefit may be diffuse and delayed, the investment in OCT over 2 decades has been recouped many times over in just a few years through better personalized therapy.

PMID: 29224686 PMCID: PMC5732022

**Ophthalmology. 2017 Dec 8. [Epub ahead of print]**

**Fully Automated Detection and Quantification of Macular Fluid in OCT Using Deep Learning.**


PURPOSE: Development and validation of a fully automated method to detect and quantify macular fluid in conventional OCT images.

DESIGN: Development of a diagnostic modality.

PARTICIPANTS: The clinical dataset for fluid detection consisted of 1200 OCT volumes of patients with neovascular age-related macular degeneration (AMD, n = 400), diabetic macular edema (DME, n = 400), or retinal vein occlusion (RVO, n = 400) acquired with Zeiss Cirrus (Carl Zeiss Meditec, Dublin, CA) (n = 600) or Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) (n = 600) OCT devices.

METHODS: A method based on deep learning to automatically detect and quantify intraretinal cystoid fluid (IRC) and subretinal fluid (SRF) was developed. The performance of the algorithm in accurately identifying fluid localization and extent was evaluated against a manual consensus reading of 2 masked reading center graders.

MAIN OUTCOME MEASURES: Performance of a fully automated method to accurately detect, differentiate, and quantify intraretinal and SRF using area under the receiver operating characteristics curves, precision, and recall.

RESULTS: The newly designed, fully automated diagnostic method based on deep learning achieved optimal accuracy for the detection and quantification of IRC for all 3 macular pathologies with a mean accuracy (AUC) of 0.94 (range, 0.91-0.97), a mean precision of 0.91, and a mean recall of 0.84. The detection and measurement of SRF were also highly accurate with an AUC of 0.92 (range, 0.86-0.98), a mean precision of 0.61, and a mean recall of 0.81, with superior performance in neovascular AMD and RVO compared with DME, which was represented rarely in the population studied. High linear correlation was confirmed between automated and manual fluid localization and quantification, yielding an average Pearson's correlation coefficient of 0.90 for IRC and of 0.96 for SRF.

CONCLUSIONS: Deep learning in retinal image analysis achieves excellent accuracy for the differential detection of retinal fluid types across the most prevalent exudative macular diseases and OCT devices. Furthermore, quantification of fluid achieves a high level of concordance with manual expert assessment. Fully automated analysis of retinal OCT images from clinical routine provides a promising horizon in improving accuracy and reliability of retinal diagnosis for research and clinical practice in ophthalmology.

PMID: 29224926

**Prog Retin Eye Res. 2017 Dec 8. [Epub ahead of print]**

**Optical coherence tomography angiography.**

Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G.

Abstract: Optical coherence tomography (OCT) was one of the biggest advances in ophthalmic imaging.
Building on that platform, OCT angiography (OCTA) provides depth resolved images of blood flow in the retina and choroid with levels of detailed far exceeding that obtained with older forms of imaging. This new modality is challenging because of the need for new equipment and processing techniques, current limitations of imaging capability, and rapid advancements in both imaging and in our understanding of the imaging and applicable pathophysiology of the retina and choroid, and the requirement for understanding the origins of image artifacts. These factors lead to a steep learning curve, even for those with a working understanding dye-based ocular angiography. All for a method of imaging that is a little more than 10 years old. This review begins with a historical account of the development of OCTA, and the methods used in OCTA, including signal processing, image generation, and display techniques. This forms the basis to understand what OCTA images show as well as how image artifacts arise. The anatomy and imaging of specific vascular layers of the eye are reviewed. The integration of OCTA in multimodal imaging in the evaluation of retinal vascular occlusive diseases, diabetic retinopathy, uveitis, inherited diseases, age-related macular degeneration, and disorders of the optic nerve is presented. OCTA is an exciting, disruptive technology. Its use is rapidly expanding in clinical practice as well as for research into the pathophysiology of diseases of the posterior pole.

PMID: 29229445

Ophthalmic Res. 2017 Dec 14. [Epub ahead of print]

Outer Retina and Choroidal Thickness in Intermediate Age-Related Macular Degeneration: Reticular Pseudodrusen Findings.

Camacho P, Dutra-Medeiros M, Cabral D, Silva R.

PURPOSE: To evaluate outer retina and choroidal thickness in subjects with intermediate age-related macular degeneration (iAMD) and to describe associations with the presence of reticular pseudodrusen (RPD).

METHODS: This was a retrospective, cross-sectional analysis of 157 consecutive eyes (specifically: 62 eyes classified as having RPD and 95 eyes with drusen ≥125 µm). Only cases with digital color fundus photographs, red-free, and infrared, obtained and graded according to the Age-Related Eye Disease Study to define iAMD, were used for this study. Outer retina and choroidal thickness were manually segmented and quantified at 12 locations in the horizontal meridian.

RESULTS: RPD appeared to be associated with thinning of the outer layers even after adjustment for gender and age. The presence of RPD in iAMD decreased with increase of choroidal thickness (total odds ratio [OR] 0.991, 95% confidence interval [CI] 0.985-0.996; nasal OR 0.992, 95% CI 0.986-0.997), with increased thickness of the myoid zone of the photoreceptors (total OR 0.812, 95% CI 0.688-0.958; nasal OR 0.863, 95% CI 0.755-0.987) and with increased thickness of the outer segment of the photoreceptors (total OR 0.850, 95% CI 0.731-0.989; nasal OR 0.857, 95% CI 0.736-0.989).

CONCLUSIONS: The greatest differences between eyes with and without RPD are found at the level of the choroidal thickness and at the level of the photoreceptors.

PMID: 29237169

Neurology. 2017 Dec 13. [Epub ahead of print]

Differential associations between retinal signs and CMBs by location: The AGES-Reykjavik Study.

OBJECTIVE: To test the hypothesis that age-related macular degeneration (AMD) and retinal microvascular signs are differentially associated with lobar and deep cerebral microbleeds (CMBs).

METHODS: CMBs in lobar regions indicate cerebral amyloid angiopathy (CAA). β-Amyloid deposits are implicated in both CAA and AMD. Deep CMBs are associated with hypertension, a major risk factor for retinal microvascular damage. This population-based cohort study included 2,502 participants in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study who undertook binocular digital retinal photographs at baseline (2002-2006) to assess retinal microvascular signs and AMD and brain MRI scan at both baseline and follow-up (2007-2011) to assess CMBs. We assessed retinal microvascular lesion burden by counting the 3 retinal microvascular signs (focal arteriolar narrowing, arteriovenous nicking, and retinopathy) concurrently present in the participant. We used multiple logistic models to examine the association of baseline retinal pathology to incident CMBs detected at follow-up.

RESULTS: During an average 5.2 years of follow-up, 461 people (18.3%) developed new CMBs, including 293 in exclusively lobar regions and 168 in deep regions. Pure geographic atrophy was significantly associated with strictly lobar CMBs (multivariable-adjusted odds ratio 2.59, 95% confidence interval [CI] 1.01-6.65) but not with deep CMBs. Concurrently having ≥2 retinal microvascular signs was associated with a 3-fold (95% CI 1.73-5.20) increased likelihood for deep CMBs but not exclusively lobar CMBs.

CONCLUSIONS: Retinal microvascular signs and pure geographic atrophy may be associated with deep and exclusively lobar CMBs, respectively, in older people. These results have implications for further research to define the role of small vessel disease in cognitive impairment.

PMID: 29237799

Retina. 2017 Dec 8. [Epub ahead of print]

COMPARISON AMONG DIFFERENT DIAGNOSTIC METHODS IN THE STUDY OF TYPE AND ACTIVITY OF CHOROIDAL NEOVASCULAR MEMBRANES IN AGE-RELATED MACULAR DEGENERATION.

Ravera V, Giani A, Pellegrini M, Oldani M, Invernizzi A, Carini E, Cigada M, Bottoni F, Staurenghi G.

PURPOSE: To determine interobserver and intraobserver agreement in classifying the subtypes of choroidal neovascularization (CNV) and the decision of retreatment in patients affected by exudative age-related macular degeneration. Different imaging techniques were evaluated individually and compared with multimaging.

METHODS: Fifty-two patients with naive CNV in age-related macular degeneration were evaluated after 3 monthly intravitreal injections of ranibizumab. Choroidal neovascularization subtype and activity were evaluated using spectral domain optical coherence tomography, infrared light, fundus autofluorescence, fluorescein angiography (FA), and indocyanine green angiography (ICGA). The evaluation was performed independently by 10 different retina specialists, 2 for each test. Other two operators analyzed all the information available together.

RESULTS: The interobserver k regarding the types of CNV was 0.69 for multimaging, 0.63 for spectral domain optical coherence tomography, 0.43 for FA, and 0.46 for ICGA. The k values for interobserver for retreatment decision were 0.77 for multimaging, 0.88 for spectral domain optical coherence tomography, 0.61 for infrared, 0.37 for fundus autofluorescence, 0.25 for FA, and 0.23 for ICGA. Fluorescein angiography, spectral domain optical coherence tomography, ICGA, and infrared showed good association with multimaging on defining CNV activity (P = 0.0003, P < 0.0001, P = 0.01, and P = 0.05, respectively).

CONCLUSION: Optical coherence tomography and infrared evaluations of CNV activity were reproducible and strongly associated with multimaging, whereas FA and ICGA evaluations showed poor reproducibility.

PMID: 29232336
Spectral-Domain Optical Coherence Tomography Angiography for the Diagnosis and Evaluation of Polypoidal Choroidal Vasculopathy.

de Carlo TE, Kokame GT, Shantha JG, Lai JC, Wee R.

PURPOSE: To compare the diagnostic ability of optical coherence tomography angiography (OCTA) with indocyanine green angiography (ICGA) in polypoidal choroidal vasculopathy (PCV).

METHODS: Retrospective review of 47 eyes with PCV imaged with ICGA and OCTA. For each eye, it was determined which imaging modality better delineated the PCV complex. The presence of a branching vascular network (BVN) and polyp(s) were noted.

RESULTS: PCV was better visualized with ICGA in 21 eyes (44.7%) and with OCTA in 9 eyes (19.2%). The results were comparable in 17 eyes (36.2%). Of the 44 eyes with BVN on ICGA, 41 eyes (93.2%) also showed BVN on OCTA. Of the 28 eyes with polyp(s) on ICGA, 22 eyes (78.6%) also showed polyp(s) on OCTA. Polyps were high-flow lesions or faint low-flow dilations on OCTA.

CONCLUSION: OCTA readily detects BVNs and can detect most polyps, but in many cases ICGA is better able to detect the PCV complex.

PMID: 29227980

Automated retinal health diagnosis using pyramid histogram of visual words and Fisher vector techniques.

Koh JEW, Ng EYK, Bhandary SV, Hagiwara Y, Laude A, Acharya UR.

Abstract: Untreated age-related macular degeneration (AMD), diabetic retinopathy (DR), and glaucoma may lead to irreversible vision loss. Hence, it is essential to have regular eye screening to detect these eye diseases at an early stage and to offer treatment where appropriate. One of the simplest, non-invasive and cost-effective techniques to screen the eyes is by using fundus photo imaging. But, the manual evaluation of fundus images is tedious and challenging. Further, the diagnosis made by ophthalmologists may be subjective. Therefore, an objective and novel algorithm using the pyramid histogram of visual words (PHOW) and Fisher vectors is proposed for the classification of fundus images into their respective eye conditions (normal, AMD, DR, and glaucoma). The proposed algorithm extracts features which are represented as words. These features are built and encoded into a Fisher vector for classification using random forest classifier. This proposed algorithm is validated with both blindfold and ten-fold cross-validation techniques. An accuracy of 90.06% is achieved with the blindfold method, and highest accuracy of 96.79% is obtained with ten-fold cross-validation. The highest classification performance of our system shows the potential of deploying it in polyclinics to assist healthcare professionals in their initial diagnosis of the eye. Our developed system can reduce the workload of ophthalmologists significantly.

PMID: 29227822

Concurrent OCT imaging of stimulus evoked retinal neural activation and hemodynamic responses.

Son T, Wang B, Lu Y, Chen Y, Cao D, Yao X.

Abstract: It is well established that major retinal diseases involve distortions of the retinal neural physiology
and blood vascular structures. However, the details of distortions in retinal neurovascular coupling associated with major eye diseases are not well understood. In this study, a multi-modal optical coherence tomography (OCT) imaging system was developed to enable concurrent imaging of retinal neural activity and vascular hemodynamics. Flicker light stimulation was applied to mouse retinas to evoke retinal neural responses and hemodynamic changes. The OCT images were acquired continuously during the pre-stimulation, light-stimulation, and post-stimulation phases. Stimulus-evoked intrinsic optical signals (IOSs) and hemodynamic changes were observed over time in blood-free and blood regions, respectively. Rapid IOSs change occurred almost immediately after stimulation. Both positive and negative signals were observed in adjacent retinal areas. The hemodynamic changes showed time delays after stimulation. The signal magnitudes induced by light stimulation were observed in blood regions and did not show significant changes in blood-free regions. These differences may arise from different mechanisms in blood vessels and neural tissues in response to light stimulation. These characteristics agreed well with our previous observations in mouse retinas. Further development of the multi-modal OCT may provide a new imaging method for studying how retinal structures and metabolic and neural functions are affected by age-related macular degeneration (AMD), glaucoma, diabetic retinopathy (DR), and other diseases, which promises novel noninvasive biomarkers for early disease detection and reliable treatment evaluations of eye diseases.

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Relationship between reticular pseudodrusen and choroidal thickness in intermediate age-related macular degeneration.

Ho CYD, Lek JJ, Aung KZ, McGuinness MB, Luu CD, Guymer RH.

IMPORTANCE: Reticular pseudodrusen (RPD) is strongly associated with late age-related macular degeneration (AMD) but their etiology remains unknown. RPD have been associated with reduced choroidal thickness but most studies are limited by small sample size and varying severity of AMD.

BACKGROUND: To investigate the relationship between choroidal thickness (ChT) and RPD in eyes with intermediate AMD (iAMD), controlling for variables known to influence ChT.

DESIGN: Retrospective cohort study PARTICIPANTS: Participants were recruited from Centre for Eye Research Australia.

METHODS: Colour fundus photographs, fundus auto fluorescence, near infrared and spectral-domain optical coherence tomography (OCT) were graded for RPD. ChT was measured from enhanced depth imaging OCT scans at the centre of fovea, 1500 μm and 3000 μm nasal, temporal, superior and inferior from centre of fovea.

MAIN OUTCOME MEASURES: ChT between RPD and non-RPD group RESULTS: 297 eyes from 152 subjects were included. 84 (28%) had RPD and were older than non-RPD group (75.1 ± 5.4 years and 68.7 ± 6.9 years, respectively; p <0.001). In unadjusted analysis, the RPD group was significantly associated with thinner choroids across all measured locations (p ≤ 0.022). After adjustment for variables, the presence of RPD was no longer associated with ChT (p ≥0.132 for all locations) but age (p <0.001) and refractive error (p = 0.002) remained significantly associated with ChT.

CONCLUSIONS: Age and refractive error, rather than RPD, was significantly associated with reduced choroidal thickness in eyes with iAMD. Choroidal insufficiency may be a less important variable in RPD etiology than previously considered.

PMID: 29236343

Skin Intrinsic Fluorescence and Age-Related Macular Degeneration: The Beaver Dam Eye Study.

Klein R, Lee KE, Maynard JD, Meuer SM, Gangnon RE, Klein BEK.

PURPOSE: To determine if skin intrinsic fluorescence (SIF), a noninvasive measure of advanced glycation endproducts and oxidative stress in skin is associated with AMD.

METHODS: SIF was measured with the SCOUT DS skin fluorescence spectrometer in a cross-sectional cohort study of 969 persons aged 68 to 102 years from the 1181 who participated in the 25-year follow-up examination in the Beaver Dam Eye Study (BDES) in 2014 to 2016. The SCOUT DS skin fluorescence spectrometer uses five light-emitting diodes, centered at 375 nm to 456 nm. AMD was assessed by grading of digital color 45° stereoscopic fundus photographs of the macula using the Wisconsin Age-Related Maculopathy grading scheme. Analyses included logistic regression with generalized estimating equations to account for correlation between the eyes of a person.

RESULTS: There were data for 1827 eyes for analyses. Early AMD was present in 22% and late AMD in 4% of the eyes. While adjusting for age, sex, smoking status, and history of cardiovascular disease, there were no significant associations of any SIF measure with any AMD or exudative AMD. SIF01 (odds ratio per 1 SD difference on the log scale, 95% confidence interval) (1.66, 1.00-2.74, P = 0.05) and SIF03 (1.81, 1.16-2.81, P = 0.008) were associated with geographic atrophy.

CONCLUSIONS: There was a suggestive relationship of two SIF measures, SIF01 and SIF03, using different correction factors from the excitation centered at 375 nm, with the prevalence of geographic atrophy in the BDES. Longitudinal follow-up is indicated to assess a temporal relationship.

PMID: 29242907


Agreement of swept-source and spectral-domain optical coherence-tomography retinal thickness measurements in neovascular age-related macular degeneration.

Hanumunthadu D, Ilginis T, Balaggan KS, Patel PJ.

PMID: 29238160 PMCID: PMC5716399

Pathogenesis

Prog Retin Eye Res. 2017 Dec 8. [Epub ahead of print]

Neural control of choroidal blood flow.

Reiner A, Fitzgerald MEC, Del Mar N, Li C.

Abstract: The choroid is richly innervated by parasympathetic, sympathetic and trigeminal sensory nerve fibers that regulate choroidal blood flow in birds and mammals, and presumably other vertebrate classes as well. The parasympathetic innervation has been shown to vasodilate and increase choroidal blood flow, the sympathetic input has been shown to vasoconstrict and decrease choroidal blood flow, and the sensory input has been shown to both convey pain and thermal information centrally and act locally to vasodilate and increase choroidal blood flow. As the choroid lies behind the retina and cannot respond readily to retinal metabolic signals, its innervation is important for adjustments in flow required by either retinal activity, by fluctuations in the systemic blood pressure driving choroidal perfusion, and possibly by retinal temperature. The former two appear to be mediated by the sympathetic and parasympathetic nervous
systems, via central circuits responsive to retinal activity and systemic blood pressure, but adjustments for ocular perfusion pressure also appear to be influenced by local autoregulatory myogenic mechanisms. Adaptive choroidal responses to temperature may be mediated by trigeminal sensory fibers. Impairments in the neural control of choroidal blood flow occur with aging, and various ocular or systemic diseases such as glaucoma, age-related macular degeneration (AMD), hypertension, and diabetes, and may contribute to retinal pathology and dysfunction in these conditions, or in the case of AMD be a precondition. The present manuscript reviews findings in birds and mammals that contribute to the above-summarized understanding of the roles of the autonomic and sensory innervation of the choroid in controlling choroidal blood flow, and in the importance of such regulation for maintaining retinal health.

PMID: 29229444


Cellular Senescence in Age-Related Macular Degeneration: Can Autophagy and DNA Damage Response Play a Role?

Blasiak J, Piechota M, Pawlowska E, Szatkowska M, Sikora E, Kaarniranta K.

Abstract: Age-related macular degeneration (AMD) is the main reason of blindness in developed countries. Aging is the main AMD risk factor. Oxidative stress, inflammation and some genetic factors play a role in AMD pathogenesis. AMD is associated with the degradation of retinal pigment epithelium (RPE) cells, photoreceptors, and choriocapillaris. Lost RPE cells in the central retina can be replaced by their peripheral counterparts. However, if they are senescent, degenerated regions in the macula cannot be regenerated. Oxidative stress, a main factor of AMD pathogenesis, can induce DNA damage response (DDR), autophagy, and cell senescence. Moreover, cell senescence is involved in the pathogenesis of many age-related diseases. Cell senescence is the state of permanent cellular division arrest and concerns only mitotic cells. RPE cells, although quiescent in the retina, can proliferate in vitro. They can also undergo oxidative stress-induced senescence. Therefore, cellular senescence can be considered as an important molecular pathway of AMD pathology, resulting in an inability of the macula to regenerate after degeneration of RPE cells caused by a factor inducing DDR and autophagy. It is too early to speculate about the role of the mutual interplay between cell senescence, autophagy, and DDR, but this subject is worth further studies.

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Antiangiogenic effect of dasatinib in murine models of oxygen-induced retinopathy and laser-induced choroidal neovascularization.

Seo S, Suh W.

PURPOSE: Vascular endothelial growth factor (VEGF) is a principal mediator of pathological ocular neovascularization, which is the leading cause of blindness in various ocular diseases. As Src, a non-receptor tyrosine kinase, has been implicated as one of the major signaling molecules in VEGF-mediated neovascularization, the present study aimed to investigate whether dasatinib, a potent Src kinase inhibitor, could suppress pathological ocular neovascularization in murine models of oxygen-induced retinopathy (OIR) and choroidal neovascularization (CNV).

METHODOLOGY: Tube formation, scratch wounding migration, and cell proliferation assays were performed to measure the inhibitory effect of dasatinib on VEGF-induced angiogenesis in human retinal microvascular endothelial cells. Murine models of OIR and laser-induced CNV were used to assess the preventive effect of an intravitreal injection of dasatinib on pathological neovascularization in the retina and choroid.
Neovascularization and Src phosphorylation were evaluated with immunofluorescence staining.

RESULTS: Dasatinib efficiently inhibited VEGF-induced endothelial proliferation, wounding migration, and tube formation. In mice with OIR and laser injury-induced CNV, eyes treated with a single intravitreal injection of dasatinib exhibited significant decreases in pathological neovascularization compared with that of controls injected with vehicle. The dasatinib-treated OIR mice also showed a decrease in Src phosphorylation in the periretinial tufts. The intravitreal injection of dasatinib did not cause ocular toxicity at the treatment dose administered.

CONCLUSIONS: These results demonstrated that dasatinib suppressed pathological neovascularization in the mouse retina and choroid. Therefore, dasatinib may be indicated for the treatment of ischemia-induced proliferative retinopathy and neovascular age-related macular degeneration.

PMID: 29225458 PMCID: PMC5710972


Pathogenesis of age-related macular degeneration - dialogue between autophagy and inflammasomes.

Kivinen N, Koskela A, Kauppinen A, Kaarniranta K.

Abstract: Age-related macular degeneration is a condition affecting central vision, and is the leading cause of blindness and visual impairment in the western countries. For a long time, inflammation has been associated with the pathogenesis of the condition, and according to current knowledge, inflammation in the retinal pigment epithelial cells (RPE) results from an impairment of intracellular cleansing systems. In combination with the degeneration of RPE cells, this eventually leads to the destruction of light-sensing cells. By influencing the accumulation or elimination of waste material or the inflammatory reaction following its accumulation we may in the future possibly slow the progression of the disease or, in the best case, even cure it.

PMID: 29243450

Genetics & gene therapy


Delivery of CR2-fH Using AAV Vector Therapy as Treatment Strategy in the Mouse Model of Choroidal Neovascularization.

Schnabolk G, Parsons N, Obert E, Annamalai B, Nasarre C, Tomlinson S, Lewin AS, Rohrer B.

Abstract: Complement activation plays a significant role in age-related macular degeneration (AMD) pathogenesis, and polymorphisms interfering with factor H (fH) function, a complement alternative pathway (AP) inhibitor, are associated with increased AMD risk. We have previously validated an AP inhibitor, a fusion protein consisting of a complement receptor 2 fragment linked to the inhibitory domain of fH (CR2-fH) as an efficacious treatment for choroidal neovascularization (CNV) when delivered intravenously. Here we tested an alternative approach of AAV-mediated delivery (AAV5-VMD2-CR2-fH or AAV5-VMD2-mCherry) using subretinal delivery in C57BL/6J mice. Secretion of CR2-fH was confirmed in polarized retinal pigment epithelium (RPE) cells. A safe concentration of AAV5-VMD2-CR2-fH was identified using electroretinography, optical coherence tomography (OCT), RPE morphology, and antibody profiling. One month after gene delivery, CNV was induced using argon laser photocoagulation. OCT assessment demonstrated reduced CNV with AAV5-VMD2-CR2-fH administration. Bioavailability studies revealed that gene-therapy delivered similar levels of CR2-fH to the RPE/choroid as treatment by intravenous injections, and C3a ELISA verified reduced CNV-associated ocular C3a production. These results contribute to existing data illustrating the importance of the AP of complement in CNV development and its potential role.
in AMD treatment. Demonstration of AAV-vector efficacy opens new avenues for the development of treatment strategies.

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Association of Rare Predicted Loss-of-Function Variants in Cellular Pathways with Sub-Phenotypes in Age-Related Macular Degeneration.


PURPOSE: To investigate the association of rare predicted loss-of-function (pLoF) variants within age-related macular degeneration (AMD) risk loci and AMD sub-phenotypes.

DESIGN: Case-control study.

PARTICIPANTS: Participants of AREDS, AREDS2, and Michigan Genomics Initiative.

METHODS: Whole genome sequencing data were analyzed for rare pLoF variants (frequency <0.1%) in the regions of previously identified 52 independent risk variants known to be associated with AMD. Frequency of the rare pLoF variants in cases with intermediate or advanced AMD was compared with controls. Variants were assigned to the complement, extracellular matrix (ECM), lipid, cell survival, immune system, metabolism, or unknown/other pathway. Associations of rare pLoF variant pathways with AMD sub-phenotypes were analyzed using logistic and linear regression, and Cox proportional hazards models.

MAIN OUTCOME MEASURES: Differences in rare pLoF variant pathway burden and association of rare pLoF variant pathways within the population with AMD were evaluated.

RESULTS: Rare pLoF variants were found in 298 of 1689 cases (17.6%) and 237 of 1518 controls (15.6%) (odds ratio [OR], 1.11; 95% confidence interval [CI], 0.91-1.36; P = 0.310). An enrichment of rare pLoF variants in the complement pathway in cases versus controls (OR, 2.94; 95% CI, 1.49-5.79; P = 0.002) was observed. Within cases, associations between all rare pLoF variants and choroidal neovascularization (CNV) (OR, 1.34; 95% CI, 1.04-1.73; P = 0.023), calcified drusen (OR, 1.33; 95% CI, 1.04-1.72; P = 0.025), higher scores on the AREDS Extended AMD Severity Scale (Standardized Coefficient Beta (β)=0.346 [0.086-0.605], P = 0.009), and progression to advanced disease (hazard ratio, 1.25; 95% CI, 1.01-1.55; P = 0.042) were observed. At the pathway level, there were associations between the complement pathway and geographic atrophy (GA) (OR, 2.17; 95% CI, 1.12-4.24; P = 0.023), the complement pathway and calcified drusen (OR, 3.75; 95% CI, 1.79-7.86; P < 0.001), and the ECM pathway and more severe levels in the AREDS Extended AMD Severity Scale (β = 0.62; 95% CI, 0.04-1.20; P = 0.035).

CONCLUSIONS: Rare pLoF variants are associated with disease progression. Variants in the complement pathway modify the clinical course of AMD and increase the risk of developing specific sub-phenotypes.

PMID: 29224928


Parafoveal Photoreceptor Abnormalities in Asymptomatic Patients With RP1L1 Mutations in Families With Occult Macular Dystrophy.


PURPOSE: To report the clinical characteristics of asymptomatic cases with RP1L1 gene mutations in four families with occult macular dystrophy (OMD).
METHODS: Four asymptomatic cases from four families were selected from a cohort of 40 subjects (16 families) with RP1L1 pathogenic variants. Clinical data of the four asymptomatic cases and three symptomatic patients in the same families were reviewed. The three asymptomatic cases did not have any visual symptoms in either eye, and one was unilaterally affected. Ophthalmologic examinations, including spectral-domain optical coherence tomography (OCT) were performed, and the morphologic characteristics of the photoreceptor layer of the asymptomatic cases were compared to those of the symptomatic patients within the same family.

RESULTS: The OCT images demonstrated photoreceptor abnormalities in the parafoveal regions in all of the four asymptomatic cases (i.e., absence of the interdigitation zone and blurring of the ellipsoid zone). However, these microstructures were preserved at the foveal center. The longitudinal reflectivity profiles clearly identified this distinct pattern in the asymptomatic cases. In contrast, no distinct abnormalities were detected by other examinations including perimetry, fundus autofluorescence images, and multifocal electroretinograms (ERGs).

CONCLUSIONS: The sparing of the central foveal photoreceptor layer accounts for the well-preserved visual acuity in the asymptomatic patients. The sparing may represent either the initial phase of typical OMD or a subtype of macular lesion associated with OMD. It is necessary to examine asymptomatic subjects in families with OMD because some of them may progress to the typical phenotype of OMD.

PMID: 29196766

Stem cells

Acta Biomater. 2017 Dec 9. [Epub ahead of print]

Fibrin hydrogels as a xenofree and rapidly degradable support for transplantation of retinal pigment epithelium monolayers.


Abstract: Recent phase 1 trials of embryonic stem cell and induced pluripotent stem cell (iPSCs) derived RPE transplants for the treatment of macular degeneration have demonstrated the relative safety of this process. However, there is concern over clumping, thickening, folding, and wrinkling of the transplanted RPE. To deliver a flat RPE monolayer, current phase 1 trials are testing synthetic substrates for RPE transplantation. These substrates, however, cause localized inflammation and fibrosis in animal models due to long degradation times. Here we describe the use of thin fibrin hydrogels as a support material for the transplantation of RPE. Fibrin was formed into a mechanically rigid support that allow for easy manipulation with standard surgical instruments. Using fibrinolytic enzymes, fibrin hydrogels were degraded on the scale of hours. The rate of degradation could be controlled by varying the fibrinolytic enzyme concentration used. RPE cells degraded fibrin spontaneously. To preserve the fibrin support during differentiation of iPSCs to RPE, media was supplemented with the protease inhibitor aprotinin. iPSC-RPE on fibrin gels remained viable, generated monolayers with characteristic cobblestone appearance and dark pigmentation, and expressed mRNA and protein markers characteristic of RPE in the eye. Following differentiation of the cells, addition of fibrinolytic enzymes fully and rapidly degraded the fibrin support leaving behind an intact, viable iPSC-RPE monolayer. In conclusion, human fibrin hydrogels provide a xeno-free support on which iPSCs can be differentiated to RPE cells for transplant which can be rapidly degraded under controlled conditions using fibrinolytic enzymes without adverse effects to the cells.

PMID: 29233750
Diet, lifestyle & low vision


A Nationwide Cohort Study on the Association Between Past Physical Activity and Neovascular Age-Related Macular Degeneration in an East Asian Population.

Rim TH, Kim HK, Kim JW, Lee JS, Kim DW, Kim SS.

IMPORTANCE:: It has been suggested that physical activity (PA) is associated with reduced risk for early age-related macular degeneration (AMD). Systematic evaluation has been examining the association between lifestyle and neovascular AMD in an East Asian population, with a particular focus on past vigorous PA.

OBJECTIVE: To investigate the association between neovascular AMD and past PA, particularly a history of vigorous exercise, in the overall study population and among 2 a priori-defined subgroups.

DESIGN, SETTING, AND PARTICIPANTS: In this propensity score-matched cohort study, individuals between ages 45 and 79 years who were included in the South Korean National Health Insurance Service database from 2002 through 2013 were evaluated. Physical activity and incident neovascular AMD were recorded at baseline (2002-2003) and at follow-up (August 1, 2009, to December 31, 2013), respectively. Using a 1:1 propensity score-matched analysis, the incidence of neovascular AMD was compared using hazard ratios (HRs) for neovascular AMD between 105,980 participants who did and 105,980 who did not (no-PA) engage in vigorous PA. The data analysis was performed from April 19, 2017, to June 5, 2017.

EXPOSURES: Physical activity.

MAIN OUTCOMES AND MEASURES: Incident cases of neovascular AMD.

RESULTS: Of the 211,960 participants (92,036 [43.4%] women; mean [SD] age, 55.1 [7.8] years), neovascular AMD was detected at follow-up in 250 (0.24%) individuals who engaged in past vigorous PA and in 198 (0.19%) of those who did not (HR, 1.23; 95% CI, 1.02-1.49). In subgroup analysis, vigorous PA was associated with a greater HR for neovascular AMD in participants aged 45 to 64 years (HR, 1.30; 95% CI, 1.04-1.63) and in men (HR, 1.36; 95% CI, 1.09-1.69). In the high-PA (≥5 times/wk: HR, 1.54; 95% CI, 1.15-2.06) and moderate-PA (1-4 times/wk: HR, 1.28; 95% CI, 1.01-1.63) groups, there was a greater incidence of neovascular AMD in the vigorous PA than in the no-PA group for men; no association was found for women.

CONCLUSIONS AND RELEVANCE: Self-reported past vigorous PA in men aged 45 to 64 years was associated with an increased risk for neovascular AMD. To our knowledge, no previous study has reported such an association; replication of the results would seem warranted to strengthen the likelihood of a cause and effect relationship.

PMID: 29242918


Analysis of the Association Between Physical Activity and Age-Related Macular Degeneration.

McGuinness MB, Simpson JA, Finger RP.

PMID: 29242921
EGHB010, a Standardized Extract of Paeoniae Radix and Glycyrrhiza Radix, Inhibits VEGF-Induced Tube Formation In Vitro and Retinal Vascular Leakage and Choroidal Neovascularization In Vivo.

Jung E, Jung W, Park SB, Kim CS, Kim JS, Kim J.

Abstract: EGHB010 is a hot water extract of the rhizome mixture of Paeonia lactiflora Pallas and Glycyrrhiza uralensis Fisch. Choroidal neovascularization (CNV) and vascular leakage are the common pathophysiology of age-related macular degeneration. In this study, we aimed to evaluate the effect of EGHB010 on retinal vascular leakage and laser-induced CNV in a rat model. Vascular endothelial growth factor- (VEGF-) induced tube formation was assayed in human retinal microvascular endothelial cells. Intravitreal VEGF-induced blood-retinal barrier breakdown was assayed in Sprague-Dawley rats. Experimental CNV was induced by laser photocoagulation in Brown Norway rats. EGHB010 (50 and 100 mg/kg/day) was administered orally for 10 days after laser photocoagulation. Choroidal flat mounts were prepared to measure the lesion size of CNV. Incubation of retinal vascular endothelial cells with EGHB010 (12.5 and 25 μg/mL) resulted in the inhibition of VEGF-induced tube formation in a dose-dependent manner. VEGF-mediated retinal vascular leakage was blocked by the oral administration of EGHB010. The CNV area was significantly lower in EGHB010-treated rats than in vehicle-treated rats. These results suggest that EGHB010 is a potent antiangiogenic agent. Thus, the oral administration of EGHB010 may have a beneficial effect in the treatment of vascular leakage and CNV in patients with age-related macular degeneration.

PMID: 29234364 PMCID: PMC5646325


Language processing in age-related macular degeneration associated with unique functional connectivity signatures in the right hemisphere.

Zhuang J, Madden DJ, Duong-Fernandez X, Chen NK, Cousins SW, Potter GG, Diaz MT, Whitson HE.

Abstract: Age-related macular degeneration (AMD) is a retinal disease associated with significant vision loss among older adults. Previous large-scale behavioral studies indicate that people with AMD are at increased risk of cognitive deficits in language processing, particularly in verbal fluency tasks. The neural underpinnings of any relationship between AMD and higher cognitive functions, such as language processing, remain unclear. This study aims to address this issue using independent component analysis of spontaneous brain activity at rest. In 2 components associated with visual processing, we observed weaker functional connectivity in the primary visual cortex and lateral occipital cortex in AMD patients compared with healthy controls, indicating that AMD might lead to differences in the neural representation of vision. In a component related to language processing, we found that increasing connectivity within the right inferior frontal gyrus was associated with better verbal fluency performance across all older adults, and the verbal fluency effect was greater in AMD patients than controls in both right inferior frontal gyrus and right posterior temporal regions. As the behavioral performance of our patients is as good as that of controls, these findings suggest that preservation of verbal fluency performance in AMD patients might be achieved through higher contribution from right hemisphere regions in bilateral language networks. If that is the case, there may be an opportunity to promote cognitive resilience among seniors with AMD or other forms of late-life vision loss.

PMID: 29223681