Drug treatment


Development and Course of Scars in the Comparison of Age-related Macular Degeneration Treatments Trials.

Daniel E, Pan W, Ying GS, Kim BJ, Grunwald JE, Ferris FL 3rd, Jaffe GJ, Toth CA, Martin DF, Fine SL, Maguire MG; Comparison of Age-related Macular Degeneration Treatments Trials.

PURPOSE: To describe risk factors for scar formation and changes to fibrotic scar through 5 years in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

DESIGN: Multicenter, prospective cohort study.

PARTICIPANTS: A total of 1061 subjects in CATT.

METHODS: Color photographic and fluorescein angiographic images from baseline and 1, 2, and 5 years were evaluated. Incidence of scar formation was estimated with Kaplan-Meier curves. Risk factors were assessed with Cox regression models.

MAIN OUTCOME MEASURES: Scar formation, fibrotic scar area, and macular atrophy associated with fibrotic scar ("atrophy").

RESULTS: Cumulative proportion of eyes with scar was 32%, 46%, and 56% at years 1, 2, and 5, respectively. Baseline factors associated with increased risk (adjusted hazards ratio [aHR] and 95% confidence interval [CI]) were classic choroidal neovascularization (CNV) (aHR, 4.49; 95% CI, 3.34-6.04) versus occult, hemorrhage >1 disc area (DA) (aHR, 2.28; 95% CI, 1.49-3.47) versus no hemorrhage, retinal thickness >212 μm (aHR, 2.58; 95% CI, 1.69-3.94) versus <120 μm, subretinal tissue complex thickness >275 μm (aHR, 2.63; 95% CI, 1.81-3.84) versus ≤75 μm, subretinal fluid thickness >25 μm (aHR, 1.31; 95% CI, 0.97-1.75) versus no fluid, visual acuity (VA) in fellow eye 20/20 (aHR, 1.72; 95% CI, 1.25-2.36) versus 20/50 or worse, retinal pigment epithelium elevation absence (aHR, 1.71; 95% CI, 1.21-2.41), and subretinal hyperreflective material (aHR, 1.72; 95% CI, 1.25-2.36). Among 68 eyes that developed fibrotic scar at year 1, VA decreased by a mean of additional 13 letters between years 1 and 5. Mean scar area was 1.2, 1.2, and 1.9 DA at 1, 2, and 5 years, respectively. Atrophy was present in 18%, 24%, and 54% of these eyes at years 1, 2, and 5, respectively; the mean areas were 1.6, 2.0, and 3.1 DA, respectively. Atrophy replaced fibrotic scar in 8 eyes at year 5. There was no significant correlation between scar growth and atrophy growth. The rate of growth for both was similar between the clinical trial and observation periods.

CONCLUSIONS: Several morphologic features, including classic CNV and large hemorrhage, are associated with scar formation. Rate of new scar formation declined after 2 years. Most fibrotic scars and accompanying macular atrophy expanded over time, reducing VA.

PMID: 29454660
Comparison of Monthly vs Treat-and-Extend Regimens for Individuals With Macular Edema Who Respond Well to Anti-Vascular Endothelial Growth Factor Medications: Secondary Outcomes From the SCORE2 Randomized Clinical Trial.

Scott IU, VanVeldhuisen PC, Ip MS, Bliod BA, Oden NL, Altaweel M, Berinstein DM; SCORE2 Investigator Group.

IMPORTANCE: Comparisons of monthly vs treat-and-extend anti-vascular endothelial growth factor (anti-VEGF) regimens for macular edema from central retinal vein occlusion or hemiretinal vein occlusion is needed.

OBJECTIVE: To compare visual acuity letter score and central subfield thickness outcomes of participants in the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2) trial who then received either monthly injections or treat-and-extend (TAE) regimens of aflibercept or bevacizumab after a good response at month 6.

DESIGN, SETTING, AND PARTICIPANTS: This randomized clinical trial enrolled participants from 66 private practice or academic centers in the United States. All participants had macular edema associated with central retinal vein occlusion or hemiretinal vein occlusion, had enrolled in the SCORE2 trial, and had a protocol-defined good response to monthly injections in the first 6 months of the trial. Participants initially assigned to receive monthly aflibercept were randomized to aflibercept on a monthly or TAE schedule, and participants initially assigned to receive monthly injections of bevacizumab were randomized to receive bevacizumab on a monthly or TAE schedule. The first participant was randomized in the SCORE2 trial on September 17, 2014, and the last month 12 visit occurred on October 24, 2016.

MAIN OUTCOMES AND MEASURES: Change from month 6 to month 12 in best-corrected electronic visual acuity letter score (per the Early Treatment Diabetic Retinopathy Study).

RESULTS: The 293 participants had a mean (SD) age of 68.9 (11.9) years; 127 (43.3%) were female. Of these, 79 were randomized to aflibercept on a monthly schedule, 80 to aflibercept on a TAE schedule, 67 to monthly bevacizumab, and 67 to bevacizumab on a TAE schedule. Mean treatment group difference (the change in visual acuity letter score in the monthly group minus the change in the TAE group) from month 6 to month 12 was 1.88 (97.5% CI, -1.07 to 4.83; P = .15) for aflibercept and 1.98 (97.5% CI, -1.08 to 5.03; P = .15) for bevacizumab. In the aflibercept arm, the mean number of injections between months 6 and 11 was 5.8 in the monthly injection group (95% CI, 5.6 to 5.9) and 3.8 in the TAE group (95% CI, 3.5 to 4.1; P < .001); in the bevacizumab arm, the mean number of injections was 5.8 (95% CI, 5.6 to 5.9) in the monthly group and 4.5 in the TAE group (95% CI, 4.2 to 4.8; P < .001).

CONCLUSIONS AND RELEVANCE: One to 2 fewer injections of aflibercept or bevacizumab were given to the TAE groups than the monthly groups in months 6 to 12 for macular edema associated with central retinal or hemiretinal vein occlusion. Because of wide confidence intervals on the differences between the groups, caution is warranted before concluding that the regimens are associated with similar vision outcomes.

PMID: 29476687

THREE-YEAR OUTCOMES IN A RANDOMIZED SINGLE-BLIND CONTROLLED TRIAL OF INTRAVITREAL RANIBIZUMAB AND ORAL SUPPLEMENTATION WITH DOCOSAHEXAENOIC ACID AND ANTIOXIDANTS FOR DIABETIC MACULAR EDEMA.


PURPOSE: To report 3-year results of a randomized single-blind controlled trial of intravitreal ranibizumab...
combined with oral docosahexaenoic acid (DHA) supplementation versus ranibizumab alone in patients with diabetic macular edema.

METHODS: There were 26 patients (31 eyes) in the DHA group and 29 (38 eyes) in the control group. Ranibizumab (0.5 mg) was administered monthly for the first 4 months followed by a pro re nata (PRN) regimen. In the experimental group, patients received oral DHA supplementation (1,050 mg/day) (Brudyretina 1.5 g).

RESULTS: At 36 months, mean decrease of central subfield macular thickness was higher in the DHA-supplementation group than in controls (275 ± 50 μm vs. 310 ± 97 μm) with significant differences at Months 25, 30, 33, and 34. Between-group differences in best-corrected visual acuity were not found, but the percentages of ETDRS gains >5 and >10 letters were higher in the DHA-supplementation group. Differences serum HbA1c, plasma total antioxidant capacity values, erythrocyte DHA content, and serum IL-6 levels were all significant in favor of the DHA-supplementation group.

CONCLUSION: The addition of a high-rich DHA dietary supplement to intravitreal ranibizumab was effective to achieve better sustained improvement of central subfield macular thickness outcomes after 3 years of follow-up as compared with intravitreal ranibizumab alone.

PMID: 29474306

Retina. 2018 Feb 22. [Epub ahead of print]

ASSOCIATION BETWEEN EARLY ANATOMIC RESPONSE TO ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY AND LONG-TERM OUTCOME IN DIABETIC MACULAR EDEMA: AN INDEPENDENT ANALYSIS OF PROTOCOL I STUDY DATA.

Dugel PU, Campbell JH, Kiss S, Loewenstein A, Shih V, Xu X, Holekamp NM, Augustin AJ, Ho AC, Gonzalez VH, Whitcup SM.

PURPOSE: This post hoc analysis explores the relationship between early retinal anatomical response and long-term anatomical and visual outcomes with ranibizumab in center-involved diabetic macular edema.

METHODS: Eyes randomized to the ranibizumab plus prompt laser and ranibizumab plus deferred laser treatment arms in the Protocol I study were categorized according to their proportional reduction (<20% vs. ≥20%) in central retinal thickness (CRT) after 12 weeks. Adjusted and unadjusted analyses assessed the association between early (Week 12) anatomical response and long-term (Weeks 52 and 156) anatomical and best-corrected visual acuity outcomes.

RESULTS: Of 335 study eyes, 118 showed limited (<20%) and 217 showed strong (≥20%) CRT reduction at Week 12. In unadjusted and adjusted analyses, limited early CRT response was negatively and significantly associated with strong CRT response at Weeks 52 and 156. Sensitivity analyses indicated that this association was robust and unrelated to any "floor effect." In unadjusted analyses, a strong early CRT response was associated with greater long-term improvement in best-corrected visual acuity; after controlling for confounders, the association lost statistical significance.

CONCLUSION: Early CRT response to ranibizumab is a significant prognostic indicator of medium- to long-term anatomical outcome in center-involved diabetic macular edema. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

PMID: 29474302
EFFICACY AND SAFETY OUTCOMES OF INTRAVITREAL AFLIBERCEPT FOCUSING ON PATIENTS WITH DIABETIC MACULAR EDEMA FROM JAPAN.


PURPOSE: To evaluate the efficacy and safety of intravitreal aflibercept injection (IAI) in Japanese patients with diabetic macular edema (DME).

METHODS: VIVID-DME was a Phase 3 study comprising patients with DME randomized 1:1:1 to IAI 2 mg every 4 weeks (2q4), IAI 2 mg every 4 weeks until Week 16 then 8-week dosing (2q8), and laser. A total of 403 patients (76 Japanese) were included in this study. VIVID-Japan (72; all Japanese patients) was a nonrandomized, open-label study comprising Japanese patients with DME receiving IAI 2q4 until Week 16, then 2q8. Primary efficacy endpoint (Week 52) of VIVID-DME was mean change from baseline in best-corrected visual acuity; VIVID-Japan evaluated safety and tolerability.

RESULTS: Mean change in best-corrected visual acuity (letters) for 2q4, 2q8, and laser groups was +10.6, +10.9, and +1.2 and +9.8, +9.5, and +1.1 in the non-Japanese and Japanese populations of VIVID-DME, respectively. In VIVID-Japan, it was +9.3 for IAI 2q8. Intravitreal aflibercept injection also provided consistently greater benefits for anatomical outcomes versus laser. Adverse events were consistent with the known safety profile of IAI.

CONCLUSION: In Japanese patients with DME, IAI treatment was superior to laser for visual and anatomical outcomes and resulted in efficacy and safety outcomes similar to those in a non-Japanese patient population. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

PMID: 29470308


Ranibizumab-induced retinal reperfusion and regression of neovascularization in diabetic retinopathy: An angiographic illustration.

Chandra S, Sheth J, Anantharaman G, Gopalakrishnan M.

PURPOSE: To report regression of neovascularization and reperfusion of ischemic areas of the retina on Wide-field Digital Fluorescein Angiography following anti-vascular endothelial growth factor injections in a patient with active Proliferative Diabetic Retinopathy.

OBSERVATIONS: Case report of sixty-one-year-old male patient with proliferative diabetic retinopathy and diabetic macular edema documented on wide field digital fluorescein angiography. The patient was treated with three intravitreal injections of ranibizumab given at monthly intervals. Repeat angiography after third intravitreal injection revealed complete regression of new vessels. Moreover, there was evident improvement in perfusion in the previously noted ischemic areas of the retina.

CONCLUSION AND IMPORTANCE: Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections are a valuable treatment option for reversing neovascularization in eyes with proliferative diabetic retinopathy with fewer side effects when compared to standard pan-retinal photocoagulation. Additionally, we also illustrate restoration of retinal perfusion post anti-VEGF therapy indicative of pre-existing salvageschismic retina tissue.

PMID: 29468217 PMCID: PMC5787882

Treatment of retinal pigment epithelial detachment secondary to exudative age-related macular degeneration.

Gonzalez A, Khurshid G.

PURPOSE: This pilot study evaluated the combination of photodynamic therapy (PDT) and anti-vascular endothelial growth factor (anti-VEGF) as a treatment in patients with a pigment epithelial detachment (PED) due to exudative age-related degeneration (AMD).

METHODS: We analyzed seven consecutive patients between September 1, 2015 and September 1, 2017 with a PED secondary to exudative AMD who were treated with full fluence standard PDT and a series of monthly intravitreal anti-VEGF injections. Follow-up ranged between 3 and 24 months. Variables collected for the purpose of this study included baseline best-corrected visual acuity converted to logMAR (logarithm of minimum angle of resolution), central macular thickness, and maximum PED height. This information was then reviewed at subsequent follow-ups.

RESULTS: The PED completely resolved in 4/7 eyes while three patients had a significant improvement in PED size with a corresponding improvement in visual acuity. Initial PED heights ranged from 147 to 423 μm and was reduced by an average of 255.7 μm (83.2% average reduction, range -143 to -405 μm). Initial CMT ranged from 223 to 719 μm and was reduced by an average of 225.7 μm (54.4% average reduction, range -88 to -529 μm). Mean logMAR VA improved from 0.669 (Snellen equivalent 20/93, [20/40 to 20/200]) to 0.269 (Snellen equivalent 20/37, [20/25 to 20/80]) at last follow-up. No complications were observed in our patients.

CONCLUSIONS AND IMPORTANCE: PED in the setting of exudative AMD showed an excellent response to a combined multimodal approach that includes PDT with intravitreal anti-VEGF injection followed by a monthly anti-VEGF schedule. Most importantly, visual acuity showed a significant improvement from baseline. If confirmed by future studies, this would offer another treatment avenue for this difficult-to-treat consequence of exudative AMD.

PMID: 29468211 PMCID: PMC5786863


Removal of choroidal neovascular membrane in a case of macular hole after anti-VEGF therapy for age-related macular degeneration.

Hirata A, Hayashi K, Murata K, Nakamura KI.

PURPOSE: The formation of macular hole after receiving anti-vascular endothelial growth factor (anti-VEGF) therapy is rare. We report a case of macular hole that occurred after intravitreal injection of an anti-VEGF agent for age-related macular degeneration (AMD) in a patient, who underwent vitrectomy combined with choroidal neovascularization (CNV) removal.

OBSERVATIONS: A 64-year-old female with AMD affecting her right eye received an intravitreal injection of an anti-VEGF agent. After treatment, we identified a full thickness macular hole (MH) that was associated with the rapid resolution of the macular edema and contraction of the CNV. After performing vitrectomy combined with CNV removal, the MH closed and her visual acuity improved. Examination of the removed CNV revealed a network of microvessels devoid of pericytes.

CONCLUSIONS: and Importance: The present findings suggest that rapid resolution of macular edema and contraction of the CNV and/or mild increase in the vitreous traction after anti-VEGF therapy could potentially cause MH. CNV removal via the MH may be an acceptable procedure, if the MH remains open, the CNV is of the classic type, and it spares a central portion of the fovea.

PMID: 29468210 PMCID: PMC5786856
Results of a Treat-and-Extend Regimen of Intravitreal Ranibizumab Injection for Macular Edema due to Branch Retinal Vein Occlusion.


Abstract: To investigate the effectiveness of a treat-and-extend regimen (TAE) of intravitreal ranibizumab injections (IVR) for macular edema (ME) due to branch retinal vein occlusion (BRVO). We retrospectively examined 35 eyes of 35 patients with ME due to BRVO who underwent TAE for 1 year. Patients whose treatment interval extended to 12 weeks were switched to a pro re nata regimen (PRN; TAE to PRN group), while TAE was continued for patients whose treatment interval was less than 12 weeks (continued TAE group). Changes in best-corrected visual acuity (BCVA), central retinal thickness (CRT), and predictive factors for inclusion in the TAE to PRN group were analyzed. BCVA and CRT both improved significantly at 1 year compared with baseline (p<0.001). Sixteen eyes (45.7%) were included in the TAE to PRN group, while 19 eyes (54.3%) were included in the continued TAE group. BCVA in the TAE to PRN group was significantly better than that in the continued TAE group at 1 year (p=0.047). BCVA at baseline and macular BRVO were significant predictive factors for inclusion in the TAE to PRN group. TAE was effective for improving BCVA and CRT. The TAE to PRN group showed significantly better prognosis.

PMID: 29463937


Association between characteristics of foveal cystoid spaces and short-term responsiveness to ranibizumab for diabetic macular edema.

Murakami T, Suzuma K, Uji A, Yoshitake S, Dodo Y, Fujimoto M, Yoshitake T, Miwa Y, Yoshimura N.

PURPOSE: To investigate the association between the characteristics of foveal cystoid spaces and short-term responsiveness to ranibizumab treatment for diabetic macular edema (DME) at 3 months from the initial injection.

METHODS: We retrospectively reviewed 66 eyes of 61 patients with center-involved DME who received three consecutive ranibizumab injections and following as-needed administrations. We evaluated the relationship between visual improvement at 3 months and the preoperative optical coherence tomography (OCT) parameters including hyperreflective foci, heterogeneous OCT reflectivity, mean levels of OCT reflectivity and height of foveal cystoid spaces.

RESULTS: Twenty-three eyes without preoperative hyperreflective foci in the foveal cystoid spaces had significantly greater improvement in the logarithm of the minimum angle of resolution visual acuity (logMAR VA) at 3 months than 43 eyes with foci (P = 0.006). That was similar to the greater reduction in CSF thickness in eyes without lesions after treatment at the same time point (P < 0.001). VA improvement at 3 months was not associated with the height (R = 0.215, P = 0.083) or the reflectivity levels (R = -0.079, P = 0.538) of foveal cystoid spaces. There were no differences in VA changes between eyes with and without heterogeneous reflectivity in foveal cystoid spaces (P = 0.297). Multivariate analyses showed that logMAR VA and the absence of hyperreflective foci in foveal cystoid spaces were associated with VA improvement at 3 months.

CONCLUSION: Hyperreflective foci in foveal cystoid spaces at baseline predict poorer short-term responsiveness to ranibizumab injections for DME.

PMID: 29460019
Switching between ranibizumab and aflibercept for the treatment of neovascular age-related macular degeneration (nAMD).

Mantel I, Gillies MC, Souied EH.

Abstract: The introduction of anti-vascular endothelial growth factor (VEGF) agents such as ranibizumab and aflibercept has revolutionized the management of neovascular age-related macular degeneration. A number of randomized clinical trials have shown that ranibizumab and aflibercept produce similar efficacy and safety outcomes. Most of the switching studies published to date that show efficacy benefits are uncontrolled, retrospective trials with limitations in terms of their selection, monitoring, numbers, and assessment criteria. Based on the published literature to date, we propose arguments for and against switching anti-VEGF agents, provide our own perspective on this topic, and suggest a focus for future research.

PMID: 29476754

Anti-vascular endothelial growth factors treatment of wet age-related macular degeneration: from neurophysiology to cost-effectiveness.

Vottonen P.

PMID: 29468838

Other treatment & diagnosis

Identifying Medical Diagnoses and Treatable Diseases by Image-Based Deep Learning.

Kermany DS, Goldbaum M, Cai W, et al

Abstract: The implementation of clinical-decision support algorithms for medical imaging faces challenges with reliability and interpretability. Here, we establish a diagnostic tool based on a deep-learning framework for the screening of patients with common treatable blinding retinal diseases. Our framework utilizes transfer learning, which trains a neural network with a fraction of the data of conventional approaches. Applying this approach to a dataset of optical coherence tomography images, we demonstrate performance comparable to that of human experts in classifying age-related macular degeneration and diabetic macular edema. We also provide a more transparent and interpretable diagnosis by highlighting the regions recognized by the neural network. We further demonstrate the general applicability of our AI system for diagnosis of pediatric pneumonia using chest X-ray images. This tool may ultimately aid in expediting the diagnosis and referral of these treatable conditions, thereby facilitating earlier treatment, resulting in improved clinical outcomes. VIDEO ABSTRACT.

PMID: 29474911

Vitrectomy in patients 85 years of age and older: surgical outcomes and visual prognosis.

Anteby R, Barzelay A, Barak A.
PURPOSE: To evaluate visual and surgical outcomes in very elderly patients (above 85 years of age) undergoing pars plana vitrectomy (PPV).

PATIENTS AND METHODS: A single-center, retrospective study was carried out on the medical records of 82 patients aged 85 years and older who had undergone PPV from 2006 to 2013. Patients ranged in age from 86 to 99 years, with a mean age of 88.9 years (±2.88). Visual results and intraoperative and postoperative complications were the main outcome measures. Visual improvement/worsening was defined as at least ±0.1 logMAR change.

RESULTS: Mean follow-up was 7.25 months (±5.35), with a range of 1-28 months. General anesthesia was used in 63% of the operations. The most common indication was retinal detachment (27%). The ocular condition necessitating PPV was secondary to trauma (most commonly after a fall) in 10 eyes (12%). Mean visual acuity (VA) improved from 1/58 preoperatively to 1/29 at the final evaluation (p=0.014). Mean improvement in VA in eyes of patients with the comorbidity of age-related macular degeneration (n=34) was 41% lower compared to eyes of patients without the disease (n=48, p=0.013). In the subgroup of patients operated on for retinal detachment, 45.4% did not reach primary anatomic success and 45.4% needed additional retina-affecting surgery. One or more major ocular complications were reported in 24 eyes (29%), while 19 eyes (23%) had minor ocular complications.

CONCLUSION: Improved VA was documented in more than half of the older adults aged 85-99 undergoing vitrectomy. Despite the rate of complications in the very elderly, the possibility of optimizing visual function may positively affect quality of life in this subgroup.

PMID: 29467571 PMCID: PMC5811174


Predicting Visual Acuity by Using Machine Learning in Patients Treated for Neovascular Age-Related Macular Degeneration.

Rohm M, Tresp V, Müller M, Kern C, Manakov I, Weiss M, Sim DA, Priglinger S, Keane PA, Kortuem K.

PURPOSE: To predict, by using machine learning, visual acuity (VA) at 3 and 12 months in patients with neovascular age-related macular degeneration (AMD) after initial upload of 3 anti-vascular endothelial growth factor (VEGF) injections.

DESIGN: Database study.

PARTICIPANTS: For the 3-month VA forecast, 653 patients (379 female) with 738 eyes and an average age of 74.1 years were included. The baseline VA before the first injection was 0.54 logarithm of the minimum angle of resolution (logMAR) (±0.39). A total of 456 of these patients (270 female, 508 eyes, average age: 74.2 years) had sufficient follow-up data to be included for a 12-month VA prediction. The baseline VA before the first injection was 0.56 logMAR (±0.42).

METHODS: Five different machine-learning algorithms (AdaBoost.R2, Gradient Boosting, Random Forests, Extremely Randomized Trees, and Lasso) were used to predict VA in patients with neovascular AMD after treatment with 3 anti-VEGF injections. Clinical data features came from a data warehouse (DW) containing electronic medical records (41 features, e.g., VA) and measurement features from OCT (124 features, e.g., central retinal thickness). The VA of patient eyes excluded from machine learning was predicted and compared with the ground truth, namely, the actual VA of these patients as recorded in the DW.

MAIN OUTCOME MEASURES: Difference in logMAR VA after 3 and 12 months upload phase between prediction and ground truth as defined.

RESULTS: For the 3-month VA forecast, the difference between the prediction and ground truth was between 0.11 logMAR (5.5 letters) mean absolute error (MAE)/0.14 logMAR (7 letters) root mean square error (RMSE) and 0.18 logMAR (9 letters) MAE/0.2 logMAR (10 letters) RMSE. For the 12-month VA
forecast, the difference between the prediction and ground truth was between 0.16 logMAR (8 letters) MAE/0.2 logMAR (10 letters) RMSE and 0.22 logMAR (11 letters) MAE/0.26 logMAR (13 letters) RMSE. The best performing algorithm was the Lasso protocol.

CONCLUSIONS: Machine learning allowed VA to be predicted for 3 months with a comparable result to VA measurement reliability. For a forecast after 12 months of therapy, VA prediction may help to encourage patients adhering to intravitreal therapy.

PMID: 29454659

Pathogenesis

Cells. 2018 Feb 23;7(2).

Impaired Cargo Clearance in the Retinal Pigment Epithelium (RPE) Underlies Irreversible Blinding Diseases.

Keeling E, Lotery AJ, Tumbarello DA, Ratnayaka JA.

Abstract: Chronic degeneration of the Retinal Pigment Epithelium (RPE) is a precursor to pathological changes in the outer retina. The RPE monolayer, which lies beneath the neuroretina, daily internalises and digests large volumes of spent photoreceptor outer segments. Impaired cargo handling and processing in the endocytic/phagosome and autophagy pathways lead to the accumulation of lipofuscin and pyridinium bis-retinoid A2E aggregates and chemically modified compounds such as malondialdehyde and 4-hydroxy nonenal within RPE. These contribute to increased proteolytic and oxidative stress, resulting in irreversible damage to post-mitotic RPE cells and development of blinding conditions such as age-related macular degeneration, Stargardt disease and choroideremia. Here, we review how impaired cargo handling in the RPE results in their dysfunction, discuss new findings from our laboratory and consider how newly discovered roles for lysosomes and the autophagy pathway could provide insights into retinopathies. Studies of these dynamic, molecular events have also been spurred on by recent advances in optics and imaging technology. Mechanisms underpinning lysosomal impairment in other degenerative conditions including storage disorders, α-synuclein pathologies and Alzheimer's disease are also discussed. Collectively, these findings help transcend conventional understanding of these intracellular compartments as simple waste disposal bags to bring about a paradigm shift in the way lysosomes are perceived.

PMID: 29473871


Proteomic analysis of the human retina reveals region-specific susceptibilities to metabolic- and oxidative stress-related diseases.

Velez G, Machlab DA, Tang PH, Sun Y, Tsang SH, Bassuk AG, Mahajan VB.

Abstract: Differences in regional protein expression within the human retina may explain molecular predisposition of specific regions to ophthalmic diseases like age-related macular degeneration, cystoid macular edema, retinitis pigmentosa, and diabetic retinopathy. To quantify protein levels in the human retina and identify patterns of differentially-expressed proteins, we collected foveomacular, juxta-macular, and peripheral retina punch biopsies from healthy donor eyes and analyzed protein content by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Protein expression was analyzed with 1-way ANOVA, gene ontology, pathway representation, and network analysis. We identified a mean of 1,974 proteins in the foveomacular retina, 1,999 in the juxta-macular retina, and 1,779 in the peripheral retina. Six hundred ninety-seven differentially-expressed proteins included those unique to and abundant in each anatomic region. Proteins with higher expression in each region include: heat-shock protein 90-alpha
(HSP90AA1), and pyruvate kinase (PKM) in the foveomacular retina; vimentin (VIM) and fructose-bisphosphate aldolase C (ALDOC); and guanine nucleotide-binding protein subunit beta-1 (GNB1) and guanine nucleotide-binding protein subunit alpha-1 (GNAT1) in the peripheral retina. Pathway analysis identified downstream mediators of the integrin signaling pathway to be highly represented in the foveomacular region (P = 6.48 e-06). Metabolic pathways were differentially expressed among all retinal regions. Gene ontology analysis showed that proteins related to antioxidant activity were higher in the juxta-macular and the peripheral retina, but present in lower amounts in the foveomacular retina. Our proteomic analysis suggests that certain retinal regions are susceptible to different forms of metabolic and oxidative stress. The findings give mechanistic insight into retina function, reveal important molecular processes, and prioritize new pathways for therapeutic targeting.

PMID: 29466423


Light action spectrum on oxidative stress and mitochondrial damage in A2E-loaded retinal pigment epithelium cells.


AIMS: Blue light is an identified risk factor for age-related macular degeneration (AMD). We investigated oxidative stress markers and mitochondrial changes in A2E-loaded retinal pigment epithelium cells under the blue-green part of the solar spectrum that reaches the retina to better understand the mechanisms underlying light-elicited toxicity.

RESULTS: Primary retinal pigment epithelium cells were loaded with a retinal photosensitizer, AE2, to mimic aging. Using a custom-made illumination device that delivers 10 nm-wide light bands, we demonstrated that A2E-loaded RPE cells generated high levels of both hydrogen peroxide (H2O2) and superoxide anion (O2•-) when exposed to blue-violet light. In addition, they exhibited perinuclear clustering of mitochondria with a decrease of both their mitochondrial membrane potential and their respiratory activities. The increase of oxidative stress resulted in increased levels of the oxidized form of glutathione and decreased superoxide dismutase (SOD) and catalase activities. Furthermore, mRNA expression levels of the main antioxidant enzymes (SOD2, catalase, and GPX1) also decreased.

CONCLUSIONS: Using an innovative illumination device, we measured the precise action spectrum of the oxidative stress mechanisms on A2E-loaded retinal pigment epithelium cells. We defined 415-455 nm blue-violet light, within the solar spectrum reaching the retina, to be the spectral band that generates the highest amount of reactive oxygen species and produces the highest level of mitochondrial dysfunction, explaining its toxic effect. This study further highlights the need to filter these wavelengths from the eyes of AMD patients.

PMID: 29459695


Distinct CD40L receptors mediate inflammasome activation and secretion of IL-1β and MCP-1 in cultured human retinal pigment epithelial cells.

Bian ZM, Field MG, Elner SG, Kahlenberg JM, Elner VM.

Abstract: CD40L signaling occurs in several diseases with inflammatory components, including ocular and retinal diseases. However, it has never been evaluated as a pathogenic mechanism in age-related macular degeneration (AMD) or as an inducer of inflammasome formation in any cell type. mRNA and protein levels of CD40, IL-1β, NALP1, NALP3, caspase-1, and caspase-5 were determined by RT-PCR, qPCR, and
Western blot. CD40L receptor (CD40, α5β1, and CD11b) expression was determined by Western and immunofluorescent staining. IL-1β, IL-18, and MCP-1 secretions were determined by ELISA. NALP1 and NALP3 inflammasome formation were determined by Co-IP. Experiments were conducted on primary human retinal pigment epithelial (hRPE) cells from four different donors. Human umbilical vein endothelial (HUVEC) and monocytic leukemia (THP-1) cells demonstrated the general applicability of our findings. In hRPE cells, CD40L-induced NALP1 and NALP3 inflammasome activation, cleavage of caspase-1 and caspase-5, and IL-1β and IL-18 secretion. Interestingly, neutralizing CD11b and α5β1 antibodies, but not CD40, reduced CD40L-induced IL-1β secretion in hRPE cells. Similarly, CD40L treatment also induced HUVEC and THP-1 cells to secret IL-1β through CD11b and α5β1. Additionally, the CD40L-induced IL-1β secretion acted in an autocrine/paracrine manner to feed back and induce hRPE cells to secrete MCP-1. This study is the first to show that CD40L induces inflammasome activation in any cell type, including hRPE cells, and that this induction is through CD11b and α5β1 cell-surface receptors. These mechanisms likely play an important role in many retinal and non-retinal diseases and provide compelling drug targets that may help reduce pro-inflammatory processes.

PMID: 29454857

Genetics & gene therapy

ATP-binding cassette subfamily A, member 4 intronic variants c.4773+3A>G and c.5461-10T>C cause Stargardt disease due to defective splicing.


PURPOSE: Inherited retinal dystrophies (IRDs) represent a group of progressive conditions affecting the retina. There is a great genetic heterogeneity causing IRDs, and to date, more than 260 genes are associated with IRDs. Stargardt disease, type 1 (STGD1) or macular degeneration with flecks, STGD1 represents a disease with early onset, central visual impairment, frequent appearance of yellowish flecks and mutations in the ATP-binding cassette subfamily A, member 4 (ABCA4) gene. A large number of intronic sequence variants in ABCA4 have been considered pathogenic although their functional effect was seldom demonstrated. In this study, we aimed to reveal how intronic variants present in patients with Stargardt from the same Swedish family affect splicing.

METHODS: The splicing of the ABCA4 gene was studied in human embryonic kidney cells, HEK293T, and in human retinal pigment epithelium cells, ARPE-19, using a minigene system containing variants c.4773+3A>G and c.5461-10T>C.

RESULTS: We showed that both ABCA4 variants, c.4773+3A>G and c.5461-10T>C, cause aberrant splicing of the ABCA4 minigene resulting in exon skipping. We also demonstrated that splicing of ABCA4 has different outcomes depending on transfected cell type.

CONCLUSION: Two intronic variants c.4773+3A>G and c.5461-10T>C, both predicted to affect splicing, are indeed disease-causing mutations due to skipping of exons 33, 34, 39 and 40 of ABCA4 gene. The experimental proof that ABCA4 mutations in STGD patients affect protein function is crucial for their inclusion to future clinical trials; therefore, functional testing of all ABCA4 intronic variants associated with Stargardt disease by minigene technology is desirable.

PMID: 29461686

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