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MD Research News

Issue 167

Tuesday 11 February, 2014

Drug treatment

Ophthalmology. 2014 Feb 1. pii: S0161-6420(13)01167-6. doi: 10.1016/j.ophtha.2013.11.041. [Epub ahead of print]

Three-Year Outcomes of Individualized Ranibizumab Treatment in Patients with Diabetic Macular Edema: The RESTORE Extension Study.

Schmidt-Erfurth U, Lang GE, Holz FG, Schlingemann RO, Lanzetta P, Massin P, Gerstner O, Bouazza AS, Shen H, Osborne A, Mitchell P; the RESTORE extension study group.

OBJECTIVE: To evaluate long-term efficacy and safety profiles during 3 years of individualized ranibizumab treatment in patients with visual impairment due to diabetic macular edema (DME).

DESIGN: Phase IIIb, multicenter, 12-month, randomized core study and 24-month open-label extension study.

PARTICIPANTS: Of the 303 patients who completed the randomized RESTORE 12-month core study, 240 entered the extension study.

METHODS: In the extension study, patients were eligible to receive individualized ranibizumab treatment as of month 12 guided by best-corrected visual acuity (BCVA) and disease progression criteria at the investigators' discretion. Concomitant laser treatment was allowed according to the Early Treatment Diabetic Retinopathy Study guidelines. Based on the treatments received in the core study, the extension study groups were referred to as prior ranibizumab, prior ranibizumab + laser, and laser.

MAIN OUTCOME MEASURES: Change in BCVA and incidence of ocular and nonocular adverse events (AEs) over 3 years.

RESULTS: Overall, 208 patients (86.7%) completed the extension study. In patients treated with ranibizumab during the core study, consecutive individualized ranibizumab treatment during the extension study led to an overall maintenance of BCVA and central retinal subfield thickness (CRST) observed at month 12 over the 2-year extension study (+8.0 letters, -142.1 μm [prior ranibizumab] and +6.7 letters, -145.9 μm [prior ranibizumab + laser] from baseline at month 36) with a median of 6.0 injections (mean, 6.8 injections; prior ranibizumab) and 4.0 (mean, 6.0 injections; prior ranibizumab + laser). In the prior laser group, a progressive BCVA improvement (+6.0 letters) and CRST reduction (-142.7 μm) at month 36 were observed after allowing ranibizumab during the extension study, with a median of 4.0 injections (mean, 6.5 injections) from months 12 to 35. Patients in all 3 treatment groups received a mean of <3 injections in the final year. No cases of endophthalmitis, retinal tear, or retinal detachment were reported. The most frequently reported ocular and nonocular adverse effects over 3 years were cataract (16.3%) and nasopharyngitis (23.3%). Eight deaths were reported during the extension study, but none were suspected

to be related to the study drug/procedure.

CONCLUSIONS: Ranibizumab was effective in improving and maintaining BCVA and CRST outcomes with a progressively declining number of injections over 3 years of individualized dosing. Ranibizumab was generally well tolerated with no new safety concerns over 3 years.

PMID: 24491642 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2014 Feb;28(1):32-8. doi: 10.3341/kjo.2014.28.1.32. Epub 2014 Jan 21.

Serum concentration of vascular endothelial growth factor after bilateral intravitreal injection of bevacizumab.

Wang D, Choi KS, Lee SJ.

PURPOSE: This study compared serum vascular endothelial growth factor (VEGF) concentration between patients given the bilateral and unilateral intravitreal injections of bevacizumab.

METHODS: In a prospective manner, serum VEGF levels in treatment-naive patients with age-related macular degeneration who underwent bilateral or unilateral intravitreal injections of bevacizumab were investigated. After informed consent, peripheral blood was collected from in patients who underwent bilateral or unilateral intravitreal injection of bevacizumab before and 1 month after the injection. Serum VEGF levels were measured by enzyme-linked immunosorbent assay after centrifugation. In addition, best-corrected visual acuity (BCVA) and central retinal thickness (CRT) before and 1 month after the injection were compared between each group.

RESULTS: Twenty patients received bilateral injections (40 eyes) and 20 patients received unilateral injections. The VEGF concentrations (pg/mL) before the bilateral injection were 235.75 ± 183.16 and 252.53 ± 233.52 for the unilateral injection. They were significantly reduced to 153.88 ± 113.26 and 189.42 ± 251.72 after 1 month, respectively ($p = 0.037$ and 0.019), which are showing no significant difference between the two groups ($p = 0.771$). And there were no significant intergroup difference in pre- and postoperative BCVA and CRT.

CONCLUSIONS: The bilateral simultaneous intravitreal injection of bevacizumab did not differ greatly from unilateral intravitreal injection in the influence on serum VEGF levels and the therapeutic outcome.

PMID: 24505199 [PubMed - in process] PMCID: PMC3913980

Am J Ophthalmol. 2014 Jan 29. pii: S0002-9394(14)00049-X. doi: 10.1016/j.ajo.2014.01.019. [Epub ahead of print]

Subfoveal choroidal thickness as a potential predictor of visual outcome and treatment response after intravitreal ranibizumab injections for typical exudative age-related macular degeneration.

Kang HM, Kwon HJ, Yi JH, Lee CS, Lee SC.

PURPOSE: To investigate prognostic implication of subfoveal choroidal thickness on treatment outcome after intravitreal ranibizumab injections for typical exudative age-related macular degeneration (AMD).

DESIGN: Retrospective study.

METHODS: A total of 40 eyes of 37 patients who completed 6-month follow-up were analyzed. Patients' data were retrieved from medical records including best-corrected visual acuity (BCVA). Subfoveal choroidal thickness at baseline, 3 months, and 6 months was measured by enhanced depth imaging optical coherence tomography, and adjusted for age and sex before statistical analysis. Treatment response was

after three monthly intravitreal ranibizumab injections. Responders (responder group) was defined as a 100 µm or more decrease or complete resolution of subretinal fluid, whereas non-responders (non-responder group) were defined as changes less than 100 µm or more than 100 µm increase of subretinal fluid by OCT.

RESULTS: Mean age at diagnosis was 72.1±8.1 years, and 22 eyes (55.0%) were responders. The responder group had thicker subfoveal choroid (257.2±108.3 µm) and smaller lesions (1.3±0.8 µm) at baseline than the non-responder group (167.1± 62.4 µm, P=.003; and 2.0±1.0 µm, P=.008). The responder group showed significantly better BCVA and thicker subfoveal choroid than the non-responder group at 3 months (P=.002; and P=.023) and 6 months (P=.004 and P=.031). Stepwise and binary regression analysis demonstrated that subfoveal choroidal thickness was significantly correlated with visual outcome (B=-0.002, P=.003) and treatment response (B=8.136, P=.018).

CONCLUSION: Subfoveal choroidal thickness may be a predictive factor for visual outcome and treatment response in typical exudative AMD after intravitreal ranibizumab injections.

PMID: 24487050 [PubMed - as supplied by publisher]

Expert Rev Clin Pharmacol. 2014 Feb 3. [Epub ahead of print]

Pharmacokinetics, pharmacodynamics and pre-clinical characteristics of ophthalmic drugs that bind VEGF.

Stewart MW.

Abstract: Drugs that prevent the binding of VEGF to its trans-membrane cognate receptors have revolutionized the treatment of the most important chorioretinal vascular disorders: exudative age-related macular degeneration, diabetic macular edema, and retinal vein occlusions. Pegaptanib, which binds to VEGF165 and longer isoforms, ranibizumab and bevacizumab, which bind all VEGF-A isoforms, and aflibercept, which binds VEGF-A, VEGF-B, and placental growth factor, all bind VEGF165 with high affinity. The drugs have relatively long half-lives (7 to 10 days) after intravitreal depot injections and clinical durations of action that usually exceed 4 weeks. Plasma VEGF concentrations decrease after intravitreal injections of bevacizumab and aflibercept because their systemic half-lives are extended by their Fc fragments. Extensive in vitro and in vivo testing shows that the drugs prevent VEGF-mediated activation of endothelial cells while exhibiting little evidence of toxicity. Further anti-VEGF drug development is on-going.

PMID: 24483136 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Am J Ophthalmol. 2014 Feb 3. pii: S0002-9394(14)00055-5. doi: 10.1016/j.ajo.2014.01.025. [Epub ahead of print]

Pseudodrusen Subtypes as Delineated by Multimodal Imaging of the Fundus.

Suzuki M, Sato T, Spaide RF.

PURPOSE: To subclassify pseudodrusen based on their appearance in the multimodal imaging.

DESIGN: Retrospective, observational series.

METHODS: The color fundus photographs and infrared scanning laser ophthalmoscope (IR-SLO) images of patients with pseudodrusen were evaluated along with spectral domain optical coherence tomography (SD-OCT) by masked readers. Distinct types of pseudodrusen could be differentiated.

RESULTS: There were 140 eyes of 93 patients with a mean age of 82.4 years. Multimodal imaging analysis showed 3 subtypes of pseudodrusen. One principal type was an orderly array of whitish discrete accumulations principally located in the perifovea, termed dot pseudodrusen. They appeared as hyporeflective spots, often with a target configuration, in IR-SLO images. The second type was interconnected bands of yellowish-white material forming a reticular pattern, called ribbon pseudodrusen, which were located in the perifovea. This subtype was faintly hyporeflective in IR-SLO imaging. Dot pseudodrusen were detected more commonly with IR-SLO imaging than color photography (P=. 014) and ribbon pseudodrusen were seen more frequently in color than in IR-SLO images (P<. 001). An uncommon third type of pseudodrusen, yellow-white globules primarily located peripheral to the perifoveal region, appeared hyperreflective in IR-SLO and were called peripheral pseudodrusen. All 3 types were seen as subretinal drusenoid deposits by SD-OCT.

CONCLUSION: Pseudodrusen may be classified into at least 3 categories, each with optimal methods of detection and only one that formed a reticular pattern. These findings suggest pseudodrusen could contain differing constituents and therefore, may vary in conferred risk for progression to advanced age-related macular disease.

PMID: 24503406 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Jan 31. pii: S0002-9394(14)00048-8. doi: 10.1016/j.ajo.2014.01.018. [Epub ahead of print]

Macular Choroidal Thickness and Volume of Eyes with Reticular Pseudodrusen Using Swept-Source Optical Coherence Tomography.

Ueda-Arakawa N, Ooto S, Ellabban AA, Takahashi A, Oishi A, Tamura H, Yamashiro K, Tsujikawa A, Yoshimura N.

PURPOSE: To investigate the choroidal thickness/volume of eyes with reticular pseudodrusen using high-penetration swept-source optical coherence tomography (SS-OCT) and to evaluate the choroidal vasculature changes using en face images.

DESIGN: Prospective cross sectional study.

METHODS: Thirty-eight eyes with reticular pseudodrusen and 14 normal eyes were studied with prototype SS-OCT. Eyes with reticular pseudodrusen were classified into 3 subgroups: eyes without late age-related macular degeneration (AMD) (group1), eyes with neovascular AMD (group2), and eyes with geographic atrophy (group3). Mean regional choroidal thickness/volume measurements were obtained by three-dimensional (3D) raster scanning. The choroidal vascular area was measured using en face images reconstructed from a 3D SS-OCT data set.

RESULTS: Mean age and axial length did not differ between eyes with reticular pseudodrusen and normal eyes. The mean choroidal thickness and volume of each sector was significantly reduced in eyes with reticular pseudodrusen compared with normal eyes ($P < 0.020$ for all). Mean choroidal thickness and volume of each area showed no significant difference between the 3 groups; however, most of them showed decreased thickness compared with normal eyes. En face images through the choroid revealed narrow and sparse choroidal vessels in eyes with reticular pseudodrusen. The area of choroidal vasculature was significantly reduced in eyes with reticular pseudodrusen compared with normal eyes ($P = 0.037$).

CONCLUSIONS: In eyes with reticular pseudodrusen, macular choroidal thickness/volume was reduced regardless of choroidal neovascularization/geographic atrophy. Thinned vessels in the choroid suggest choroidal involvement in the pathogenesis of reticular pseudodrusen.

PMID: 24491418 [PubMed - as supplied by publisher]

J Mater Sci Mater Med. 2014 Feb 4. [Epub ahead of print]

Development of a surface to increase retinal pigment epithelial cell (ARPE-19) proliferation under reduced serum conditions.

Zuber AA, Robinson DE, Short RD, Steele DA, Whittle JD.

Abstract: Age related macular degeneration of the eye is brought about by damage to the retinal pigment epithelium (RPE) and is a major cause of adult blindness. One potential treatment method is transplantation of RPE cells grown in vitro. Maintaining RPE cell viability and physiological function in vitro is a challenge, and this must also be achieved using materials that can be subsequently used to deliver an intact cell sheet into the eye. In this paper, plasma polymerisation has been used to develop a chemically modified surface for maintaining RPE cells in vitro. Multiwell plates modified with a plasma copolymer of allylamine and octadiene maintained RPE cell growth at a level similar to that of TCPS. However, the addition of bound glycosaminoglycans (GAGs) to the plasma polymerised surface significantly enhanced RPE proliferation. Simply adding GAG to the culture media had no positive effect. It is shown that a combination of plasma polymer and GAG is a promising method for developing suitable surfaces for cell growth and delivery, that can be applied to any substrate material.

PMID: 24493476 [PubMed - as supplied by publisher]

Pathogenesis

PLoS One. 2014 Jan 28;9(1):e87530. doi: 10.1371/journal.pone.0087530. eCollection 2014.

IKK2 Inhibition Attenuates Laser-Induced Choroidal Neovascularization.

Lu H, Lu Q, Gaddipati S, Kasetti RB, Wang W, Pasparakis M, Kaplan HJ, Li Q.

Abstract: Choroidal neovascularization (CNV) is aberrant angiogenesis associated with exudative age-related macular degeneration (AMD), a leading cause of blindness in the elderly. Inflammation has been suggested as a risk factor for AMD. The IKK2/NF-κB pathway plays a key role in the inflammatory response through regulation of the transcription of cytokines, chemokines, growth factors and angiogenic factors. We investigated the functional role of IKK2 in development of the laser-induced CNV using either Ikk2 conditional knockout mice or an IKK2 inhibitor. The retinal neuronal tissue and RPE deletion of IKK2 was generated by breeding Ikk2(-/flox) mice with Nestin-Cre mice. Deletion of Ikk2 in the retina caused no obvious defect in retinal development or function, but resulted in a significant reduction in laser-induced CNV. In addition, intravitreal or retrobulbar injection of an IKK2 specific chemical inhibitor, TPCA-1, also showed similar inhibition of CNV. Furthermore, in vitro inhibition of IKK2 in ARPE-19 cells significantly reduced heat shock-induced expression of NFKBIA, IL1B, CCL2, VEGFA, PDGFA, HIF1A, and MMP-2, suggesting that IKK2 may regulate multiple molecular pathways involved in laser-induced CNV. The in vivo laser-induced expression of VEGFA, and HIF1A in RPE and choroidal tissue was also blocked by TPCA-1 treatment. Thus, IKK2/NF-κB signaling appears responsible for production of pro-inflammatory and pro-angiogenic factors in laser-induced CNV, suggesting that this intracellular pathway may serve as an important therapeutic target for aberrant angiogenesis in exudative AMD.

PMID: 24489934 [PubMed - in process] PMCID: PMC3905033

Curr Eye Res. 2014 Feb 6. [Epub ahead of print]

Level of Vascular Endothelial Growth Factor 165b in Human Aqueous Humor.

Baba T, Bikbova G, Kitahashi M, Yokouchi H, Oshitari T, Yamamoto S.

Abstract Purpose: Vascular endothelial growth factor 165b (VEGF165b) is a splice variant of VEGF-A and is an anti-angiogenic form as opposed to a pro-angiogenic form of VEGF. We compared the level of VEGF165b in the aqueous humor of 77 eyes with exudative age-related macular degeneration (AMD) and 38 eyes with retinal vein occlusion (RVO). Design: A prospective, interventional case series. Methods: The concentration of aqueous VEGF165b was measured by enzyme-linked immunosorbent assay (ELISA), and its level in the subgroups of AMD, classic and occult choroidal neovascularization (CNV) and polypoidal choroidal vasculopathy (PCV), was compared. The relationships between the VEGF165b level and the greatest linear dimension (GLD), central foveal thickness (CFT), and the height of the subretinal fluid (SRF) were determined for the AMD and RVO cases. Results: The level of VEGF165b was higher than the lower limit of detection (15 pg/ml) in 57% of the AMD cases (median, 16.4; range, <15-98 pg/ml) and 63% of the controls (median, 20.6; range, <15-46 pg/ml). The percentage of eyes with >15 pg/ml of VEGF165b was significantly lower in eyes with RVO (32%, p = 0.038). The VEGF165b level was not significantly different among the AMD subtypes, and it was not significantly correlated with the GLD, CFT, and SRF. In the RVO cases, the CFT and SRF thickness were greater in eyes with a VEGF level <15 pg/ml (p = 0.006, 0.048 respectively). Conclusions: The anti-angiogenic VEGF165b was low in eyes with RVO. Therapy based on balancing the pro- and anti-angiogenic factors might be a new approach to treat ocular vascular disorders.

PMID: 24502617 [PubMed - as supplied by publisher]

Biomaterials. 2014 Jan 29. pii: S0142-9612(14)00018-0. doi: 10.1016/j.biomaterials.2014.01.016. [Epub ahead of print]

The effect of retinal pigment epithelial cell patch size on growth factor expression.

Vargis E, Peterson CB, Morrell-Falvey JL, Retterer ST, Collier CP.

Abstract: The spatial organization of retinal pigment epithelial (RPE) cells grown in culture was controlled using micropatterning techniques in order to examine the effect of patch size on cell health and differentiation. Understanding this effect is a critical step in the development of multiplexed high throughput fluidic assays and provides a model for replicating disease states associated with the deterioration of retinal tissue during age-related macular degeneration (AMD). Microcontact printing of fibronectin on polystyrene and glass substrates was used to promote cell attachment, forming RPE patches of controlled size and shape. These colonies mimic the effect of atrophy and loss-of-function that occurs in the retina during degenerative diseases such as AMD. After 72 h of cell growth, levels of vascular endothelial growth factor (VEGF), an important biomarker of AMD, were measured. Cells were counted and morphological indicators of cell viability and tight junction formation were assessed via fluorescence microscopy. Up to a twofold increase of VEGF expression per cell was measured as colony size decreased, suggesting that the local microenvironment of, and connections between, RPE cells influences growth factor expression leading to the initiation and progression of diseases such as AMD.

PMID: 24485792 [PubMed - as supplied by publisher]

Biomaterials. 2014 Jan 28. pii: S0142-9612(14)00032-5. doi: 10.1016/j.biomaterials.2014.01.030. [Epub ahead of print]

Monitoring the VEGF level in aqueous humor of patients with ophthalmologically relevant diseases via ultrahigh sensitive paper-based ELISA.

Hsu MY, Yang CY, Hsu WH, Lin KH, Wang CY, Shen YC, Chen YC, Chau SF, Tsai HY, Cheng CM.

Abstract: The vascular endothelial growth factor (VEGF) level in aqueous humor has been used as an indicator to monitor specific diseases in the retinal ischemic condition. For clinical diagnosis, only about 200 μL of aqueous humor can be collected from the anterior chamber before the threat of anterior chamber

collapse. It is necessary to develop an inexpensive diagnostic approach with the characteristics of highly sensitive, short operation duration, and requires small clinical sample quantities. To achieve the main objective of this study, we first prepared bevacizumab to be conjugated with HRP. We then deposited 2 μL aqueous humor from patients with different diseases onto each test zone of paper-based 96-well plates. After the colorimetric results were performed via ELISA protocol, the output signals were recorded using a commercial desktop scanner for analysis. In this study, only 2 μL from the aqueous humor of each patient was required for paper-based ELISA. The mean aqueous VEGF level was 14.4 pg/mL from thirteen patients (N = 13) with senile cataract as the control. However, the mean aqueous VEGF level from other patients with proliferative diabetic retinopathy (N = 14), age-related macular degeneration (N = 17), and retinal vein occlusion (N = 10) showed VEGF increases to 740.1 pg/mL, 383 pg/mL, and 219.4 pg/mL, respectively.

PMID: 24484673 [PubMed - as supplied by publisher]

Curr Eye Res. 2014 Feb 6. [Epub ahead of print]

Baicalin Attenuates Laser-Induced Choroidal Neovascularization.

Yang SJ, Jo H, Kim JG, Jung SH.

Abstract Purpose: To determine whether intravitreally-injected baicalin inhibits the growth of choroidal neovascularization (CNV) experimentally induced via laser photocoagulation through analysis of angiogenic factors.

Materials and methods: Six CNVs were induced in the left eyes of 8-week-old male Brown Norway rats. Immediately after the induction of CNV, 4 μl of baicalin solution (0.1, 1 or 5 nmol) and 4 μl of a solution containing 100 μg of bevacizumab were slowly injected into the vitreous cavity under direct observation with an operating microscope. At 14 days after CNV induction, fluorescein angiography (FA) was performed, and choroidal flat mounts were produced for quantitative assessment of CNV. The levels of the anti-angiogenic proteins vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and matrix metalloproteinase-2 (MMP-2) were determined via Western blot analysis.

Results: FA of bevacizumab- and baicalin-treated rats showed significantly reduced CNV and leakage from the CNV lesions compared to control rats at day 14. Choroidal flat mounts revealed that baicalin inhibited the growth of CNV lesions in a dose-dependent manner. Western blot analysis demonstrated that baicalin significantly attenuated the up-regulation of VEGF, PDGF and MMP-2.

Conclusion: Baicalin suppressed laser-induced CNV formation in rats. These results suggest that baicalin should be considered as a candidate drug for treating exudative age-related macular degeneration.

PMID: 24502359 [PubMed - as supplied by publisher]

PLoS One. 2014 Feb 5;9(2):e88248. doi: 10.1371/journal.pone.0088248. eCollection 2014.

Visual space and object space in the cerebral cortex of retinal disease patients.

Goesaert E, Van Baelen M, Spileers W, Wagemans J, Op de Beeck HP.

Abstract: The lower areas of the hierarchically organized visual cortex are strongly retinotopically organized, with strong responses to specific retinotopic stimuli, and no response to other stimuli outside these preferred regions. Higher areas in the ventral occipitotemporal cortex show a weak eccentricity bias, and are mainly sensitive for object category (e.g., faces versus buildings). This study investigated how the mapping of eccentricity and category sensitivity using functional magnetic resonance imaging is affected by a retinal lesion in two very different low vision patients: a patient with a large central scotoma, affecting

central input to the retina (juvenile macular degeneration), and a patient where input to the peripheral retina is lost (retinitis pigmentosa). From the retinal degeneration, we can predict specific losses of retinotopic activation. These predictions were confirmed when comparing stimulus activations with a no-stimulus fixation baseline. At the same time, however, seemingly contradictory patterns of activation, unexpected given the retinal degeneration, were observed when different stimulus conditions were directly compared. These unexpected activations were due to position-specific deactivations, indicating the importance of investigating absolute activation (relative to a no-stimulus baseline) rather than relative activation (comparing different stimulus conditions). Data from two controls, with simulated scotomas that matched the lesions in the two patients also showed that retinotopic mapping results could be explained by a combination of activations at the stimulated locations and deactivations at unstimulated locations. Category sensitivity was preserved in the two patients. In sum, when we take into account the full pattern of activations and deactivations elicited in retinotopic cortex and throughout the ventral object vision pathway in low vision patients, the pattern of (de)activation is consistent with the retinal loss.

PMID: 24505449 [PubMed - in process] PMCID: PMC3914958

J Biol Chem. 2014 Feb 6. [Epub ahead of print]

Doxycycline inhibits polarization of macrophages to the proangiogenic M2-type and subsequent neovascularization.

He L, Marneros AG.

Abstract: Macrophages occur along a continuum of functional states between M1-type polarized macrophages with antiangiogenic and antitumor activity, and M2-type polarized macrophages, which have been implicated to promote angiogenesis and tumor growth. Proangiogenic M2-type macrophages promote various pathologic conditions, including choroidal neovascularization in models of neovascular age-related macular degeneration or certain cancers, such as glioblastoma multiforme. Thus, a potential novel therapeutic approach to target pathological angiogenesis in these conditions would be to inhibit polarization of macrophages towards the proangiogenic M2-type. However, no pharmacological inhibitors of M2-type macrophage polarization have been identified yet. Here, we performed an unbiased pharmacological and small chemical screen to identify drugs that inhibit proangiogenic M2-type macrophage polarization and block pathologic macrophage-driven neovascularization. We identified the well-tolerated and commonly used antibiotic doxycycline as a potent inhibitor of M2-type polarization of macrophages. Doxycycline inhibited in a dose-dependent manner M2-type polarization of human and of bone marrow-derived mouse macrophages without affecting cell viability. Furthermore, doxycycline inhibited M2-type macrophage polarization and subsequent neovascularization in vivo in a laser-injury model of choroidal neovascularization. Thus, doxycycline could be used to enhance current antiangiogenic treatment approaches in various conditions that are promoted by proangiogenic M2-type macrophages, including neovascular age-related macular degeneration or certain cancers.

PMID: 24505138 [PubMed - as supplied by publisher]

Eye (Lond). 2014 Feb 7. doi: 10.1038/eye.2014.19. [Epub ahead of print]

Zebrafish-on the move towards ophthalmological research.

Chhetri J, Jacobson G, Gueven N.

Abstract: Millions of people are affected by visual impairment and blindness globally, and the prevalence of vision loss is likely to increase as we are living longer. However, many ocular diseases remain poorly controlled due to lack of proper understanding of the pathogenesis and the corresponding lack of effective therapies. Consequently, there is a major need for animal models that closely mirror the human eye

pathology and at the same time allow higher-throughput drug screening approaches. In this context, zebrafish as an animal model organism not only address these needs but can in many respects reflect the human situation better than the current rodent models. Over the past decade, zebrafish have become an established model to study a variety of human diseases and are more recently becoming a valuable tool for the study of human ophthalmological disorders. Many human ocular diseases such as cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration have already been modelled in zebrafish. In addition, zebrafish have become an attractive model for pre-clinical drug toxicity testing and are now increasingly used by scientists worldwide for the discovery of novel treatment approaches. This review presents the advantages and uses of zebrafish for ophthalmological research.Eye advance online publication, 7 February 2014; doi:10.1038/eye.2014.19.

PMID: 24503724 [PubMed - as supplied by publisher]

Epidemiology

Am J Ophthalmol. 2014 Jan 31. pii: S0002-9394(14)00053-1. doi: 10.1016/j.ajo.2014.01.023. [Epub ahead of print]

Risk Factors Associated with Reticular Pseudodrusen versus Large Soft Drusen.

Boddu S, Lee MD, Marsiglia M, Marmor M, Freund KB, Smith RT.

PURPOSE: To investigate genetic, environmental, and systemic risk factors in prospectively identified subjects with the age-related macular degeneration (AMD) phenotypes of (a) reticular pseudodrusen without large soft drusen and (b) large soft drusen without reticular pseudodrusen.

DESIGN: Prospective case-case comparison.

METHODS: In a clinical practice setting, patients with AMD were sequentially screened using clinical examination and scanning laser ophthalmoscopy imaging to prospectively identify subjects (n=73) with the phenotypes of (a) reticular pseudodrusen without large soft drusen (n=30) or (b) large soft drusen without reticular pseudodrusen (n=43). Subjects were genotyped for two alleles associated with AMD, age-related maculopathy susceptibility 2 (ARMS2) and complement factor H (CFH). A questionnaire was administered to collect history of smoking, hypertension, diabetes, and hyperlipidemia, as well as personal and family history of AMD.

RESULTS: The reticular pseudodrusen group was older (median age 87 vs. 81 years, P=0.04) and had more females (83.3% vs. 48.8%, P=0.003), later ages of AMD onset (83 vs. 70 years, P=0.0005), and a greater frequency of hypertension (76.7% vs. 55.8%, P=0.08). No significant differences were found in the distribution of the ARMS2 risk allele (P=0.4) between the reticular pseudodrusen (homozygous=20.0%; heterozygous=56.7%) and large soft drusen (homozygous=19.0%; heterozygous=42.9%) phenotypes, or in the distribution of the CHF risk allele (P=0.7) between the reticular pseudodrusen (homozygous=26.7%; heterozygous=56.7%) and large soft drusen (homozygous=21.4%; heterozygous=66.7%) phenotypes.

CONCLUSIONS: The reticular pseudodrusen phenotype was associated with increased age, later age of AMD onset, and female gender.

PMID: 24491417 [PubMed - as supplied by publisher]

Eye (Lond). 2014 Feb 7. doi: 10.1038/eye.2014.8. [Epub ahead of print]

Age-related macular degeneration and protective effect of HMG Co-A reductase inhibitors (statins): results from the National Health and Nutrition Examination Survey 2005-2008.

Barbosa DT, Mendes TS, Cíntron-Colon HR, Wang SY, Bhisitkul RB, Singh K, Lin SC.

Purpose: To determine the association of hydroxymethylglutarylcoenzyme A (HMG Co-A) reductase inhibitor (statin) use with the prevalence of age-related macular degeneration (AMD).

Methods: This cross-sectional study included 5604 participants in the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2008, ≥40 years of age, who were ascertained with regard to the diagnosis of AMD, the use of statins, and comorbidities and health-related behaviors such as smoking.

Results: The mean age of participants denying or confirming a history of AMD was 68 (SEM 0.90) and 55 (SEM 0.36) years, respectively. Individuals 68 years of age or older who were classified as long-term users of statins had statistically significant less self-reported AMD (odds ratio (OR) 0.64, 95% confidence interval (CI) 0.49-0.84; P=0.002), after adjusting for potential confounding variables. No significant association was found between the prevalence of AMD and statin consumption among subjects between 40 and 67 years of age (OR 1.61, 95% CI 0.85-3.03; P=0.137).

Conclusions: Our results suggest a possible beneficial effect of statin intake for the prevention of AMD in individuals 68 years of age or older.

PMID: 24503725 [PubMed - as supplied by publisher]

Genetics

Ophthalmic Genet. 2014 Feb 5. [Epub ahead of print]

CETP Gene may be Associated with Advanced Age-related Macular Degeneration in the Chinese Population.

Wang D, Zhou J, Hou X, Nguyen DH, Cao G, Li G, Qiu G, Zhang K, Zhang M, Su Z.

Abstract Objectives: This study aims to investigate whether variations in LIPC, CETP, ABCA1 and LPL, which are involved in high-density lipoprotein (HDL) metabolism, are associated with advanced age-related macular degeneration (AMD) in the Chinese population.

Design and Methods: A total of 119 Chinese patients with advanced AMD and 99 control individuals were recruited. Genomic DNA was extracted from peripheral blood leukocytes. Genotypes of seven single nucleotide polymorphisms (SNPs) including rs1061170 and rs1410996 in CFH, rs10490924 in HTRA1, rs10468017 in LIPC, rs3764261 in CETP, rs1883025 in ABCA1 and rs12678919 near LPL were determined by polymerase chain reaction (PCR) followed by allele-specific restriction enzyme digestion or SNaPshot. Unconditional logistic regression analyses were performed to generate a risk predictive model.

Results: We observed the frequency of allele A of rs3764261 in CETP to be significantly lower in advanced AMD after Bonferroni correction (15.5% in patients with AMD and 20.7% in controls; OR = 0.49, 95% CI: 0.29-0.85; p = 0.011). Furthermore, we found that it was also associated with reduced risk of both unilateral AMD (OR = 0.52, 95% CI: 0.28-0.98; p = 0.043) and bilateral AMD (OR = 0.45, 95% CI: 0.22-0.91; p = 0.026). Rs10468017 in LIPC, rs12678919 near LPL and rs1883025 in ABCA1 were not found to be associated with advanced AMD (all p > 0.05).

Conclusion: Our data suggested that the allele A in rs3764261 in CETP gene may be associated with a decreased risk of advanced AMD in Chinese population.

PMID: 24498989 [PubMed - as supplied by publisher]

PLoS One. 2014 Jan 31;9(1):e87047. doi: 10.1371/journal.pone.0087047. eCollection 2014.

Three New Genetic Loci (R1210C in CFH, Variants in COL8A1 and RAD51B) Are Independently Related to Progression to Advanced Macular Degeneration.

Seddon JM, Reynolds R, Yu Y, Rosner B.

OBJECTIVES: To assess the independent impact of new genetic variants on conversion to advanced stages of AMD, controlling for established risk factors, and to determine the contribution of genes in predictive models.

METHODS: In this prospective longitudinal study of 2765 individuals, 777 subjects progressed to neovascular disease (NV) or geographic atrophy (GA) in either eye over 12 years. Recently reported genetic loci were assessed for their independent effects on incident advanced AMD after controlling for 6 established loci in 5 genes, and demographic, behavioral, and macular characteristics. New variants which remained significantly related to progression were then added to a final multivariate model to assess their independent effects. The contribution of genes to risk models was assessed using reclassification tables by determining risk within cross-classified quintiles for alternative models.

RESULTS: THREE NEW GENETIC VARIANTS WERE SIGNIFICANTLY RELATED TO PROGRESSION: rare variant R1210C in CFH (hazard ratio (HR) 2.5, 95% confidence interval [CI] 1.2-5.3, P=0.01), and common variants in genes COL8A1 (HR 2.0, 95% CI 1.1-3.5, P=0.02) and RAD51B (HR 0.8, 95% CI 0.60-0.97, P=0.03). The area under the curve statistic (AUC) was significantly higher for the 9 gene model (.884) vs the 0 gene model (.873), P=.01. AUC's for the 9 vs 6 gene models were not significantly different, but reclassification analyses indicated significant added information for more genes, with adjusted odds ratios (OR) for progression within 5 years per one quintile increase in risk score of 2.7, P<0.001 for the 9 vs 6 loci model, and OR 3.5, P<0.001 for the 9 vs. 0 gene model. Similar results were seen for NV and GA.

CONCLUSIONS: Rare variant CFH R1210C and common variants in COL8A1 and RAD51B plus six genes in previous models contribute additional predictive information for advanced AMD beyond macular and behavioral phenotypes.

PMID: 24498017 [PubMed - in process] PMCID: PMC3909074

Hum Mol Genet. 2014 Feb 4. [Epub ahead of print]

Validation of GWAS Alleles with Patient-specific Stem Cell Lines.

Yang J, Li Y, Chan L, Tsai YT, Wu WH, Nguyen HV, Hsu CW, Li X, Brown LM, Egli D, Sparrow JR, Tsang SH.

Abstract: While the past decade has seen great progress in mapping loci for common diseases, studying how these risk alleles lead to pathology remains a challenge. Age-related macular degeneration (AMD) affects nine million older Americans, and is characterized by loss of the retinal pigment epithelium (RPE). Although the closely linked genome-wide association studies (GWAS) ARMS2/HTRA1 genes, located at the chromosome 10q26 locus, are strongly associated with the risk of AMD, their downstream targets are unknown. Low population frequencies of risk alleles in tissue banks make it impractical to study their function in cells derived from autopsied tissue. Moreover, autopsy eyes from end-stage AMD patients, where age-related RPE atrophy and fibrosis are already present, cannot be used to determine how abnormal ARMS2/HTRA1 expression can initiate RPE pathology. Instead, induced pluripotent stem (iPS) cell-derived RPE from patients provides us with earlier stage AMD patient-specific cells and allows us to analyze the underlying mechanisms at this critical time point. An unbiased proteome screen of A2E-aged patient-specific iPS-derived RPE cell lines identified SOD2-mediated antioxidative defense in the genetic allele's susceptibility of AMD. The AMD-associated risk haplotype (T-in/del-A) impairs the ability of the RPE to defend against aging-related oxidative stress. SOD2 defense is impaired in RPE homozygous for the risk

haplotype (T-in/del-A; T-in/del-A), while the effect was less pronounced in RPE homozygous for the protective haplotype (G-Wt-G; G-Wt-G). ARMS2/HTRA1 risk alleles decrease SOD2 defense, making RPE more susceptible to oxidative damage and thereby contributing to AMD pathogenesis.

PMID: 24497574 [PubMed - as supplied by publisher]

Diet & lifestyle

Br J Nutr. 2014 Feb 6:1-7. [Epub ahead of print]

Consumption of dairy products and the 15-year incidence of age-related macular degeneration.

Gopinath B, Flood VM, Louie JC, Wang JJ, Burlutsky G, Rochtchina E, Mitchell P.

Abstract: Habitual consumption of dairy products has been shown to play an important role in the prevention of several chronic diseases. We aimed to prospectively assess the relationship between the change in dairy product consumption (both regular fat and low/reduced fat) and the 15-year incidence of age-related macular degeneration (AMD). In the Blue Mountains Eye Study, 2037 participants aged 49 years or above at baseline were re-examined at follow-up in 1997-9, 2002-4 and/or 2007-9. AMD was assessed from retinal photographs. Dietary data were collected using a semi-quantitative FFQ, and servings of dairy product consumption calculated. Over the 15-year follow-up, there were 352, 268 and eighty-four incident cases of any, early and late AMD, respectively. After adjusting for age, sex, current smoking, white cell count and fish consumption, a significant linear trend (P for trend = 0·003) was observed with decreasing consumption of total dairy foods and the 15-year incidence of late AMD, comparing the lowest v. highest quintile of intake (OR 2·80, 95 % CI 1·21, 3·04). Over the 15 years, decreased consumption of reduced-fat dairy foods was associated with an increased risk of incident late AMD, comparing the lowest to highest quintile of intake (OR 3·10, 95 % CI 1·18, 8·14, P for trend = 0·04). Decreasing total dietary Ca intake over the 15 years was also associated with an increased risk of developing incident late AMD (multivariable-adjusted P for trend = 0·03). A lower consumption of dairy products (regular and low fat) and Ca was independently associated with a higher risk of developing incident late AMD in the long term. Additional cohort studies are needed to confirm these findings.

PMID: 24502821 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2014 Jan;62(1):16-22. doi: 10.4103/0301-4738.126168.

2-ethylpyridine, a cigarette smoke component, causes mitochondrial damage in human retinal pigment epithelial cells in vitro.

Mansoor S, Gupta N, Falatoonzadeh P, Kuppermann BD, Kenney MC.

Purpose: Our goal was to identify the cellular and molecular effects of 2-ethylpyridine (2-EP, a component of cigarette smoke) on human retinal pigment epithelial cells (ARPE-19) in vitro.

Materials and Methods: ARPE-19 cells were exposed to varying concentrations of 2-EP. Cell viability (CV) was measured by a trypan blue dye exclusion assay. Caspase-3/7 and caspase-9 activities were measured by fluorochrome assays. The production of reactive oxygen/nitrogen species (ROS/RNS) was detected with a 2',7'-dichlorodihydrofluorescein diacetate dye assay. The JC-1 assay was used to measure mitochondrial membrane potential (ΔΨm). Mitochondrial redox potential was measured using a RedoxSensor Red kit and mitochondria were evaluated with Mitotracker dye.

Results: After 2-EP exposure, ARPE-19 cells showed significantly decreased CV, increased caspase-3/7 and caspase-9 activities, elevated ROS/RNS levels, decreased ΔΨm value and decreased redox fluorescence when compared with control samples.

Conclusions: These results show that 2-EP treatment induced cell death by caspase-dependent apoptosis associated with an oxidative stress and mitochondrial dysfunction. These data represent a possible mechanism by which smoking contributes to age-related macular degeneration and other retinal diseases and identify mitochondria as a target for future therapeutic interventions.

PMID: 24492497 [PubMed - in process]

Free Radic Biol Med. 2014 Jan 28. pii: S0891-5849(14)00038-0. doi: 10.1016/ j.freeradbiomed.2014.01.025. [Epub ahead of print]

Salvianolic acid A protects RPE cells against oxidative stress through activation of Nrf2/HO-1 signaling.

Zhang H, Liu YY, Jiang Q, Li KR, Zhao YX, Cao C, Yao J.

Abstract: Reactive oxygen species (ROS) impair the physiological functions of retinal pigment epithelial (RPE) cells, which is known as one major cause of age-related macular degeneration. Salvianolic acid A (Sal A) is the main effective aqueous extract of Salvia miltiorrhiza. The aim of this study was to test the potential role of Sal A against oxidative stress in cultured RPE cells and to investigate the underlying mechanistic signaling pathways. We observed that Sal A significantly inhibited hydrogen peroxide (H2O2)-induced primary and transformed RPE cell death and apoptosis. H2O2-stimulated mitogen-activated protein kinase activation, ROS production, and subsequent proapoptotic AMP-activated protein kinase activation were largely inhibited by Sal A. Further, Sal A stimulation resulted in a fast and dramatic activation of Akt/mammalian target of rapamycin complex 1 (mTORC1) signaling, followed by phosphorylation, accumulation, and nuclear translocation of the NF-E2-related factor 2 (Nrf2), along with increased expression of the antioxidant-response element-dependent gene heme oxygenase-1 (HO-1). Both Nrf2 and HO-1 were required for Sal A-mediated cytoprotective effect, as Nrf2/HO-1 inhibition abolished Sal A-induced beneficial effects against H2O2. Meanwhile, the PI3K/Akt/mTORC1 chemical inhibitors not only suppressed Sal A-induced Nrf2/HO-1 activation, but also eliminated its cytoprotective effect in RPE cells. These observations suggest that Sal A activates the Nrf2/HO-1 axis in RPE cells and protects against oxidative stress via activation of Akt/mTORC1 signaling.

PMID: 24486344 [PubMed - as supplied by publisher]