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MD Research News

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Drug treatment

Br J Ophthalmol. 2014 Sep 23. [Epub ahead of print]

Outcomes of persistently active neovascular age-related macular degeneration treated with VEGF inhibitors: observational study data.

Barthelmes D, Walton R, Campain AE, Simpson JM, Arnold JJ, McAllister IL, Guymer RH, Hunyor AP, Essex RW, Morlet N, Gillies MC; for the Fight Retinal Blindness! Project Investigators.

AIM: To describe outcomes of eyes with wet age-related macular degeneration (AMD) subdivided by lesion activity in a large multicentre cohort study.

METHODS: Treatment-naive eyes with subfoveal choroidal neovascularisation receiving antivascular endothelial growth factor therapy enrolled in the Fight Retinal Blindness observational study were included. Lesions were graded at each visit as active if there was intraretinal or subretinal fluid attributable to leak from choroidal neovascularisation lesion or fresh haemorrhage. Eyes were divided into four groups; based on the proportion of visits, each eye was graded as active during the first 12 months of treatment (persistent, high, moderate and low activity).

RESULTS: 655 eyes were included. Similar mean visual acuity changes compared with baseline were observed in all four groups at 12 months (+6.8, +8.3, +6.2 and +5.5 letters for the low, moderate, high and persistent groups, respectively; p<0.001 for each group). The mean number of injections given increased only modestly in groups with more active lesions (7.6, 7.9, 8.4 and 8.3, respectively, p=0.015). Occult and minimally classic lesions were more frequent in the more active groups (p=0.024).

CONCLUSIONS: Persistent activity of neovascular lesions during 12 months after starting intravitreal therapy was not associated with worse visual outcomes in this observational study of AMD.

PMID: 25249615 [PubMed - as supplied by publisher]

Drug Saf. 2014 Sep 27. [Epub ahead of print]

Ranibizumab and Risk of Hospitalisation for Ischaemic Stroke and Myocardial Infarction in Patients with Age-Related Macular Degeneration: A Self-Controlled Case-Series Analysis.

Pratt NL, Ramsay EN, Kemp A, Kalisch-Ellett LM, Shakib S, Caughey GE, Ryan P, Graves S, Roughead EE.

BACKGROUND: Ranibizumab, a vascular endothelial growth factor (VEGF) inhibitor, is used in the

treatment of age-related macular degeneration. Inhibition of VEGF has an anti-angiogenic action and is associated with thrombogenicity, thus, myocardial infarction and ischaemic stroke are potential side effects of VEGF inhibitors.

OBJECTIVE: Our objective was to assess the association between use of ranibizumab and risk of hospitalisation for ischaemic stroke (IS) and myocardial infarction (MI).

METHODS: The self-controlled case series design was used, including subjects exposed to ranibizumab (Anatomical Therapeutic Chemical [ATC] code S01LA04) who were hospitalized for IS (International Classification of Diseases, tenth edition [ICD-10] code I63) or the combined endpoint of stroke or transient ischaemic attack (TIA) (ICD-10 code G45) or MI (ICD-10 code I21) were identified between August 2007 and March 2013. Rate ratios in exposed periods compared with unexposed periods were calculated using conditional Poisson regression.

RESULTS: A total of 323 subjects received ranibizumab and were hospitalized for IS, 490 for IS or TIA, and 391 for MI. Median period of exposure was 8-9 months with follow-up times of approximately 2.8 years. No elevated risk of IS was seen in the 1-30 days post initiation (incidence rate ratio [IRR] 1.36; 95 % confidence interval [CI] 0.98-1.88); however, elevated risk was observed for those who received therapy for 31-60 days (IRR 1.91; 95 % CI 1.13-3.24). Sensitivity analyses adjusting for time-varying confounders found elevated risk in both the 1-30 days and 31-60 days periods. Similar results to those for IS were observed for the combined endpoint of IS or TIA. No association was seen for MI in either time period (1-30 days IRR 0.90, 95 % CI 0.65-1.23; 31-60 days IRR 0.98, 95 % CI 0.54-1.79).

CONCLUSION: This case-series analysis suggests an increased risk of hospitalisation for ischaemic stroke for patients receiving ranibizumab in the 31-60 days risk period. Studies with larger populations are required to confirm the risk in the 1-30 days risk period. No evidence of increased risk of hospitalisation for MI was observed.

PMID: 25260802 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2014 Sep 22. [Epub ahead of print]

Corneal and Conjunctival Sensitivity Changes Following Intravitreal Ranibizumab Injection in Diabetic Retinopathy.

Ornek N, Ornek K, Erbahçeci IE.

Purpose: To evaluate corneal and conjunctival sensitivity changes following intravitreal ranibizumab (IVR) injection in eyes with diabetic retinopathy.

Methods: Forty-six eyes of 46 patients with diabetic macular edema who underwent intravitreal injection of ranibizumab were included in this prospective study. Fifty eyes of 50 type 2 diabetes mellitus patients served as controls. Each participant underwent a complete ophthalmological examination. Fundus florescein angiography and optical coherence tomography were performed to assess the posterior segment details. IVR (0.5 mg/0.05 mL) was injected from the lower temporal quadrant. Corneal and conjunctival sensitivities were measured using the Cochet-Bonnet esthesiometer.

Results: Corneal sensitivity (CS) increased significantly at first day in temporal and nasal corneas in treated eyes (P=0.005 and P=0.000, respectively). At first week the increase continued and the difference was significant in central, temporal, and nasal corneas (all P=0.000). In fellow eyes, CS increased significantly only in nasal cornea (P=0.004). Only nasal conjunctival sensitivity increased significantly both in treated and fellow eyes at first week (P=0.000 and P=0.005, respectively).

Conclusion: IVR may have a potential to increase corneal and conjunctival sensitivities in diabetic retinopathy.

PMID: 25244301 [PubMed - as supplied by publisher]

Pharm Dev Technol. 2014 Sep 26:1-7. [Epub ahead of print]

Triamcinolone acetonide nanoparticles incorporated in thermoreversible gels for age-related macular degeneration.

Hirani A, Grover A, Lee YW, Pathak Y, Sutariya V.

Abstract: Age-related macular degeneration (AMD) is one of the leading causes of blindness in the US affecting millions yearly. It is characterized by intraocular neovascularization, inflammation and retinal damage which can be ameliorated through intraocular injections of glucocorticoids. However, the complications that arise from repetitive injections as well as the difficulty posed by targeting the posterior segment of the eye make this interesting territory for the development of novel drug delivery systems (DDS). In the present study, we described the development of a DDS composed of triamcinolone acetonide -encapsulated PEGylated PLGA nanoparticles (NP) incorporated into PLGA-PEG-PLGA thermoreversible gel and its use against VEGF expression characteristic of AMD. We found that the NP with mean size of 208 ± 1.0 nm showed uniform size distribution and exhibited sustained release of the drug. We also demonstrated that the polymer can be injected as a solution and transition to a gel phase based on the biological temperature of the eye. Additionally, the proposed DDS was non-cytotoxic to ARPE-19 cells and significantly reduced VEGF expression by 43.5 ± 3.9% as compared to a 1.53 ± 11.1% reduction with triamcinolone. These results suggest the proposed DDS will contribute to the development of novel therapeutic strategies for AMD.

PMID: 25259682 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Sep 24. [Epub ahead of print]

Baseline Choroidal Thickness as a Predictor for Response to Anti-Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema.

Rayess N, Rahimy E, Ying GS, Bagheri N, Ho AC, Regillo CD, Vander JF, Hsu J.

PURPOSE: To determine the association between baseline subfoveal choroidal thickness and short-term response to intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy in diabetic macular edema (DME).

DESIGN: Retrospective, consecutive case series.

METHODS: 53 eyes from 42 patients diagnosed with treatment-naïve DME and treated with 3 monthly intravitreal injections of ranibizumab or bevacizumab. Serial enhanced depth imaging optical coherence tomography scans were used to measure subfoveal choroidal thickness and central macular thickness (CMT). Anatomical response (CMT decrease ≥50 μm) and functional response (best-corrected visual acuity gain ≥1 line) were assessed at 3 months follow-up using univariate and multivariate analyses.

RESULTS: After 3 monthly anti-VEGF treatments, subfoveal choroidal thickness decreased significantly (225μm at baseline, 201μm at 3 months, P<0.0001). The anatomical responder group (32 eyes) had a greater baseline choroidal thickness (243 ± 15μm) than the non-responder group (21 eyes, 198 ± 13μm, P=0.03). Similarly, the functional responder group (28 eyes) tended to have a greater baseline subfoveal choroidal thickness (239 ± 12μm) than the non-responder group (25 eyes, 211 ± 16μm, P=0.08). Multivariate analyses revealed that a greater baseline subfoveal choroidal thickness was associated with a better anatomical (Odds ratio=1.12 for every 10μm increase, P=0.03) and functional response (Odds ratio=8.45 for >200μm vs. ≤200μm, P=0.008).

CONCLUSION: Baseline subfoveal choroidal thickness may help predict which patients with DME will respond more favorably in the short-term to intravitreal anti-VEGF pharmacotherapy. In this study, eyes with a thicker baseline subfoveal choroidal thickness had better short-term anatomical and functional responses.

PMID: 25261844 [PubMed - as supplied by publisher]

Expert Opin Investig Drugs. 2014 Sep 22:1-17. [Epub ahead of print]

Drugs in Phase II clinical trials for the treatment of age-related macular degeneration.

Tolentino MJ, Dennrick A, John E, Tolentino MS.

Introduction: The clinical development of anti-VEGF therapies for the treatment of exudative age-related macular degeneration (wet AMD) has revolutionized ophthalmology. Indeed, it has provided clinicians and patients with treatments that lessen visual loss from in a disease that once was uniformly blinding. Although blindness is yet to be eradicated from AMD, repeated intraocular anti-VEGF injections are required to preserve a patient's vision. Therefore, further advances in this field are necessary.

Areas covered: This review provides an overview of the agents that are in mid-stage phase trials for both exudative (wet AMD) and nonexudative macular degeneration (dry AMD). For wet AMD, new agents intend to enhance efficacy, develop alternative delivery such as eye drops, investigate alternate targets and construct sustained release strategies. For advanced dry AMD, the goal is to develop a strategy to slow or stop progressive loss of retinal tissue seen in geographic atrophy, the hallmark of advanced dry AMD.

Expert opinion: It is important to develop better more sensitive biomarkers, validating different approvable clinical trial endpoints and stratifying patients on their genetic polymorphisms. These developments should help to progress the already rapidly developing field of macular degeneration therapy.

PMID: 25243494 [PubMed - as supplied by publisher]

Zhonghua Yan Ke Za Zhi. 2014 Jun;50(6):426-33.

[Economic evaluation of bevacizumab versus ranibizumab in neovascular age-related macular degeneration].[Article in Chinese]

Li H, Li X, Xie F.

OBJECTIVE: To evaluate the cost-effectiveness of bevacizumab versus ranibizumab for patients with neovascular age-related macular degeneration (AMD) in China.

METHODS: A Markov model was constructed to compare cost per quality-adjusted life year of bevacizumab with ranibizumab in patients with neovascular AMD. In the Markov model, with cycle length of 3 months and time horizon of 10 years, three health states were defined by visual acuity. One way deterministic and probabilistic sensitivity analyses were conducted to explore the uncertainties from a number of variables.

RESULTS: In the base case analysis, patients in ranibizumab group obtained 0.007 QALY more than patients in bevacizumab group, while the average total cost was ¥794 400 higher. The ICUR reached ¥109.23 million per QALY. In all sensitivity analyses, the ICURs were over ¥ 2.48 million per QALY between ranibizumab and bevacizumab groups.

CONCLUSIONS: Ranibizumab for neovascular AMD patients gained similar QALY at significantly higher costs in comparison with bevacizumab. The ICURs generated in this study were much higher than the possible QALY threshold in the society of China. Compared with ranibizumab, bevacizumab was cost-effective for neovascular AMD patients.

PMID: 25241975 [PubMed - in process]

Zhonghua Yan Ke Za Zhi. 2014 Jun;50(6):406-13.

[Attention to the non-responders to anti-VEGF treatment of wet age-related macular disease].

[Article in Chinese]

Zhang M.

Abstract: Intravitreal administration of anti-vascular endothelial growth factor (anti-VEGF) drugs has become the standard treatment for exudative age-related macular degeneration (AMD). However, there are some patients who do not have a sufficient response to the treatment, and some patients fail to respond to those drugs. The mechanisms of non-response to the treatment in these cases are poorly understood. These may be associated with wAMD types, vitreomacularabnormity, genetic factors, andtachyphylaxis, etc. Ophthalmologists should pay attention to those non-responders and give them the correct treatment, avoid the anti-VEGF drugs abuse and explore the best personalized treatment for those patients.

PMID: 25241972 [PubMed - in process]

Curr Opin Ophthalmol. 2014 Sep 17. [Epub ahead of print]

Presumed ocular histoplasmosis.

Thuruthumaly C, Yee DC, Rao PK.

PURPOSE OF REVIEW: To update the knowledge on the risk factors and treatment options for choroidal neovascular membrane due to ocular histoplasmosis and to provide a treatment algorithm.

RECENT FINDINGS: Smoking has been shown to be a strong risk factor in the development of choroidal neovascularization. Alleles that have been identified as a risk factor for the development of choroidal neovascularization in age-related macular degeneration have not shown to be associated with Presumed Ocular Histoplasmosis Syndrome-related choroidal neovascularization. Treatment has largely moved away from submacular surgery and macular photocoagulation to antivascular endothelial growth factor therapy.

SUMMARY: This review highlights the devastating vision loss that may occur in ocular histoplasmosis from the development of an atrophic scar at the fovea or following choroidal neovascularization. Many therapies have been tried with varied amounts of success. Antivascular endothelial growth factor therapy appears to be the gold-standard treatment with the possibility of combined photodynamic therapy in refractory cases.

PMID: 25237930 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Eye (Lond). 2014 Sep 19. doi: 10.1038/eye.2014.214. [Epub ahead of print]

Optical coherence tomography for the diagnosis of neovascular age-related macular degeneration: a systematic review.

Castillo MM, Mowatt G, Lois N, Elders A, Fraser C, Amoaku W, Burr JM, Lotery AJ, Ramsay CR, Azuara-Blanco A.

Abstract: The purpose is to study the diagnostic performance of optical coherence tomography (OCT) and alternative diagnostic tests for neovascular age-related macular degeneration (nAMD). Methods employed are as follows:systematic review and meta-analysis; Index test: OCT including time-domain (TD-OCT) and the most recently developed spectral domain (SD-OCT); comparator tests: visual acuity, clinical evaluation (slit lamp), Amsler chart, colour fundus photographs, infra-red reflectance, red-free images/blue reflectance, fundus autofluorescence imaging (FAF), indocyanine green angiography (ICGA), preferential hyperacuity perimetry (PHP), and microperimetry; reference standard: fundus fluorescein angiography. Databases searched included MEDLINE, MEDLINE In Process, EMBASE, Biosis, SCI, the Cochrane Library, DARE, MEDION, and HTA database. Last literature searches: March 2013. Risk of bias assessed using QUADAS-

2. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic (HSROC) curves. Twenty-two studies (2 abstracts and 20 articles) enrolling 2124 participants were identified, reporting TD-OCT (12 studies), SD-OCT (1 study), ICGA (8 studies), PHP (3 studies), Amsler grid, colour fundus photography and FAF (1 study each). Most studies were considered to have a high risk of bias in the patient selection (55%, 11/20), and flow and timing (40%, 8/20) domains. In a meta-analysis of TD-OCT studies, sensitivity and specificity (95% CI) were 88% (46-98%) and 78% (64-88%), respectively. There was insufficient information to undertake meta-analysis for other tests. TD-OCT is a sensitive test for detecting nAMD, although specificity was only moderate. Data on SD-OCT are sparse. Diagnosis of nAMD should not rely solely on OCT.

PMID: 25233820 [PubMed - as supplied by publisher]

Bioconjug Chem. 2014 Sep 24. [Epub ahead of print]

Molecular Probes for Imaging of Hypoxia in the Retina.

Evans S, Kim K, Moore C, Uddin I, Capozzi ME, Craft J, Sulikowski GA, Jayagopal A.

Abstract: Hypoxia has been associated with retinal diseases which lead causes of irreversible vision loss, including diabetic retinopathy, retinopathy of prematurity, and age-related macular degeneration. Therefore, technologies for imaging hypoxia in the retina are needed for early disease detection, monitoring of disease progression, and assessment of therapeutic responses in the patient. Toward this goal, we developed two hypoxia-sensitive imaging agents based on nitroimidazoles which are capable of accumulating in hypoxic cells in vivo. 2-Nitroimidazole or Pimonidazole were conjugated to fluorescent dyes to yield the imaging agents HYPOX-1 and HYPOX-2. Imaging agents were characterized in cell culture and animal models of retinal vascular diseases which exhibit hypoxia. Both HYPOX-1 and -2 were capable of detecting hypoxia in cell culture models with > 10:1 signal to noise ratios without acute toxicity. Furthermore, intraocular administration of contrast agents in mouse models of retinal hypoxia enabled ex vivo detection of hypoxic tissue. These imaging agents are a promising step towards translation of hypoxia-sensitive molecular imaging agents in preclinical animal models and patients.

PMID: 25250692 [PubMed - as supplied by publisher]

Retina. 2014 Sep 23. [Epub ahead of print]

FEASIBILITY AND CLINICAL UTILITY OF ULTRA-WIDEFIELD INDOCYANINE GREEN ANGIOGRAPHY.

Klufas MA, Yannuzzi NA, Pang CE, Srinivas S, Sadda SR, Freund KB, Kiss S.

PURPOSE: To evaluate the feasibility and clinical utility of a novel noncontact scanning laser ophthalmoscope-based ultra-widefield indocyanine green angiographic system.

METHODS: Ultra-widefield indocyanine green angiographic images were captured using a modified Optos P200Tx that produced high-resolution images of the choroidal vasculature with up to a 200° field. Ultra-widefield indocyanine green angiography was performed on patients with a variety of retinal conditions to assess utility of this imaging technique for diagnostic purposes and disease treatment monitoring.

RESULTS: Ultra-widefield indocyanine green angiography was performed on 138 eyes of 69 patients. Mean age was 58 ± 16.9 years (range, 24-85 years). The most common ocular pathologies imaged included central serous chorioretinopathy (24 eyes), uveitis (various subtypes, 16 eyes), age-related macular degeneration (12 eyes), and polypoidal choroidal vasculopathy (4 eyes). In all eyes evaluated with ultra-widefield indocyanine green angiography, high-resolution images of choroidal and retinal circulation were obtained with sufficient detail out to 200° of the fundus.

CONCLUSION: In this series of 138 eyes, scanning laser ophthalmoscope-based ultra-widefield indocyanine green angiography was clinically practical and provided detailed images of both the central and peripheral choroidal circulation. Future studies are needed to refine the clinical value of this imaging modality and the significance of peripheral choroidal vascular changes in the diagnosis, monitoring, and treatment of ocular diseases.

PMID: 25250480 [PubMed - as supplied by publisher]

Doc Ophthalmol. 2014 Sep 25. [Epub ahead of print]

Multifocal electroretinography in subjects with age-related macular degeneration.

Yavas GF, Küsbeci T, Inan UU.

PURPOSE: To evaluate retinal function objectively in subjects with different stages of age-related macular degeneration (AMD) using multifocal electroretinography (mfERG) and compare it with age-matched control group.

METHODS: A total of 42 subjects with AMD and 37 age-matched healthy control group aged over 55 years were included in this prospective study. mfERG test was performed to all subjects. Average values in concentric ring analysis in four rings (ring 1, from 0° to 5° of eccentricity relative to fixation; ring 2, from 5° to 10°; ring 3, from 10° to 15°; ring 4, over 15°) and in quadrant analysis (superior nasal quadrant, superior temporal quadrant, inferior nasal quadrant and inferior temporal quadrant) were recorded. Test results were evaluated by one-way ANOVA test and independent samples t test.

RESULTS: In mfERG concentric ring analysis, N1 amplitude, P1 amplitude and N2 amplitude were found to be lower and N1 implicit time, P1 implicit time and N2 implicit time were found to be delayed in subjects with AMD compared to control group. In quadrant analysis, N1, P1 and N2 amplitude was lower in all quadrants, whereas N1 implicit time was normal and P1 and N2 implicit times were prolonged in subjects with AMD.

CONCLUSION: mfERG is a useful test in evaluating retinal function in subjects with AMD. AMD affects both photoreceptors and inner retinal function at late stages.

PMID: 25253559 [PubMed - as supplied by publisher]

Clin Exp Optom. 2014 Sep 22.

The short-sighted perspective of long-term eye health-care.

Jamous KF, Kalloniatis M, Boon MY, Jalbert I, Zangerl B.

Abstract: Eye health-care in Australia encompasses patients with chronic disorders being referred to ophthalmologists for detailed assessment and subsequent management. An increasing case load and relative decrease in ophthalmologists predicted over the next few years portend of an upcoming bottleneck in care delivery. To improve the efficiency and effectiveness of patient care within a rapidly changing health system, we propose that minor adjustments to existing services could improve the proficiency of resources. Such changes will require service providers to rethink their positions and roles and actively collaborate with each other for improved patient outcomes.

PMID: 25243594 [PubMed - as supplied by publisher]

Comput Biol Med. 2014 Sep 6;54C:116-128. [Epub ahead of print]

Automated retinal layers segmentation in SD-OCT images using dual-gradient and spatial correlation smoothness constraint.

Niu S, Chen Q, de Sisternes L, Rubin DL, Zhang W, Liu Q.

Abstract: Automatic segmentation of retinal layers in spectral domain optical coherence tomography (SD-OCT) images plays a vital role in the quantitative assessment of retinal disease, because it provides detailed information which is hard to process manually. A number of algorithms to automatically segment retinal layers have been developed; however, accurate edge detection is challenging. We developed an automatic algorithm for segmenting retinal layers based on dual-gradient and spatial correlation smoothness constraint. The proposed algorithm utilizes a customized edge flow to produce the edge map and a convolution operator to obtain local gradient map in the axial direction. A valid search region is then defined to identify layer boundaries. Finally, a spatial correlation smoothness constraint is applied to remove anomalous points at the layer boundaries. Our approach was tested on two datasets including 10 cubes from 10 healthy eyes and 15 cubes from 6 patients with age-related macular degeneration. A quantitative evaluation of our method was performed on more than 600 images from cubes obtained in five healthy eyes. Experimental results demonstrated that the proposed method can estimate six layer boundaries accurately. Mean absolute boundary positioning differences and mean absolute thickness differences (mean±SD) were 4.43±3.32μm and 0.22±0.24μm, respectively.

PMID: 25240102 [PubMed - as supplied by publisher]

J Chin Med Assoc. 2014 Sep 17. [Epub ahead of print]

Retinal stem cells and potential cell transplantation treatments.

Lin TC, Hsu CC, Chien KH, Hung KH, Peng CH, Chen SJ.

Abstract: The retina, histologically composed of ten delicate layers, is responsible for light perception and relaying electrochemical signals to the secondary neurons and visual cortex. Retinal disease is one of the leading clinical causes of severe vision loss, including age-related macular degeneration, Stargardt's disease, and retinitis pigmentosa. As a result of the discovery of various somatic stem cells, advances in exploring the identities of embryonic stem cells, and the development of induced pluripotent stem cells, cell transplantation treatment for retinal diseases is currently attracting much attention. The sources of stem cells for retinal regeneration include endogenous retinal stem cells (e.g., neuronal stem cells, Müller cells, and retinal stem cells from the ciliary marginal zone) and exogenous stem cells (e.g., bone mesenchymal stem cells, adipose-derived stem cells, embryonic stem cells, and induced pluripotent stem cells). The success of cell transplantation treatment depends mainly on the cell source, the timing of cell harvesting, the protocol of cell induction/transplantation, and the microenvironment of the recipient's retina. This review summarizes the different sources of stem cells for regeneration treatment in retinal diseases and surveys the more recent achievements in animal studies and clinical trials. Future directions and challenges in stem cell transplantation are also discussed.

PMID: 25238708 [PubMed - as supplied by publisher]

Pathogenesis

FEBS J. 2014 Sep 22. [Epub ahead of print]

MiR-184 Regulates Ezrin, LAMP-1 Expression, Affects Phagocytosis in Human Retinal Pigment Epithelium and is Down-Regulated in Age-related Macular Degeneration.

Murad N, Kokkinaki M, Gunawardena N, Gunawan MS, Hathout Y, Janczura KJ, Theos AC, Golestaneh N.

Abstract: MicroRNA 184 (miR-184) is known to play a key role in neurological development and apoptosis and is highly expressed in mouse brain, mouse corneal epithelium, zebrafish lens, and human retinal pigment epithelium (RPE). However, the role of miR-184 in RPE is largely unknown. We investigated the role of miR-184 in RPE and its possible implication in age-related macular degeneration (AMD). Proteomic analysis identified the Ezrin (EZR) gene as a target of miR-184 in human RPE. EZR is a membrane cytoskeleton cross-linker that is also known to bind to Lysosomal-Associated Membrane Protein 1 (LAMP-1) during the formation of phagocytic vacuoles. In ARPE-19 cells, inhibition of miR-184 resulted in up-regulation of EZR mRNA and EZR protein, and induced down-regulation of LAMP-1. The inhibition of miR-184 decreased EZR-bound LAMP-1 protein levels and affected phagocytic activity in ARPE19 cells. In primary culture of human RPE isolated from eyes of AMD donors (AMD RPE), miR-184 was significantly down-regulated compared to control (normal) RPE. Down-regulation of miR-184 was consistent with significantly lower levels of LAMP-1 protein in AMD RPE, and overexpression of MIR-184 in AMD RPE was able to rescue LAMP-1 protein expression to normal levels. All together, these observations suggest a novel role for miR-184 in RPE health and support a model proposing that down-regulation of miR-184 expression during aging may result in dysregulation of RPE function, contributing to retinal degeneration.

PMID: 25251993 [PubMed - as supplied by publisher]

Curr Eye Res. 2014 Sep 24:1-6. [Epub ahead of print]

Oxidative Stress Induces Biphasic ERK1/2 Activation in the RPE with Distinct Effects on Cell Survival at Early and Late Activation.

Koinzer S, Reinecke K, Herdegen T, Roider J, Klettner A.

Purpose: Oxidative stress is considered a major factor in the deterioration of retinal pigment epithelium (RPE) cells in dry age-related macular degeneration (AMD). The MAPK ERK1/2 can be activated by oxidative stress, may exert both pro- and anti-apoptotic functions, and has recently been proposed as a major factor in RPE degeneration in atrophic changes. Nrf2 is a master regulator of oxidative stress defense and ERK1/2 is an upstream activator of Nrf2. In this study, we investigate the participation of ERK1/2 in oxidative stress pathways in connection with Nrf2.

Methods: Nrf2 knock-out and wild-type primary RPE cells were prepared from mouse eyes. Oxidative stress was induced by different concentrations of t-butylhydroperoxide. Mitogen-activated protein kinases (MAPKs) were blocked by commercially available inhibitors (SB203580, U0126, SP600125). Cell viability was determined by MTT assay. ERK1/2 expression and activation were assessed by Western blotting.

Results: Oxidative stress induced concentration dependent cell death, which occurred at lower concentrations in Nrf2 knock-out RPE. Western blot analysis displayed a biphasic activation of ERK1/2 in murine wild-type RPE and the inhibition of late, but not early activation of ERK1/2 exerted protection in wild-type murine RPE cells. The biphasic activation of ERK1/2 is lost in Nrf2 knock-out mice, and inhibition of ERK1/2 was generally protective. The inhibition of MAPK JNK or p38 exerted no protection, irrespective of Nrf2.

Conclusion: RPE cells display a biphasic activation of ERK1/2 after oxidative insult, of which the late activation is pro-apoptotic. The biphasic activation is lost in Nrf2 knock-outs, suggesting that early ERK1/2 activation may be connected to Nrf2 signaling. In addition, ERK1/2 activation in Nrf2 knock-outs mediates oxidative stress-induced cell death.

PMID: 25251900 [PubMed - as supplied by publisher]

Aging Cell. 2014 Sep 25. [Epub ahead of print]

Increased Lipocalin-2 in the retinal pigment epithelium of Cryba1 cKO mice is associated with a chronic inflammatory response.

Valapala M, Edwards M, Hose S, Grebe R, Bhutto IA, Cano M, Berger T, Mak TW, Wawrousek E, Handa JT, Lutty GA, Samuel Zigler J Jr, Sinha D.

Abstract: Although chronic inflammation is believed to contribute to the pathology of age-related macular degeneration (AMD), knowledge regarding the events that elicit the change from para-inflammation to chronic inflammation in the pathogenesis of AMD is lacking. We propose here that lipocalin-2 (LCN2), a mammalian innate immunity protein that is trafficked to the lysosomes, may contribute to this process. It accumulates significantly with age in retinal pigment epithelial (RPE) cells of Cryba1 conditional knockout (cKO) mice, but not in control mice. We have recently shown that these mice, which lack βA3/A1-crystallin specifically in RPE, have defective lysosomal clearance. The age-related increase in LCN2 in the cKO mice is accompanied by increases in chemokine (C-C motif) ligand 2 (CCL2), reactive gliosis, and immune cell infiltration. LCN2 may contribute to induction of a chronic inflammatory response in this mouse model with AMD-like pathology.

PMID: 25257511 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Sep 23. [Epub ahead of print]

Characterization of oxygen-induced retinopathy in mice carrying an inactivating point mutation in the catalytic site of ADAM15.

Maretzky T, Blobel CP, Guaiquil VH.

Purpose: Retinal neovascularization is found in diseases such as macular degeneration, diabetic retinopathy or retinopathy of prematurity and is usually caused by alterations in oxygen supply. We have previously described that mice lacking the membrane-anchored metalloproteinase ADAM15 (a Disintegrin and Metalloprotease 15) have decreased pathological neovascularization of the retina in the oxygen-induced retinopathy (OIR) model. The main purpose of the present study was to determine the contribution of the catalytic activity of ADAM15 to OIR.

Methods: To address this question, we generated knock-in mice carrying an inactivating Glutamate to Alanine (E>A) point mutation in the catalytic site of ADAM15 (Adam15E>A mice) and subjected these animals to the OIR model and a heterotopic tumor model. Moreover, we used cell-based assays to determine whether ADAM15 can process cell surface receptors involved in angiogenesis.

Results: We found that pathological neovascularization in the OIR model in Adam15E>A mice was comparable to that observed in wild type mice, but tumor implantation by heterotopically injected melanoma cells was reduced. In cell-based assays, overexpressed ADAM15 could process the FGFR2iiib, but was unable to process several receptors with roles in angiogenesis.

Conclusions: Collectively, these results suggest that the catalytic activity of ADAM15 is not crucial for its function in promoting pathological neovascularization in the mouse OIR model, most likely because of the very limited substrate repertoire of ADAM15. Instead, other non-catalytic functions of ADAM15 must be important for its role in the OIR model.

PMID: 25249606 [PubMed - as supplied by publisher]

Mol Immunol. 2014 Sep 19. [Epub ahead of print]

The role of heparan sulfate as determining pathogenic factor in complement factor H-associated

diseases.

Loeven MA, Rops AL, Berden JH, Daha MR, Rabelink TJ, van der Vlag J.

Abstract: Complement factor H (FH) systemically inhibits excessive complement activation in the microenvironment of host cells, but for instance not on microbes. This self-recognition is mediated by two binding sites that recognize distinctly sulfated heparan sulfate (HS) domains. The interaction with HS not only concentrates FH on host cells, but directly affects its activity, evoking novel models of conformational activation. Genetic aberrations in the HS-binding domains systemically disturb the protective function of FH, yet the resulting loss of complement control affects mainly ocular and renal tissues. Recent results suggest that the specific expression of HS domains in these tissues restricts the interaction of HS to a single binding site within FH. This lack of redundancy could predispose eyes and kidneys to complement-mediated damage, making HS a central determinant for FH-associated diseases.

PMID: 25246018 [PubMed - as supplied by publisher]

Zhonghua Yan Ke Za Zhi. 2014 Jun;50(6):471-5.

[Research advances of platelet derived growth factor family and its significance in neovascular eye diseases].[Article in Chinese]

Bo Q, Zhang Y, Wu Y, Wang F.

Abstract: Platelet derived growth factor (PDGF) is a family of peliotropic growth factors that regulate cell proliferation and differentiation in an autocrine or paracrine manner through receptor mediated signal transduction pathways. Recent studies have demonstrated that PDGF plays an important role in ocular neovascularization, and the application of PDGF has a broad prospect in treatment of ocular neovascularization. Here, we summarize the current understanding of structure, function and expression of PDGF in the eye; the effects of PDGF on the blood vessel forming cells, as well as the interaction between PDGF and other pro-angiogenic factors. In addition, the role of PDGF in neovascular eye diseases, including retinopathy of prematurity, diabetic retinopathy, age-related macular degeneration, corneal neovascularization, and neovascular glaucoma, is also discussed.

PMID: 25241980 [PubMed - in process]

Zhonghua Yan Ke Za Zhi. 2014 Jun;50(6):464-70.

[Pathogenesis of dry age-related macular degeneration: updates].[Article in Chinese]

Zhang GM, Chen Y.

Abstract: Dry age-related macular degeneration (AMD) is one of the major causes of blindness in the elderly population and it is the consequence of interactions of multiple factors. Although the pathogenesis of dry AMD hasn't been fully elucidated, much progress has been made in the genetics, inflammation, oxidative stress, aging of retinal pigment epithelium (RPE) cells and metabolic changes. Identification of dry AMD related genes and predisposing loci facilitates the development of risk evaluation of dry AMD. Presence of β-amyloid in the drusen implies similarities between AMD and other degenerative diseases. Dysfunction of complement system, discovery of Nod-like receptor family containing pyrin domain 3 inflammasome and the concept of parainflammation reinforce the role of inflammation. Oxidative stress, mitochondrial dysfunction and decreased autophagy capacity, which are related to aging of RPE cells, demonstrate the critical role of it and metabolic changes in the pathogenesis.

PMID: 25241979 [PubMed - in process]

Mol Neurobiol. 2014 Sep 19. [Epub ahead of print]

Is There a Molecular Logic That Sustains Neuronal Functional Integrity and Survival? Lipid Signaling Is Necessary for Neuroprotective Neuronal Transcriptional Programs.

Bazan NG.

Abstract: A challenge to civilization is the growing incidence in the loss of sight and cognition due to increased life expectancy. Therefore, we are confronted with a rise in the occurrence of photoreceptor- and neuronal-survival failure, as reflected mainly by age-related macular degeneration (AMD) and Alzheimer's disease (AD). Nervous system development is driven by neuronal apoptotic cell death, and thereafter, for the entire lifespan of an organism, neurons are postmitotic cells. In neurodegenerative diseases, apoptosis and other forms of cells death lead to selective neuronal loss. Although age is the main risk factor, not everyone develops these diseases during aging. Despite decades of important findings about neuronal cell death, the specific mechanisms that regulate neuronal survival remain incompletely understood.

PMID: 25236258 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Sep 24. [Epub ahead of print]

7-ketocholesterol accumulates in ocular tissues as a consequence of aging and is present in high levels in drusen.

Rodriguez IR, Clark ME, Lee JW, Curcio CA.

PMID: 25261634 [PubMed - as supplied by publisher]

Epidemiology

Br J Ophthalmol. 2014 Sep 23. [Epub ahead of print]

Severity of coronary artery disease is independently associated with the frequency of early age-related macular degeneration.

Wang SB, Mitchell P, Chiha J, Liew G, Plant AJ, Thiagalingam A, Burlutsky G, Gopinath B.

BACKGROUND/AIMS: To describe the prevalence of early, late and any age-related macular degeneration (AMD) in a clinical cohort (Australian Heart Eye Study, AHES) and to determine whether associations exist between extent and severity of coronary artery disease (CAD) and AMD, independent of traditional cardiovascular risk factors.

METHODS: The AHES is an observational study that surveyed 1680 participants between 2009 and 2012 who presented to a tertiary referral hospital for the evaluation of potential CAD by coronary angiography. Severity and extent of CAD was assessed using three scoring systems: (1) segment/vessel scores, (2) Gensini and (3) extent scores.

RESULTS: Prevalence of early and late AMD was 5.8% (n=86) and 1.4% (n=21), respectively. After multivariable adjustment, patients with stenosis >50% in any coronary artery segment (vessel score) had approximately twofold higher odds of early AMD, OR 1.95 (95% CI 1.07 to 3.57). Patients with obstructive coronary stenosis in all three main coronary arteries (segment score) had greater than twofold higher likelihood of early AMD, OR 2.67 (95% CI 1.24 to 5.78). Participants in the highest versus lowest tertile of Gensini scores were also twice as likely to have early AMD, multivariable-adjusted OR 2.27 (95% CI 1.12 to 4.58). Extent scores were not associated with AMD. There was no significant association between CAD and late AMD.

CONCLUSIONS: Severity of coronary stenosis and the presence of stenotic lesions were independently associated with early AMD. These findings could have potential clinical significance as they suggest that individuals with evidence of CAD may be screened for early AMD.

PMID: 25249614 [PubMed - as supplied by publisher]

J Pak Med Assoc. 2014 Jun;64(6):664-9.

Assessment of serum lipids in patients with age related macular degeneration from Pakistan.

Ambreen F, Khan WA, Qureshi N, Qureshi IZ.

OBJECTIVE: To determine serum lipids in patients with age related macular degeneration from Pakistani population.

METHODS: The study was a cross sectional, randomized and case-control. Selected subjects ages were > or = 50 years and were normotensive, non-diabetic with no family history of any such disease and no complication of posterior ocular chamber other than age related macular degeneration (AMD). Controls were age matched healthy individuals with no symptoms of AMD. Diagnosis of AMD was done through conventional diagnostic techniques by professional ophthalmologists. Serum samples were analyzed for total cholesterol, triglycerides, LDL and HDL using commercially available kits. Data were compared with Student's t-test. Pearson correlation was calculated for relationship between different parameters. $P < 0.05$ was considered significant.

RESULTS: Compared to controls, AMD patients had significantly greater total cholesterol concentration ($p < 0.041$), and power HDL/LDL ratio ($p < 0.038$), while serum triglycerides, HDL and LDL were non-significantly different from control subjects. Total cholesterol in AMD patients was significantly correlated with TG, LDL and HDL ($p < 0.0001$).

CONCLUSION: The study indicates that high cholesterol might be a predictor of AMD and can be a diagnostic parameter.

PMID: 25252486 [PubMed - in process]

PLoS One. 2014 Sep 19;9(9):e108196. eCollection 2014.

Diabetes Mellitus and Risk of Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis.

Chen X, Rong SS, Xu Q, Tang FY, Liu Y, Gu H, Tam PO, Chen LJ, Brelén ME, Pang CP, Zhao C.

Abstract: Age-related macular degeneration (AMD) is a major cause of severe vision loss in elderly people. Diabetes mellitus is a common endocrine disorder with serious consequences, and diabetic retinopathy (DR) is the main ophthalmic complication. DR and AMD are different diseases and we seek to explore the relationship between diabetes and AMD. MEDLINE, EMBASE, and the Cochrane Library were searched for potentially eligible studies. Studies based on longitudinal cohort, cross-sectional, and case-control associations, reporting evaluation data of diabetes as an independent factor for AMD were included. Reports of relative risks (RRs), hazard ratios (HRs), odds ratio (ORs), or evaluation data of diabetes as an independent factor for AMD were included. Review Manager and STATA were used for the meta-analysis. Twenty four articles involving 27 study populations were included for meta-analysis. In 7 cohort studies, diabetes was shown to be a risk factor for AMD (OR, 1.05; 95% CI, 1.00-1.14). Results of 9 cross-sectional studies revealed consistent association of diabetes with AMD (OR, 1.21; 95% CI, 1.00-1.45), especially for late AMD (OR, 1.48; 95% CI, 1.44-1.51). Similar association was also detected for AMD (OR, 1.29; 95% CI, 1.13-1.49) and late AMD (OR, 1.16; 95% CI, 1.11-1.21) in 11 case-control studies. The pooled ORs for risk

of neovascular AMD (nAMD) were 1.10 (95% CI, 0.96-1.26), 1.48 (95% CI, 1.44-1.51), and 1.15 (95% CI, 1.11-1.21) from cohort, cross-sectional and case-control studies, respectively. No obvious divergence existed among different ethnic groups. Therefore, we find diabetes a risk factor for AMD, stronger for late AMD than earlier stages. However, most of the included studies only adjusted for age and sex; we thus cannot rule out confounding as a potential explanation for the association. More well-designed prospective cohort studies are still warranted to further examine the association.

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Genetics

Eye (Lond). 2014 Sep 19. [Epub ahead of print]

The role of epigenetics in age-related macular degeneration.

Gemenetzi M, Lotery AJ.

Abstract: It is becoming increasingly evident that epigenetic mechanisms influence gene expression and can explain how interactions between genetics and the environment result in particular phenotypes during development. The extent to which this epigenetic effect contributes to phenotype heritability in age-related macular degeneration (AMD) is currently ill defined. However, emerging evidence suggests that epigenetic changes are relevant to AMD and as such provide an exciting new avenue of research for AMD. This review addresses information on the impact of posttranslational modification of the genome on the pathogenesis of AMD, such as DNA methylation changes affecting antioxidant gene expression, hypoxia-regulated alterations in chromatin structure, and histone acetylation status in relation to angiogenesis and inflammation. It also contains information on the role of non-coding RNA-mediated gene regulation in AMD at a posttranscriptional (before translation) level. Our aim was to review the epigenetic mechanisms that cause heritable changes in gene activity without changing the DNA sequence. We also describe some long-term alterations in the transcriptional potential of a cell, which are not necessarily heritable but remains to be defined in the future. Increasing understanding of the significance of common and rare genetic variants and their relationship to epigenetics and environmental influences may help in establishing methods to assess the risk of AMD. This in turn may allow new therapeutic interventions for the leading cause of central vision impairment in patients over the age of 50 years in developed countries.Search strategyWe searched the MEDLINE/PubMed database following MeSH suggestions for articles including the terms: 'ocular epigenetic mechanisms', 'human disease epigenetics', and 'age-related macular degeneration genetics'. The headline used to locate related articles in PubMed was 'epigenetics in ocular disease', and to restrict search, we used the headlines 'DNA methylation in age related macular degeneration', 'altered gene expression in AMD pathogenesis'. A manual search was also based on references from these articles as well as review articles.

PMID: 25233816 [PubMed - as supplied by publisher]

Diet & lifestyle

Case Rep Med. 2014;2014:754147. Epub 2014 Aug 28.

AREDS Formula, Warfarin, and Bleeding: A Case Report from the Michigan Anticoagulation Quality Improvement Initiative.

Puroll E, Heidt ST, Haymart B, Froehlich JB, Kline-Rogers E, Barnes GD.

Importance: The anticoagulant warfarin has been shown to interact with other medications, vitamin K containing foods, and over-the-counter products. These interactions may inhibit or potentiate the effect of

warfarin, resulting in serious clotting or bleeding events.

Observations: We report the case of an 84-year-old woman with atrial fibrillation, prescribed warfarin in May 2010 for stroke prevention. Her international normalized ratio (INR) was stable until April 2013, when she was prescribed AREDS (Age Related Eye Disease Study) formula pills, an eye vitamin compound, to slow the progression of age-related macular degeneration. This change was not reported to the Anticoagulation Service. Eighteen days later, she presented to the ED with groin and back pain and an INR of 10.4. An abdominal CT revealed a retroperitoneal hemorrhage with extension in multiple muscles. Both warfarin and AREDS were discontinued and the patient was discharged to subacute rehabilitation. This case was reviewed by the Anticoagulation Service and actions were taken to prevent similar adverse events.

Conclusions: This report provides an example of the potential danger of supplement use, in this case, AREDS formula, in patients prescribed warfarin, and the importance of communicating medication changes to the providers responsible for warfarin management.

PMID: 25250052 [PubMed] PMCID: PMC4163395

J Trace Elem Med Biol. 2014 Sep 16. [Epub ahead of print]

Impact of the discovery of human zinc deficiency on health.

Prasad AS.

Abstract: The essentiality of zinc in humans was established in 1963. During the past 50y, tremendous advances in both clinical and basic sciences of zinc metabolism in humans have been observed. Growth retardation; cell-mediated immune dysfunction, and cognitive impairment are major clinical effects in human. At present we know of >300 enzymes and >1000 transcription factors that require zinc for their activities. Zinc is a second messenger of immune cells, and intracellular free zinc in these cells participate in signaling events. Zinc has been very successfully used as a therapeutic modality for the management of acute diarrhea in children, Wilson's disease, the common cold and for the prevention of blindness in patients with age-related dry type of macular degeneration. Zinc not only modulates cell-mediated immunity but is also an antioxidant and anti-inflammatory agent. Zinc supplementation in the elderly results in decreased incidence of infections, decreased oxidative stress and decreased generation of inflammatory cytokines.

PMID: 25260885 [PubMed - as supplied by publisher]