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Drug treatment

Br J Ophthalmol. 2014 Aug 8. pii: bjophthalmol-2014-305076. doi: 10.1136/bjophthalmol-2014-305076. [Epub ahead of print]

Efficacy and safety of intravitreal aflibercept injection in wet age-related macular degeneration: outcomes in the Japanese subgroup of the VIEW 2 study.

Ogura Y, Terasaki H, Gomi F, Yuzawa M, Iida T, Honda M, Nishijo K, Sowade O, Komori T, Schmidt-Erfurth U, Simader C, Chong V; for the VIEW 2 Investigators.

BACKGROUND/AIMS: To evaluate efficacy and safety of intravitreal aflibercept (IVT-AFL) in Japanese patients with wet age-related macular degeneration (wAMD) from the VIEW 2 trial.

METHODS: In this double-masked study, patients were randomised to: 0.5 mg IVT-AFL every 4 weeks (0.5q4); 2 mg IVT-AFL every 4 weeks (2q4); 2 mg IVT-AFL every 8 weeks (2q8) after 3 monthly injections; or 0.5 mg ranibizumab every 4 weeks (Rq4). Main efficacy outcomes included vision maintenance and best-corrected visual acuity (BCVA) at week 52.

RESULTS: At week 52, all Japanese patients in the IVT-AFL groups (n=70) maintained vision, compared with 96% of Japanese patients (n=23/24) treated with ranibizumab. Japanese patients in all treatment groups showed improvement in BCVA after treatment. The Rq4, 2q4 and 2q8 groups experienced similar gains in BCVA from baseline. The 0.5q4 group had higher gains due to an unexpected drop in BCVA between screening and baseline. Central retinal thickness and mean area of choroidal neovascularisation decreased in all treatment groups with similar magnitude. Ocular treatment-emergent adverse events were balanced across treatment groups.

CONCLUSIONS: IVT-AFL was effective and well tolerated in Japanese patients. Outcomes in this population were consistent with those in the overall VIEW 2 population.

PMID: 25107900 [PubMed - as supplied by publisher]

Retina. 2014 Aug 7. [Epub ahead of print]

BEVACIZUMAB VERSUS RANIBIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: A Meta-analysis of Randomized Controlled Trials.

Chen G, Li W, Tzekov R, Jiang F, Mao S, Tong Y.

PURPOSE: To evaluate the relative efficacy and safety of bevacizumab versus ranibizumab for the treatment of the neovascular form of age-related macular degeneration.

METHODS: A comprehensive literature search using the Cochrane Methodology Register to identify randomized controlled trials comparing bevacizumab with ranibizumab in patients with neovascular age-related macular degeneration. Efficacy estimates were determined by comparing weighted mean differences in the change of best-corrected visual acuity and central macular thickness from baseline. Safety estimates were determined by calculating the risk ratio for rates of death, arteriothrombotic events, venous thrombotic events, and at least 1 serious systemic adverse event. Statistical analysis was performed using the RevMan 5.1 software.

RESULTS: A total of 6 randomized controlled trials were selected for this meta-analysis, including 2,612 patients (1,292 patients in the bevacizumab group and 1,320 patients in the ranibizumab group). There were no significant differences between bevacizumab and ranibizumab in best-corrected visual acuity mean change at 1 year or 2 years (weighted mean difference = -0.40, 95% confidence interval [CI], -1.48 to 0.69, $P = 0.47$ and weighted mean difference = -1.16, 95% CI, -2.82 to 0.51, $P = 0.17$, respectively). Ranibizumab was found to be more efficacious in reducing central macular thickness at 1 year (weighted mean difference = 4.35, 95% CI, 0.92-7.78, $P = 0.01$). The pooled risk ratios comparing the rates of serious systemic adverse events at 1 year and 2 years were slightly in favor of ranibizumab (risk ratio = 1.24, 95% CI, 1.04-1.48, $P = 0.02$ and risk ratio = 1.20, 95% CI, 1.05-1.37, $P = 0.008$, respectively), whereas the rates of death, arteriothrombotic events, and venous thrombotic events did not differ statistically.

CONCLUSION: Bevacizumab and ranibizumab had equivalent efficacy for best-corrected visual acuity in the treatment of neovascular age-related macular degeneration. Ranibizumab tended to have a better anatomical outcome. There were no differences between drugs in rates of death, arteriothrombotic events or venous thrombotic events, and differences in rates of serious systemic adverse events that require further study.

PMID: 25105318 [PubMed - as supplied by publisher]

Retina. 2014 Aug 7. [Epub ahead of print]

INTRAVITREAL RANIBIZUMAB INJECTIONS WITH AND WITHOUT PNEUMATIC DISPLACEMENT FOR TREATING SUBMACULAR HEMORRHAGE SECONDARY TO NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Cho HJ, Koh KM, Kim JH, Kim HS, Han JI, Lew YJ, Lee TG, Kim JW.

PURPOSE: To evaluate the efficacy of intravitreal ranibizumab with and without pneumatic displacement for the treatment of submacular hemorrhage secondary to neovascular age-related macular degeneration.

METHODS: We retrospectively reviewed the medical records of 93 treatment-naïve patients (93 eyes) with submacular hemorrhage secondary to neovascular age-related macular degeneration. All patients were treated with an initial series of 3 monthly intravitreal ranibizumab injections, followed by as-needed injections. For the patients treated with pneumatic displacement, expansive gas was injected at the time of the first ranibizumab injection.

RESULTS: Mean submacular hemorrhage area was 8.2 ± 5.8 disk areas, and mean symptom duration was 8.2 ± 5.2 days at baseline. Twelve months into treatment, the mean logarithm of the minimum angle of resolution of best-corrected visual acuity of all subjects significantly improved from 1.19 ± 0.55 (20/309) at baseline to 0.96 ± 0.39 (20/182, $P = 0.007$) at 12 months. The mean central foveal thickness also significantly improved from 473 ± 223 μm at baseline to 279 ± 134 μm ($P < 0.001$) at 12 months. However, no significant difference in best-corrected visual acuity and mean central foveal thickness between ranibizumab monotherapy (58 eyes) and combination therapy groups (35 eyes) was observed at 12 months.

CONCLUSION: Intravitreal ranibizumab injections with and without pneumatic displacement are viable treatment options for submacular hemorrhage secondary to neovascular age-related macular degeneration.

PMID: 25105310 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2014 Aug;49(4):367-76. doi: 10.1016/j.jcjo.2014.05.010.

Intravitreal ranibizumab for the treatment of fibrovascular pigment epithelial detachment in age-related macular degeneration.

Iordanous Y, Powell AM, Mao A, Hooper PL, Eng KT, Schwartz C, Kertes PJ, Sheidow TG.

OBJECTIVE: To determine the response of predominantly fibrovascular pigment epithelial detachments (PED)-type lesions (secondary to age-related macular degeneration [AMD]) to intravitreal ranibizumab.

DESIGN: This was an open-label prospective study.

PARTICIPANTS: Thirty-two patients with predominantly fibrovascular PED-type lesions secondary to AMD were included in this study. Three patients were excluded from the final analysis.

METHODS: Patients received monthly intravitreal ranibizumab injections for 6 months (induction). At 6 months, patients not experiencing a visual improvement from baseline Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity or not showing a reduction in PED height (based on optical coherence tomography [OCT]) were deemed ranibizumab nonresponders and received no further injections but underwent re-evaluation at 12 months. Patients deemed responders continued with OCT-guided active treatment on an as-needed basis for an additional 6 months.

RESULTS: Twenty-four patients (82.8%) were ranibizumab responders and 5 were (17.2%) nonresponders. For ranibizumab responders, mean ETDRS visual acuity improved by 7.2 ± 9.8 letters at 6 months ($p = 0.002$) and 6.3 ± 8.6 letters at 12 months ($p = 0.002$). Ranibizumab nonresponders experienced a decline in mean visual acuity of 8.2 ± 4.6 letters at 6 months ($p = 0.02$) and 18.2 ± 10.11 letters at 12 months ($p = 0.02$). At baseline, responders had a mean PED height of $345.8 \pm 96.0 \mu\text{m}$, which decreased to $111.6 \pm 133.2 \mu\text{m}$ at 6 months ($p < 0.001$) and had a slight increase at 12 months to $144.8 \pm 146.3 \mu\text{m}$ ($p < 0.001$). Two responders (8.3%) and 2 nonresponders (40%) developed retinal pigment epithelium tears while on treatment.

CONCLUSIONS: Intravitreal ranibizumab appears to be a well-tolerated treatment option for patients with fibrovascular PED. Further large-scale, prospective studies may assist in delineating the best treatment protocol.

PMID: 25103655 [PubMed - in process]

Indian J Ophthalmol. 2014 Jul;62(7):761-7. doi: 10.4103/0301-4738.138615.

The methodological quality of systematic reviews comparing intravitreal bevacizumab and alternates for neovascular age related macular degeneration: A systematic review of reviews.

George PP, DeCastro Molina JA, Heng BH.

OBJECTIVE: To systematically collate and evaluate the evidence from recent SRs of bevacizumab for neovascular age related macular degeneration.

MATERIALS AND METHODS: Literature searches were carried out in Medline, Embase, Cochrane databases for all systematic reviews (SRs) on the effectiveness of bevacizumab for neo-vascular age related macular degeneration, published between 2000 and 2013. Titles and abstracts were assessed against the inclusion/exclusion criteria using Joanna Briggs Institute (JBI) study eligibility form. Data was extracted using the JBI data extraction form. The quality of the SRs was assessed using JBI critical appraisal checklist for SRs. Decisions on study eligibility and quality were made by two reviewers; any disagreements were resolved by discussion.

RESULTS: Nine relevant reviews were identified from 30 citations, of which 5 reviews fulfilled the review's inclusion criteria. All 5 reviews showed bevacizumab to be effective for neovascular AMD in the short-term when used alone or in combination with PDT or Pegaptanib. The average quality score of the reviews was 7; 95% confidence interval 6.2 to 7.8 (maximum possible quality score is 10). The selection and publication

bias were not addressed in all included reviews. Three-fifth of the reviews had a quality score of 7 or lower, these reviews had some methodological limitations, search strategies were only identified in 2 (40%) reviews, independent study selection and quality assessment of included studies (4 (80%)) were infrequently performed.

CONCLUSION: Overall, the reviews on the effectiveness of intravitreal/systemic bevacizumab for neovascularage-related macular generation (AMD) received good JBI quality scores (mean score = 7.0 points), with a few exceptions. The study also highlights the suboptimal reporting of SRs on this topic. Reviews with poor methodology may limit the validity of the reported results; hence efforts should be made to improve the design, reporting and publication of SRs across all journals.

PMID: 25116765 [PubMed - in process]

J Ophthalmol. 2014;2014:502174. doi: 10.1155/2014/502174. Epub 2014 Jul 10.

Aqueous interleukin-6 levels are superior to vascular endothelial growth factor in predicting therapeutic response to bevacizumab in age-related macular degeneration.

Chalam KV, Grover S, Sambhav K, Balaiya S, Murthy RK.

Objective: To prospectively evaluate the effect of intravitreal bevacizumab on aqueous levels of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) in patients with exudative age-related macular degeneration (AMD) and correlate clinical outcomes with cytokine levels.

Methods: 30 eyes of 30 patients with exudative AMD underwent intravitreal injection of bevacizumab three times at monthly intervals. The aqueous samples prior to the 1st injection (baseline) and 3rd injection were analyzed for VEGF and IL-6 levels. Subjects were subgrouped based upon change in the central subfield (CSF) macular thickness on SD-OCT at 8 weeks. Group 1 included patients (n = 14) with a decrease in CSF thickness greater than 10% from the baseline (improved group). Group 2 included patients (n = 16) who had a decrease in CSF thickness 10% or less (treatment-resistant).

Results: In subgroup analysis, in both groups 1 and 2 patients, compared to aqueous VEGF, aqueous IL-6 levels showed a better correlation with CSF thickness on SD-OCT ($r = 0.72$ and 0.71 , resp.).

Conclusions: Aqueous IL-6 may be an important marker of treatment response or resistance in wet macular degeneration. Future therapeutic strategies may include targeted treatment against both VEGF and IL-6, in patients who do not respond to anti-VEGF treatment alone.

PMID: 25110587 [PubMed] PMCID: PMC4121253

Clin Experiment Ophthalmol. 2014 Aug 11. doi: 10.1111/ceo.12405. [Epub ahead of print]

Survey of Victorian Ophthalmologists who use ranibizumab to treat age related macular degeneration: to identify current practice and modifiable risk factors relevant to post-injection endophthalmitis.

Buck DA, Dawkins R, Kawasaki R, Sandhu SS, Allen PJ.

PMID: 25112536 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmology. 2014 Aug 8. pii: S0161-6420(14)00568-5. doi: 10.1016/j.ophtha.2014.06.034. [Epub ahead of print]

Optical Coherence Tomography-Defined Changes Preceding the Development of Drusen-Associated Atrophy in Age-Related Macular Degeneration.

Wu Z, Luu CD, Ayton LN, Goh JK, Lucci LM, Hubbard WC, Hageman JL, Hageman GS, Guymer RH.

PURPOSE: To characterize the pathological changes preceding the development of drusen-associated atrophy in eyes with age-related macular degeneration (AMD) using spectral-domain optical coherence tomography (SD-OCT).

DESIGN: Longitudinal and cross-sectional retrospective observational study.

PARTICIPANTS: A total of 181 participants with intermediate AMD in at least 1 eye (141 unilateral, 40 bilateral) were assessed longitudinally. A total of 230 participants with bilateral intermediate AMD (40 longitudinal participants with an additional 190 participants) were analyzed cross-sectionally.

METHODS: Spectral-domain OCT, color fundus photography (CFP), near-infrared reflectance, and fundus autofluorescence imaging were performed in all participants at cross-section and every 3 months for up to 30 months in the longitudinal study. Spectral-domain OCT volume scans were examined for features that portend the development of drusen-associated atrophy, and the topography, prevalence, and risk factors of these features were determined through cross-sectional analysis.

MAIN OUTCOME MEASURES: The pathological features on SD-OCT preceding the development of drusen-associated atrophy and the characteristics of these features.

RESULTS: Twenty areas from 16 eyes of 16 participants developed drusen-associated atrophy after an average of 20 months (range, 8-30 months). Spectral-domain OCT features unique in these areas included: subsidence of the outer plexiform layer (OPL) and inner nuclear layer (INL), and development of a hyporeflective wedge-shaped band within the limits of the OPL. These characteristics were termed "nascent geographic atrophy" (nGA), describing features that portend the development of drusen-associated atrophy. Cross-sectional examination of participants with bilateral intermediate AMD revealed that independent risk factors for the presence of nGA included the presence of pigmentary changes (odds ratio [OR], 16.84; 95% confidence interval [CI], 2.42-117.24) and nGA in the fellow eye (OR, 4.15; 95% CI, 1.12-15.34); nGA was present in 21.9% of participants with drusen >125 µm and pigmentary changes in both eyes.

CONCLUSIONS: This study identified pathological changes occurring before the development of drusen-associated atrophy using SD-OCT, which we defined as nGA. Although nGA is undetectable on CFP, it is important for determining the risk of future vision loss in AMD and could be used as an earlier surrogate end point in interventional trials targeting the early stages of AMD.

PMID: 25109931 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Aug 12. pii: S0002-9394(14)00490-5. doi: 10.1016/j.ajo.2014.08.010. [Epub ahead of print]

Punctate Hyperfluorescence Spot as a Common Choroidopathy of Central Serous Chorioretinopathy and Polypoidal Choroidal Vasculopathy.

Park SJ, Kim BH, Park KH, Woo SJ.

PURPOSE: To characterize punctate hyperfluorescence spot as common choroidopathy in central serous chorioretinopathy (CSC) and polypoidal choroidal vasculopathy (PCV).

DESIGN: Cross-sectional retrospective study.

METHODS: A total of 150 patients with 50 each allocated to CSC, PCV, and typical neovascular age-related macular degeneration (AMD) groups were included. Punctate hyperfluorescence spot was determined using mid-to-late phase indocyanine green angiography and subfoveal choroidal thickness by enhanced-depth imaging optical coherence tomography. Each group was subcategorized based on concurrent punctate hyperfluorescence spot.

RESULTS: The punctate hyperfluorescence spot incidence was higher in CSC (80.0%) and PCV (86.0%) than AMD (40.0%, $P < 0.001$), with similar contralateral findings (86.1%, 86.7%, and 60%, respectively, $p = 0.014$). Punctate hyperfluorescence spot lesions comprised clustered polyps connected to vascular networks mimicking PCV. Choroidal thickness was $370.7 \pm 81.9 \mu\text{m}$, $332.6 \pm 101.6 \mu\text{m}$, and $172.5 \pm 80.1 \mu\text{m}$ in affected eyes ($p < 0.001$) and $323.0 \pm 70.5 \mu\text{m}$, $306.4 \pm 94.4 \mu\text{m}$, and $180.2 \pm 83.6 \mu\text{m}$ in contralateral eyes ($p < 0.001$) in CSC, PCV, and AMD groups, respectively. In AMD group, choroidal thickness was greater in eyes with punctate hyperfluorescence spot ($204.8 \pm 92.3 \mu\text{m}$) than in those without punctate hyperfluorescence spot ($150.2 \pm 62.9 \mu\text{m}$, $p = 0.028$) in affected eyes, however, the difference was not observed in contralateral eyes in AMD group and in both eyes in CSC and PCV groups.

CONCLUSIONS: Based on angiography and OCT, punctate hyperfluorescence spot may be a form of PCV, and CSC and PCV may share common choroidopathy distinct from typical neovascular AMD. However, infrequent PHS lesions along with thickened choroids in AMD eyes suggest that AMD may encompass a wide choroidal pathologic spectrum shared in part with PCV.

PMID: 25127698 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2014 Aug;49(4):339-44. doi: 10.1016/j.jcjo.2014.04.018.

Spectral-domain optical coherence tomography features preceding new-onset neovascular membrane formation.

Michalewski J, Nawrocki J, Trebinska M, Michalewska Z.

OBJECTIVE: To determine the frequency and characteristic spectral-domain optical coherence tomography (SD-OCT) features preceding new-onset choroidal neovascularization (CNV) in the fellow eye of neovascular age-related macular degeneration (AMD) with SD-OCT.

DESIGN: A prospective, observational study.

PARTICIPANTS: Sixty-eight fellow eyes of patients with unilateral CNV.

METHODS: SD-OCT was performed at baseline and then monthly. The main outcome measure is the description of retinal morphology 1 month before new onset of neovascularization.

RESULTS: During the 48-month observation period, new-onset CNV was observed in 27 fellow eyes. Several morphologic features characterized SD-OCT images ≥ 1 months before new onset of CNV. These included new retinal pigment epithelium defects (2 eyes), new photoreceptor defects (7 eyes), drusen touching the photoreceptor layer and the external limiting membrane (13 eyes), and new drusen (4 eyes) hyperreflective spots probably representing new growing vessels (5 eyes).

CONCLUSIONS: Monthly SD-OCT screening of fellow eyes of patients treated with anti-vascular endothelial growth factor enables identification of morphologic changes that may predispose or precede CNV formation. Rapid identification of CNV formation enhances treatment immediacy.

PMID: 25103650 [PubMed - in process]

Comput Biol Med. 2014 Jul 30;53C:55-64. doi: 10.1016/j.compbio.2014.07.015. [Epub ahead of print]

Automated diagnosis of Age-related Macular Degeneration using greyscale features from digital

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fundus images.

Mookiah MR, Acharya UR, Koh JE, Chandran V, Chua CK, Tan JH, Lim CM, Ng EY, Noronha K, Tong L, Laude A.

Abstract: Age-related Macular Degeneration (AMD) is one of the major causes of vision loss and blindness in ageing population. Currently, there is no cure for AMD, however early detection and subsequent treatment may prevent the severe vision loss or slow the progression of the disease. AMD can be classified into two types: dry and wet AMDs. The people with macular degeneration are mostly affected by dry AMD. Early symptoms of AMD are formation of drusen and yellow pigmentation. These lesions are identified by manual inspection of fundus images by the ophthalmologists. It is a time consuming, tiresome process, and hence an automated diagnosis of AMD screening tool can aid clinicians in their diagnosis significantly. This study proposes an automated dry AMD detection system using various entropies (Shannon, Kapur, Renyi and Yager), Higher Order Spectra (HOS) bispectra features, Fractional Dimension (FD), and Gabor wavelet features extracted from greyscale fundus images. The features are ranked using t-test, Kullback-Liebert Divergence (KLD), Chernoff Bound and Bhattacharyya Distance (CBB), Receiver Operating Characteristics (ROC) curve-based and Wilcoxon ranking methods in order to select optimum features and classified into normal and AMD classes using Naive Bayes (NB), k-Nearest Neighbour (k-NN), Probabilistic Neural Network (PNN), Decision Tree (DT) and Support Vector Machine (SVM) classifiers. The performance of the proposed system is evaluated using private (Kasturba Medical Hospital, Manipal, India), Automated Retinal Image Analysis (ARIA) and STandardized Analysis of the Retina (STARE) datasets. The proposed system yielded the highest average classification accuracies of 90.19%, 95.07% and 95% with 42, 54 and 38 optimal ranked features using SVM classifier for private, ARIA and STARE datasets respectively. This automated AMD detection system can be used for mass fundus image screening and aid clinicians by making better use of their expertise on selected images that require further examination.

PMID: 25127409 [PubMed - as supplied by publisher]

Med Biol Eng Comput. 2014 Aug 12. [Epub ahead of print]

Decision support system for age-related macular degeneration using discrete wavelet transform.

Mookiah MR, Acharya UR, Koh JE, Chua CK, Tan JH, Chandran V, Lim CM, Noronha K, Laude A, Tong L.

Abstract: Age-related macular degeneration (AMD) affects the central vision and subsequently may lead to visual loss in people over 60 years of age. There is no permanent cure for AMD, but early detection and successive treatment may improve the visual acuity. AMD is mainly classified into dry and wet type; however, dry AMD is more common in aging population. AMD is characterized by drusen, yellow pigmentation, and neovascularization. These lesions are examined through visual inspection of retinal fundus images by ophthalmologists. It is laborious, time-consuming, and resource-intensive. Hence, in this study, we have proposed an automated AMD detection system using discrete wavelet transform (DWT) and feature ranking strategies. The first four-order statistical moments (mean, variance, skewness, and kurtosis), energy, entropy, and Gini index-based features are extracted from DWT coefficients. We have used five (t test, Kullback-Liebert Divergence (KLD), Chernoff Bound and Bhattacharyya Distance, receiver operating characteristics curve-based, and Wilcoxon) feature ranking strategies to identify optimal feature set. A set of supervised classifiers namely support vector machine (SVM), decision tree, [Formula: see text]-nearest neighbor ([Formula: see text]-NN), Naive Bayes, and probabilistic neural network were used to evaluate the highest performance measure using minimum number of features in classifying normal and dry AMD classes. The proposed framework obtained an average accuracy of 93.70 %, sensitivity of 91.11 %, and specificity of 96.30 % using KLD ranking and SVM classifier. We have also formulated an AMD Risk Index using selected features to classify the normal and dry AMD classes using one number. The proposed system can be used to assist the clinicians and also for mass AMD screening programs.

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Pathogenesis

Molecules. 2014 Aug 13;19(8):12150-72. doi: 10.3390/molecules190812150.

Epigallocatechin-3-gallate Inhibits Ocular Neovascularization and Vascular Permeability in Human Retinal Pigment Epithelial and Human Retinal Microvascular Endothelial Cells via Suppression of MMP-9 and VEGF Activation.

Lee HS, Jun JH, Jung EH, Koo BA, Kim YS.

Abstract: Epigallocatechin-3-gallate (EGCG) is the main polyphenol component of green tea (leaves of *Camellia sinensis*). EGCG is known for its antioxidant, anti-inflammatory, antiviral, and anti-carcinogenic properties. Here, we identify EGCG as a new inhibitor of ocular angiogenesis and its vascular permeability. Matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF) play a key role in the processes of extracellular matrix (ECM) remodeling and microvascular permeability during angiogenesis. We investigated the inhibitory effects of EGCG on ocular neovascularization and vascular permeability using the retina oriented cells and animal models induced by VEGF and alkaline burn. EGCG treatment significantly decreased mRNA and protein expression levels of MMP-9 in the presence of 12-O-tetradecanoylphorbol-13-acetate (TPA) and tumor necrosis factor alpha (TNF- α) in human retinal pigment epithelial cells (HRPECs). EGCG also effectively protected ARPE-19 cells from cell death and attenuated mRNA expressions of key angiogenic factors (MMP-9, VEGF, VEGF Receptor-2) by inhibiting generation of reactive oxygen species (ROS). EGCG significantly inhibited proliferation, vascular permeability, and tube formation in VEGF-induced human retinal microvascular endothelial cells (HRMECs). Furthermore, EGCG significantly reduced vascular leakage and permeability by blood-retinal barrier breakdown in VEGF-induced animal models. In addition, EGCG effectively limited upregulation of MMP-9 and platelet endothelial cell adhesion molecule (PECAM/CD31) on corneal neovascularization (CNV) induced by alkaline burn. Our data suggest that MMP-9 and VEGF are key therapeutic targets of EGCG for treatment and prevention of ocular angiogenic diseases such as age-related macular degeneration, diabetic retinopathy, and corneal neovascularization.

PMID: 25123184 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2014 Aug 12. pii: IOVS-14-14349. doi: 10.1167/iov.14-14349. [Epub ahead of print]

TAK-1 Inhibition Accelerates Cellular Senescence of Retinal Pigment Epithelial Cells.

Dvashi Z, Green Y, Pollack A.

PURPOSE. Oxidative stress and cellular senescence are known to contribute to the development of age-related macular degeneration (AMD), however, the mechanism is not fully understood. This study investigated the role of transforming growth factor- β activated kinase 1 (TAK1) in the senescence of retinal pigment epithelial (RPE) cells as a model for the development of dry AMD.

METHODS. Cultured human RPE cells were treated with the TAK1 inhibitor 5Z-7-oxozeaenol for 1 hour, and then treated with 200 μ M hydrogen peroxide for 1 hour. Human RPE cells that were not pretreated with TAK1 inhibitor for one hour served as controls. Senescence-associated β -galactosidase (SA- β -gal) activity was detected by histochemistry, and p53 expression by immunoblotting. Cell cycle and apoptosis rate in RPE cells were determined by flow cytometry.

RESULTS. TAK1 expression in human RPE cells was high and was altered upon oxidative stress. TAK1 inhibition led to reduction in cell proliferation, cell-cycle arrest at G0/G1 and increased SA- β -gal expression, all known to be features of cell senescence. Exposure of cells to oxidative stress combined with inhibition of TAK1 activity decreased the expression of apoptotic proteins such as p53 and promoted cellular senescence. Aberrant TAK1 activity in RPE cells triggered their secretion of factors that induced hypertrophy and fibrotic changes in neighboring cells.

CONCLUSIONS. The in-vitro evidence indicated a role for TAK1 in the onset of RPE cells senescence. The

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8

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data shown hereby demonstrated that TAK1 activity is essential for maintaining RPE cells normal function. Elucidation of its role in mechanisms underlying RPE cellular senescence induction may potentiate development of powerful tools for halting the development of dry AMD.

PMID: 25118260 [PubMed - as supplied by publisher]

Curr Ophthalmol Rep. 2014 Mar 1;2(1):14-19.

The Immune System and AMD.

Frederick PA, Kleinman ME.

Abstract: Age related macular degeneration (AMD) is a complex, multifactorial disease that has yet to be completely understood. Significant efforts in the basic and clinical sciences have unveiled numerous areas which appear to be critical in the pathogenesis of this disease. The alternative complement pathway, immune cell activation, and autoimmunity are all emerging as important themes to the suspected immunologic origins of this disease. Advancement toward a complete understanding of these processes is important in development of new techniques for disease monitoring and treatment.

PMID: 25110625 [PubMed] PMCID: PMC4122127

Invest Ophthalmol Vis Sci. 2014 Aug 7. pii: IOVS-14-14325. doi: 10.1167/iov.14-14325. [Epub ahead of print]

Characterization of a mouse model with complete RPE loss and its use for RPE cell transplantation.

Carido M, Zhu Y, Postel K, Benkner B, Cimalla P, Karl MO, Kurth T, Paquet-Durand F, Koch E, Münch T, Tanaka EM, Ader M.

Purpose: Age-related macular degeneration (AMD) is a major leading cause of visual impairment and blindness with no cure currently established. Cell replacement of RPE is discussed as a potential therapy for AMD. Previous studies were performed in animal models with severe limitations in recapitulating the disease progression. We describe in detail the effect of systemic injection of sodium iodate in the mouse retina. We further evaluate the usefulness of this animal model to analyze cell-specific effects following transplantation of human embryonic stem cell (hESC)-derived RPE cells.

Methods: Morphological, functional and behavioral changes following sodium iodate injection were monitored by histology, gene expression analysis, electroretinography and optokinetic head tracking. hESC-derived RPE cells were transplanted one week after sodium iodate injection and experimental retinæ were analyzed three weeks later.

Results: Injection of sodium iodate caused complete RPE cell loss, photoreceptor degeneration and altered gene and protein expression in outer and inner nuclear layers. Retinal function was severely affected by day 3 and abolished from day 14. Following transplantation, donor hESC-derived RPE cells formed extensive monolayers that displayed wild type RPE cell morphology, organization and function, including phagocytosis of host photoreceptor outer segments.

Conclusions: Systemic injection of sodium iodate has considerable effects on RPE, photoreceptors and inner nuclear layer neurons, and provides a model to assay reconstitution and maturation of RPE cell transplants. The availability of an RPE-free Bruch's membrane in this model likely allows the unprecedented formation of extensive polarized cell monolayers from donor hESC-derived RPE cell suspensions.

PMID: 25103259 [PubMed - as supplied by publisher]

J Nutr Biochem. 2014 Jul 17. pii: S0955-2863(14)00136-3. doi: 10.1016/j.jnutbio.2014.06.004. [Epub ahead of print]

Genistein attenuates choroidal neovascularization.

Kinoshita S, Noda K, Tagawa Y, Inafuku S, Dong Y, Fukuhara J, Dong Z, Ando R, Kanda A, Ishida S.

Abstract: Genistein is a dietary-derived flavonoid abundantly present in soybeans and known to possess various biological effects including anti-inflammation and anti-angiogenic activity. To investigate the effects of genistein on intraocular neovascularization, we used an animal model of laser-induced choroidal neovascularization (CNV). Male C57BL/6J mice were treated in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. CNV was induced by laser photocoagulation. The animals were fed a mixture diet containing 0.5% genistein or a control diet ad libitum for 7 days before laser photocoagulation and the treatment was continued until the end of the study. Seven days after laser injury, the size of CNV lesions was quantified. Retinal pigment epithelium (RPE)-choroid complex was also harvested 1 or 3 days after laser injury and the level of monocyte chemoattractant protein (MCP)-1, intercellular adhesion molecule (ICAM)-1, and matrix metalloproteinase (MMP)-9 were measured by enzyme-linked immunosorbent assay. Expression levels of Ets-1 and F4/80 were examined by real-time PCR. A significant decrease in CNV size was observed in animals treated with genistein ($15441.9 \pm 1511.8 \mu\text{m}^2$) compared to control mice ($21074.0 \pm 1940.7 \mu\text{m}^2$, $P < .05$). Genistein significantly reduced the protein level of MCP-1, ICAM-1, and MMP-9 in the RPE-choroid complex ($P < .05$). In addition, genistein suppressed the expression levels of Ets-1 and F4/80 ($P < .05$). The current data indicate the anti-angiogenic property of genistein during CNV formation.

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Epidemiology

Lancet Glob Health. 2014 Feb;2(2):e65-6. doi: 10.1016/S2214-109X(13)70163-3. Epub 2014 Jan 3.

Global prevalence of age-related macular degeneration.

Jonas JB.

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Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis.

Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, Wong TY.

BACKGROUND: Numerous population-based studies of age-related macular degeneration have been reported around the world, with the results of some studies suggesting racial or ethnic differences in disease prevalence. Integrating these resources to provide summarised data to establish worldwide prevalence and to project the number of people with age-related macular degeneration from 2020 to 2040 would be a useful guide for global strategies.

METHODS: We did a systematic literature review to identify all population-based studies of age-related macular degeneration published before May, 2013. Only studies using retinal photographs and standardised grading classifications (the Wisconsin age-related maculopathy grading system, the international classification for age-related macular degeneration, or the Rotterdam staging system) were included. Hierarchical Bayesian approaches were used to estimate the pooled prevalence, the 95% credible intervals (CrI), and to examine the difference in prevalence by ethnicity (European, African, Hispanic, Asian) and region (Africa, Asia, Europe, Latin America and the Caribbean, North America, and Oceania). UN World Population Prospects were used to project the number of people affected in 2014 and

2040. Bayes factor was calculated as a measure of statistical evidence, with a score above three indicating substantial evidence.

FINDINGS: Analysis of 129 664 individuals (aged 30-97 years), with 12 727 cases from 39 studies, showed the pooled prevalence (mapped to an age range of 45-85 years) of early, late, and any age-related macular degeneration to be 8.01% (95% CrI 3.98-15.49), 0.37% (0.18-0.77), and 8.69% (4.26-17.40), respectively. We found a higher prevalence of early and any age-related macular degeneration in Europeans than in Asians (early: 11.2% vs 6.8%, Bayes factor 3.9; any: 12.3% vs 7.4%, Bayes factor 4.3), and early, late, and any age-related macular degeneration to be more prevalent in Europeans than in Africans (early: 11.2% vs 7.1%, Bayes factor 12.2; late: 0.5% vs 0.3%, 3.7; any: 12.3% vs 7.5%, 31.3). There was no difference in prevalence between Asians and Africans (all Bayes factors <1). Europeans had a higher prevalence of geographic atrophy subtype (1.11%, 95% CrI 0.53-2.08) than Africans (0.14%, 0.04-0.45), Asians (0.21%, 0.04-0.87), and Hispanics (0.16%, 0.05-0.46). Between geographical regions, cases of early and any age-related macular degeneration were less prevalent in Asia than in Europe and North America (early: 6.3% vs 14.3% and 12.8% [Bayes factor 2.3 and 7.6]; any: 6.9% vs 18.3% and 14.3% [3.0 and 3.8]). No significant gender effect was noted in prevalence (Bayes factor <1.0). The projected number of people with age-related macular degeneration in 2020 is 196 million (95% CrI 140-261), increasing to 288 million in 2040 (205-399).

INTERPRETATION: These estimates indicate the substantial global burden of age-related macular degeneration. Summarised data provide information for understanding the effect of the condition and provide data towards designing eye-care strategies and health services around the world.

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Lancet Glob Health. 2013 Dec;1(6):e339-49. doi: 10.1016/S2214-109X(13)70113-X. Epub 2013 Nov 11.

Causes of vision loss worldwide, 1990-2010: a systematic analysis.

Bourne RR, Stevens GA, White RA, Smith JL, Flaxman SR, Price H, Jonas JB, Keeffe J, Leasher J, Naidoo K, Pesudovs K, Resnikoff S, Taylor HR; Vision Loss Expert Group.

BACKGROUND: Data on causes of vision impairment and blindness are important for development of public health policies, but comprehensive analysis of change in prevalence over time is lacking.

METHODS: We did a systematic analysis of published and unpublished data on the causes of blindness (visual acuity in the better eye less than 3/60) and moderate and severe vision impairment ([MSVI] visual acuity in the better eye less than 6/18 but at least 3/60) from 1980 to 2012. We estimated the proportions of overall vision impairment attributable to cataract, glaucoma, macular degeneration, diabetic retinopathy, trachoma, and uncorrected refractive error in 1990-2010 by age, geographical region, and year.

FINDINGS: In 2010, 65% (95% uncertainty interval [UI] 61-68) of 32.4 million blind people and 76% (73-79) of 191 million people with MSVI worldwide had a preventable or treatable cause, compared with 68% (95% UI 65-70) of 31.8 million and 80% (78-83) of 172 million in 1990. Leading causes worldwide in 1990 and 2010 for blindness were cataract (39% and 33%, respectively), uncorrected refractive error (20% and 21%), and macular degeneration (5% and 7%), and for MSVI were uncorrected refractive error (51% and 53%), cataract (26% and 18%), and macular degeneration (2% and 3%). Causes of blindness varied substantially by region. Worldwide and in all regions more women than men were blind or had MSVI due to cataract and macular degeneration.

INTERPRETATION: The differences and temporal changes we found in causes of blindness and MSVI have implications for planning and resource allocation in eye care.

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Association between blood cadmium level and age-related macular degeneration in a representative Korean population.

Kim EC, Cho E, Jee D.

Purpose: To investigate the association between blood cadmium level and age-related macular degeneration (AMD).

Methods: This population based cross-sectional study using a nation-wide, systemically stratified, multistage clustered sampling method included 4,933 subjects >40 years who participated in the Korean National Health and Nutrition Examination Survey between 2008-2012 and had fundus photographs taken. All participants underwent a standardized interview, evaluation of blood cadmium concentrations, and comprehensive ophthalmic examination. A 45° digital fundus photograph was taken from both eyes under physiologic mydriasis, and were graded using the international classification and grading system for AMD.

Results: Mean blood cadmium levels were 1.47 µg/L in women and 1.19 µg/L in men. After adjusting for potential confounders, including age, sex, and smoking status, the odds ratio (OR) for AMD was significantly increased in the highest quintile blood cadmium group (OR, 1.96; 95% confidence interval [CI], 1.17-3.29; P for trend = 0.017). This association between blood cadmium level and AMD was significant in men (OR, 2.11; 95%CI, 1.11-4.02; P for trend = 0.024) but not in women (OR, 1.29; 95%CI, 0.70-2.52; P for trend = 0.158).

Conclusions: This study provides the first epidemiologic evidence that higher blood cadmium level is associated with AMD. Results of the present study indicate that an elevated cadmium burden may increase the risk of AMD development.

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Sunlight Exposure, Pigmentation, and Incident Age-Related Macular Degeneration.

Klein BE, Howard KP, Iyengar SK, Sivakumaran TA, Meyers K, Cruickshanks KJ, Klein R.

Purpose: Examine potential effects of sunlight exposure, hair color, eye color, and selected gene single-nucleotide polymorphisms (SNPs) on incidence of age-related macular degeneration (AMD).

Methods: Subjects participated in up to 5 examinations over a 20-year period. Eye color, self-reported hair color as a teenager, and sunlight exposure were ascertained at the baseline examination. Presence and severity of AMD and its lesions were determined via fundus photographs. Genetic data were available on a subset of participants. The SNPs CFH Y402H rs1061170 and ARMS2 A69S rs10490924 were used to analyze genetic risk of AMD; OCA2 rs4778241 and HERC2 rs12913832 represented genetic determinants of eye color.

Results: Incidence of early AMD was higher in blond/red-haired persons compared to brown/black-haired persons (hazard ratio [HR] 1.25, P=0.02) and in persons with high sun exposure in their thirties (HR 1.41, P=0.02). However, neither was significant after adjustment for multiple comparisons. Eye (HR 1.36, P=0.006) and hair color (HR 1.42, P=0.003) were associated with incidence of any retinal pigmentary abnormalities (RPAs). Both remained significant after adjustment for multiple comparisons. Neither presence of alleles for light-colored eyes nor those associated with high risk of late AMD altered the association of eye or hair color with early AMD. None of the characteristics studied were significantly associated with late AMD.

Conclusions: Modest associations of eye color, hair color, and HERC2 genotype with any RPAs were found. Genes for AMD did not affect these associations. Eye color phenotype was more strongly associated

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12

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with outcomes than HERC2 or OCA2 genotype.

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Genetics

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Clinical Applications of Age-Related Macular Degeneration Genetics.

SanGiovanni JP, Chew EY.

Abstract: Understanding genetic causes of age-related macular degeneration (AMD) will eventually yield effective discoveries and improvements in predictive/prognostic methods. These include, but are not limited to, reliable disease prediction (screening for increased discrimination of clinical risk), differential classification of AMD subtypes with biomarkers (development of risk-linked molecular taxonomies), selection of optimal preventive and therapeutic interventions (guided by a biologically meaningful understanding of treatment response), and drug dosing. In this review, we discuss clinical applications informed by key findings in AMD genetics, and provide commentary on leveraging extant and forthcoming evidence to improve AMD risk prediction, AMD classification, and knowledge on the genetic basis of drug activity and toxicity. Advances in translating AMD genetics findings for AMD risk prediction require development of a genetics-based causality for AMD incidence and progression. Molecular subtyping of AMD phenotypes requires a set of dynamic biomarkers presenting prognostic value; although these have yet to be identified, the formation of multidisciplinary teams and their participation in large-scale consortia may yield promising results. Drugs targeting complement and vascular endothelial growth factor (VEGF) systems are under evaluation, and forthcoming work on rare variants and noncoding DNA in AMD pathogenesis will likely reveal biochemical pathways enriched with AMD-associated genetic variants. Pharmacologic targets in these pathways may inform a rational and effective therapeutic approach to preventing and treating this sight-threatening disease.

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Complotype affects the extent of down-regulation by Factor I of the C3b feedback cycle in-vitro.

Lay E, Nutland S, Smith JE, Hiles I, Smith RA, Seilly DJ, Buchberger A, Schwaeble W, Lachmann PJ.

Abstract: Sera from a large panel of normal subjects were typed for three common polymorphisms, one in C3 (R102G) and two in Factor H (V62I and Y402H) that influence predisposition to age related macular degeneration and to some forms of kidney disease. Three groups of sera were tested; those that were homozygous for the three risk alleles; those that were heterozygous for all three; and those homozygous for the low risk alleles. These groups vary in their response to the addition of exogenous Factor I when the alternative complement pathway is activated by zymosan. Both the reduction in the maximum amount of iC3b formed and the rate at which the iC3b is converted to C3dg are affected. For both reactions the at-risk complotype requires higher doses of Factor I to produce similar down-regulation. Since iC3b reacting with the complement receptor CR3 is a major mechanism by which complement activation gives rise to inflammation the breakdown of iC3b to C3dg can be seen to have major significance for reducing complement induced inflammation. These findings demonstrate for the first time that sera from subjects with different complement alleles do behave as predicted in an in-vitro assay of the down-regulation of the alternative complement pathway by increasing the concentration of Factor I. These results support the hypothesis that exogenous Factor I may be a valuable therapeutic for down-regulating hyperactivity of the C3b feedback cycle and thereby providing a treatment for age-related macular degeneration and other inflammatory diseases of later life.

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Genomic aspects of age-related macular degeneration.

Horie-Inoue K, Inoue S.

Abstract: Age-related macular degeneration (AMD) is a major late-onset posterior eye disease that causes central vision to deteriorate among elderly populations. The predominant lesion of AMD is the macula, at the interface between the outer retina and the inner choroid. Recent advances in genetics have revealed that inflammatory and angiogenic pathways play critical roles in the pathophysiology of AMD. Genome-wide association studies have identified ARMS2/HTRA1 and CFH as major AMD susceptibility genes. Genetic studies for AMD will contribute to the prevention of central vision loss, the development of new treatment, and the maintenance of quality of vision for productive aging.

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Bull Exp Biol Med. 2014 Aug 12. [Epub ahead of print]

Expression of Genes for AhR and Nrf2 Signal Pathways in the Retina of OXYS Rats during the Development of Retinopathy and Melatonin-Induced Changes in This Process.

Perepechaeva ML, Stefanova NA, Grishanova AY.

Abstract: Modulation of oxidative stress is one of the experimental approaches to the therapy of age-related macular degeneration. Melatonin holds much promise in this respect. It was hypothesized that the efficiency of melatonin in age-related macular degeneration is associated with its ability to modulate gene expression for the AhR and Nrf2 signal pathways. Experiments were performed on premature aging OXYS rats, which serve as a reliable model of age-related macular degeneration in humans. We studied the effect of melatonin on gene mRNA for the AhR and Nrf2 signal pathways. Melatonin was shown to decrease the level of mRNA for AhR-dependent genes of CYP1A2 and CYP1B1 cytochromes in the retina, but had no effect on the content of mRNA for Nrf2-dependent genes in OXYS rats.

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Application and Interpretation of Genome-Wide Association (GWA) Studies for Informing Pharmacogenomic Research -- Examples from the Field of Age-Related Macular Degeneration.

SanGiovanni JP1, Rosen R, Kaushal S.

Author information

Abstract: Genome-wide association (GWA) studies apply broad DNA scans on hundreds-of-thousands of common sequence variants in thousands of people for the purpose of mapping trait- or disease-related loci. We provide examples of ligand- and target-based studies from the field of age-related macular degeneration (AMD) to demonstrate the value of the GWA approach in confirmatory and exploratory pharmacogenomics research. Complementing this genomic analysis, we used a simple biochemical retinal pigment epithelium (RPE) oxidative, apoptotic high throughput screening (HTS) assay to identify compounds. This ligand-to-target-to DNA sequence variant-to disease approach provided guidance on rational design of preclinical studies and identified associations between: 1) valproic acid and advanced AMD-associated genes with the capacity to alter GABA-succinate signaling (ALDH5A1, CACNA1C, SUCLA2, and GABBR2) and chromatin remodeling (HDAC9); and 2) Ropinirole and a geographic atrophy-associated gene (DRD3) with the capacity to alter systems involved in cAMP-PKA signaling. In both applications of our method, the breadth of GWA findings allowed efficient expansion of results to identify enriched pathways and additional ligands capable of targeting pathway constituents. A disease associated

SNP-to gene-to target-to ligand approach provided guidance to inform preventive and therapeutic preclinical studies investigating roles of targets in: 1) PPAR-RXR transcription complex constituents for neovascular AMD; and 2) the stress activated MAPK signaling cascade constituents for advanced AMD. Our conclusion is that publically available data from GWA studies can be used successfully with open-access genomics, proteomics, structural chemistry, and pharmacogenomics databases in an efficient, rational approach to streamline the processes of planning and implementation for confirmatory and exploratory pre-clinical studies of preventive or therapeutic pharmacologic treatments for complex diseases.

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