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MD Research News

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Drug treatment

Ophthalmology. 2014 Feb 8. pii: S0161-6420(13)01250-5. doi: 10.1016/j.ophtha.2013.12.032. [Epub ahead of print]

The Impact of Anti-Vascular Endothelial Growth Factor Treatment on Quality of Life in Neovascular Age-related Macular Degeneration.

Finger RP, Guymer RH, Gillies MC, Keeffe JE.

PURPOSE: To assess the impact of anti-vascular endothelial growth factor (VEGF) treatment in routine medical practice on vision-related quality of life (VRQoL) in neovascular age-related macular degeneration (AMD).

DESIGN: Prospective case series.

PARTICIPANTS: A total of 169 patients with neovascular AMD undergoing anti-VEGF treatment.

METHODS: The VRQoL interviews at baseline (n = 169), 6 months (n = 138), and 12 months (n = 120), routine anti-VEGF treatment with up to monthly follow-ups, and re-treatment as indicated. The Impact of Vision Impairment (IVI) questionnaire was subjected to Rasch analysis to assess its measurement performance and generate interval-level estimates of VRQoL at all time points, anchoring the instrument to its baseline measurement characteristics. Factors associated with a change in reported VRQoL were assessed using generalized linear regression models.

MAIN OUTCOME MEASURES: The VRQoL as measured by the IVI using its 3 subscales: Accessing Information, Mobility, and Emotional Well-being.

FINDINGS: The mean age was 70 years (±6 years standard deviation [SD]); 56% were female. Visual acuity (VA) improved by a mean of 8 letters (±17 SD), and mean retinal thickness decreased by 87 (±89.7) μm with an average of 6.5 (±2.6) injections over 12 months. Those who lost >2 lines (n = 13, 11%) reported worse VRQoL at 12 months on the Accessing Information and Mobility subscales (P = 0.007 and P = 0.050, respectively). Conversely, those who gained >2 lines (n = 29, 24%) reported better VRQoL on the Accessing Information and Emotional Well-being subscales (P = 0.009 and P = 0.008, respectively). Patients who did not experience a change in VA reported no change in their VRQoL. In multivariate analyses, only a change in VA but not whether the better or worse eye was treated predicted a change in VRQoL on the Accessing Information (P = 0.004) and the Emotional Well-being (P = 0.008) subscales.

CONCLUSIONS: We confirmed that anti-VEGF treatment for neovascular AMD improves patients' VRQoL in those who gain vision and maintains VRQoL in those who maintain VA in their treated eye, irrespective of whether the worse or better eye is treated. Against this background, the best possible outcomes should be

aimed for even if the worse eye is treated because a loss of VA in the worse eye will adversely affect patients' VRQoL.

PMID: 24518613 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2014 Feb 11. doi: 10.1136/bjophthalmol-2013-304736. [Epub ahead of print]

Aflibercept treatment for patients with exudative age-related macular degeneration who were incomplete responders to multiple ranibizumab injections (TURF trial).

Wykoff CC, Brown DM, Maldonado ME, Croft DE.

AIM: To determine the efficacy of 2.0 mg aflibercept in the management of patients with recalcitrant exudative age-related macular degeneration (AMD).

METHODS: In this prospective, open-label, single-arm clinical trial, patients were seen monthly and given mandatory 2.0 mg aflibercept at baseline, months 1, 2 and 4. Pro re nata (PRN) retreatment at months 3 and 5 was performed upon evidence of disease on spectral domain-optical coherence tomography (SD-OCT). End point at month 6: mean change in Early Treatment Diabetic Retinopathy Study best corrected visual acuity (ETDRS BCVA) and central subfield thickness (CST), mean number of aflibercept injections, percentage of PRN injections required, patients with no fluid on SD-OCT and patients losing >15 letters.

RESULTS: At baseline, 46 patients with a mean of 42 prior antivascular endothelial growth factor-A (anti-VEGF) intravitreal treatments had a mean of 74.2 letters (Snellen equivalent 20/32) and mean CST of 347 µm. ETDRS letters remained stable throughout the trial; at month 6, mean BCVA change was +0.2 letters (range -10 to +13, p=0.71). Anatomically, mean CST improved significantly from baseline at each study visit including -23.6 µm at month 1 and -27.3 µm at month 6 (p=0.018). Seventy-one of 90 (79%) possible PRN injections were required and a mean of 5.6 aflibercept injections out of the maximum six were administered. Ten of 45 (22%) patients had no retinal fluid on SD-OCT at month 6. No patient lost >15 letters.

CONCLUSIONS: Aflibercept 2.0 mg treatment maintained mean visual acuity improvements previously achieved with high-dose 2.0-mg ranibizumab injections in recalcitrant wet AMD patients. Aflibercept 2.0 mg treatment led to significant anatomic improvement and was required monthly in most patients.

PMID: 24518078 [PubMed - as supplied by publisher]

J Med Case Rep. 2014 Feb 12;8(1):48. [Epub ahead of print]

Rupture of abdominal aortic aneurysm after intravitreal bevacizumab injection: a case report.

Baek SU, Kwon SI.

INTRODUCTION: We describe the case of a man who died of an abdominal aortic aneurysm rupture after an intravitreal injection of bevacizumab for neovascular age-related macular degeneration.

CASE PRESENTATION: A 74-year-old Korean man presented with visual disturbance in his right eye. He had previously been diagnosed with diabetes and hypertension, which were controlled with oral medications. We diagnosed him with neovascular age-related macular degeneration and he was treated by intravitreal injection of bevacizumab three times per month. Four days after his third intravitreal bevacizumab injection, he died of an abdominal aortic aneurysm rupture and uncontrolled bleeding.

CONCLUSION: Abdominal aortic aneurysm rupture is highly lethal and there is a possible correlation with intravitreal injection of bevacizumab. Thus, we need to consider the risks of intravitreal bevacizumab injections for patients with abdominal aortic aneurysms.

PMID: 24520842 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Feb 13. [Epub ahead of print]

Predictive value of VEGF A and VEGFR2 polymorphisms in the response to intravitreal ranibizumab treatment for wet AMD.

Cruz-Gonzalez F, Cabrillo-Estévez L, López-Valverde G, Cieza-Borrella C, Hernández-Galilea E, González -Sarmiento R.

BACKGROUND: To determine whether gene polymorphisms of the vascular endothelial growth factor A (VEGF A) and its receptor (VEGFR) influence the response to a variable-dosing treatment regimen with ranibizumab for age-related macular degeneration.

METHODS: This prospective cohort study included 94 patients (94 eyes) with exudative age-related macular degeneration (AMD) treated with ranibizumab. Patients underwent a 1-year treatment as in the Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (SUSTAIN). Injections were administered monthly during 3 months to all the patients diagnosed of neovascular AMD; reinjections were made when a patient lost 5 letters on the Early Treatment Diabetic Retinopathy Study chart or gained 100 μm in central subfield retinal thickness measured by OCT. Genotypes (VEGF A (rs 699947, rs833061) and VEGFR (rs 2071559)) were analyzed using TaqMan probes. Best-corrected visual acuity (BCVA), subjective improvement, and macular thickness measured with OCT values were compared with VEGF A and VEGFR genotypes. Multiple regression analysis was used to assess the statistical significance.

RESULTS: We found statistically significant differences in allelic distribution of VEGF A rs833061 polymorphism in relation with the response to intravitreal ranibizumab regarding to visual acuity improvement [p = 0,.34; OR: 1.619 (1.098-2.386)]. Patients carrying "protector" genotype CC had higher probability of best corrected visual acuity improvement. When we analyzed VEGF A rs699947 polymorphism we found that patients expressing AA genotype had a higher chance of increasing their best corrected visual acuity [p:0,022; OR 1,532 (1,015-2,313)]. We did not find statistically significant differences reagarding VEGFR rs2071559 polymorphism and treatment response.

CONCLUSIONS: Polymorphisms of VEGF A seem to influence the different response to antiangiogenic treatment in patients with AMD in our population, although further investigation is needed to know the mechanisms of this relationship.

PMID: 24522370 [PubMed - as supplied by publisher]

BMJ Open. 2014 Feb 10;4(2):e004120. doi: 10.1136/bmjopen-2013-004120.

Treatments for macular oedema following central retinal vein occlusion: systematic review.

Ford JA, Clar C, Lois N, Barton S, Thomas S, Court R, Shyangdan D, Waugh N.

OBJECTIVES: To review systematically the randomised controlled trial (RCT) evidence for treatment of macular oedema due to central retinal vein occlusion (CRVO).

DATA SOURCES: MEDLINE, EMBASE, CDSR, DARE, HTA, NHSEED, CENTRAL and meeting abstracts (January 2005 to March 2013).

STUDY ELIGIBILITY CRITERIA, PARTICIPANTS AND INTERVENTIONS: RCTs with at least 12 months of follow-up assessing pharmacological treatments for CRVO were included with no language restrictions.

STUDY APPRAISAL AND SYNTHESIS METHODS: 2 authors screened titles and abstracts and conducted data extracted and Cochrane risk of bias assessment. Meta-analysis was not possible due to lack of comparable studies.

RESULTS: 8 studies (35 articles, 1714 eyes) were included, assessing aflibercept (n=2), triamcinolone

(n=2), bevacizumab (n=1), pegaptanib (n=1), dexamethasone (n=1) and ranibizumab (n=1). In general, bevacizumab, ranibizumab, aflibercept and triamcinolone resulted in clinically significant increases in the proportion of participants with an improvement in visual acuity of ≥15 letters, with 40-60% gaining ≥15 letters on active drugs, compared to 12-28% with sham. Results for pegaptanib and dexamethasone were mixed. Steroids were associated with cataract formation and increased intraocular pressure. No overall increase in adverse events was found with bevacizumab, ranibizumab, aflibercept or pegaptanib compared with control. Quality of life was poorly reported. All studies had a low or unclear risk of bias.

LIMITATIONS: All studies evaluated a relatively short primary follow-up (1 year or less). Most had an unmasked extension phase. There was no head-to-head evidence. The majority of participants included had non-ischaemic CRVO.

CONCLUSIONS AND IMPLICATIONS OF KEY FINDINGS: Bevacizumab, ranibizumab, aflibercept and triamcinolone appear to be effective in treating macular oedema secondary to CRVO. Long-term data on effectiveness and safety are needed. Head-to-head trials and research to identify 'responders' is needed to help clinicians make the right choices for their patients. Research aimed to improve sight in people with ischaemic CRVO is required.

PMID: 24513867 [PubMed]

ScientificWorldJournal. 2014 Jan 8;2014:989501. eCollection 2014.

Intravitreal Steroids for the Treatment of Retinal Diseases.

Sarao V, Veritti D, Boscia F, Lanzetta P.

Abstract: Diabetic macular edema (DME), pseudophakic cystoid macular edema (CME), age-related macular degeneration (AMD), retinal vascular occlusion (RVO), and uveitis are ocular conditions related to severe visual impairment worldwide. Corticosteroids have been widely used in the treatment of these retinal diseases, due to their well-known antiangiogenic, antiedematous, and anti-inflammatory properties. Intravitreal steroids have emerged as novel and essential tools in the ophthalmologist's armamentarium, allowing for maximization of drug efficacy and limited risk of systemic side effects. Recent advances in ocular drug delivery methods led to the development of intraocular implants, which help to provide prolonged treatment with controlled drug release. Moreover, they may add some potential advantages over traditional intraocular injections by delivering certain rates of drug directly to the site of action, amplifying the drug's half-life, contributing in the minimization of peak plasma levels of the drug, and avoiding the side effects associated with repeated intravitreal injections. The purpose of this review is to provide an update on the use of intravitreal steroids as a treatment option for a variety of retinal diseases and to review the current literature considering their properties, safety, and adverse events.

PMID: 24526927 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2014 Feb 13:1-4. doi: 10.3928/23258160-20140205-02. [Epub ahead of print]

Neovascular AMD With Marked Macular Fluid and Rapid Response to Anti-VEGF Therapy.

Wood E, Chang JS, Flynn HW Jr, Kitchens JW.

Abstract: The authors describe the clinical management and spectral-domain optical coherence tomography (SD-OCT) findings of three unusual cases of neovascular age-related macular degeneration (AMD). Each patient presented with decreased vision and a diagnosis of neovascular AMD, with SD-OCT findings of marked macular fluid. Macular fluid was noted to be subretinal fluid, pigment epithelial detachment, or both. In each case, visual acuity improved and the fluid resolved rapidly with monthly anti-

vascular endothelial growth factor therapy.

PMID: 24512809 [PubMed - as supplied by publisher]

BMJ Case Rep. 2014 Feb 13;2014. pii: bcr2013202075. doi: 10.1136/bcr-2013-202075.

Burkholderia cepacia endophthalmitis, in a penicillin allergic patient, following a ranibizumab injection.

Saffra N, Moriarty E.

Abstract: Burkholderia cepacia, a Gram-negative bacterium commonly found in water and soil, is a rare cause of endophthalmitis. The authors report a case of a penicillin-allergic patient who presented 15 days after an uneventful injection of ranibizumab for neovascular age-related macular degeneration with culture-positive B cepacia endophthalmitis. Initial antibiotic therapy using non-penicillin-based medications was not successful in eradicating the bacteria. Subsequent treatment with a third-generation cephalosporin resulted in complete resolution of the infection. B cepacia should be included among the bacterial species that may cause endophthalmitis after intravitreal injections.

PMID: 24526197 [PubMed - in process]

Other treatment & diagnosis

Ophthalmology. 2014 Feb 8. pii: S0161-6420(13)01255-4. doi: 10.1016/j.ophtha.2013.12.034. [Epub ahead of print]

Reticular Pseudodrusen: A Risk Factor for Geographic Atrophy in Fellow Eyes of Individuals with Unilateral Choroidal Neovascularization.

Finger RP, Wu Z, Luu CD, Kearney F, Ayton LN, Lucci LM, Hubbard WC, Hageman JL, Hageman GS, Guymer RH.

PURPOSE: To determine whether reticular pseudodrusen (RPD) confer an increased risk of progression to late-stage age-related macular degeneration (AMD) in fellow eyes of those recently diagnosed with unilateral choroidal neovascularization (CNV).

DESIGN: Retrospective study.

PARTICIPANTS: Two hundred consecutive participants with CNV secondary to AMD in 1 eye and no signs of late-stage AMD in the fellow eye.

METHODS: Clinical examination and comprehensive retinal imaging, including spectral-domain optical coherence tomography, near-infrared reflectance (NIR), and color fundus photography, at baseline and every follow-up visit.

MAIN OUTCOME MEASURES: Incidence of geographic atrophy (GA) and CNV in the fellow eye.

RESULTS: Mean age ± standard deviation was 77±7 years, and 61% of the cohort were female. Fifty-eight percent (n = 116) had RPD, 68% had drusen of 125 μm or more, 36% had pigmentary changes, 10% had both drusen of 125 μm or more and pigmentary changes, and 17% had only RPD in their fellow eyes. After a mean follow-up of 2.3 years, CNV developed in 36% of patients and GA developed in 14% of patients. Those with RPD demonstrated late-stage AMD (61% vs. 33.4%; P <0.001) and GA (22.4% with RPD vs. 2.4% without RPD; P <0.001) more often. The presence of reticular pseudodrusen was an independent risk factor for the development of GA (hazard ratio [HR], 4.93; P = 0.042), but not for CNV (HR, 1.19; P = 0.500), at least within the follow-up of this study. Both drusen of 125 μm or more and pigmentary changes

at baseline were significant risk factors for the development of CNV and GA (HR, 1.96-11.73; P ≤0.020).

CONCLUSIONS: Reticular pseudodrusen seem to confer an increased risk of progression to GA, in addition to drusen and pigmentary changes. The presence of RPD needs to be taken into account when discussing a patient's prognosis and planning management.

PMID: 24518615 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Feb 11. pii: iovs.13-13754v1. doi: 10.1167/iovs.13-13754. [Epub ahead of print]

Structural and Biochemical Analyses of Choroidal Thickness in Human Donor Eyes.

Sohn EH, Khanna A, Tucker BA, Abràmoff MD, Stone EM, Mullins RF.

Purpose: The choroid plays a vital role in the health of the outer retina. While measurements of choroid using optical coherence tomography show altered thickness in aging and macular disease, detailed histopathologic and proteomic analyses are lacking. In this study we sought to evaluate biochemical differences in human donor eyes between very thin and thick choroids.

Methods: One hundred forty-one eyes from 104 donors (mean age+standard deviation, 81.5+2.2) were studied. Macular sections were collected and the distance between Bruch's membrane and the inner surface of the sclera was measured in control, early/dry age-related macular degeneration (AMD), neovascular AMD, and geographic atrophy eyes. Proteins from the RPE-choroid of eyes with thick and thin choroids were analyzed using two dimensional electrophoresis and/or mass spectrometry. Two proteins with altered abundance were confirmed using Western blot analysis.

Results: Donor eyes showed a normal distribution of thicknesses. Eyes with geographic atrophy had significantly thinner choroids than age-matched controls or early AMD eyes. Proteomic analysis showed higher levels of the serine protease SERPINA3 in thick choroids and increased levels of tissue inhibitor of metalloproteinases-3 (TIMP3) in thin choroids.

Conclusions: Consistent with clinical imaging observations, geographic atrophy was associated with choroidal thinning. Biochemical data suggest an alteration in the balance between proteases and protease inhibitors in eyes that lie at the extremes of choroidal thickness. An improved understanding of the basic mechanisms associated with choroidal thinning may guide the development of new therapies for AMD.

PMID: 24519422 [PubMed - as supplied by publisher]

Stem Cell Reports. 2014 Jan 23;2(2):205-18. doi: 10.1016/j.stemcr.2013.12.007. eCollection 2014.

Characterization of human induced pluripotent stem cell-derived retinal pigment epithelium cell sheets aiming for clinical application.

Kamao H, Mandai M, Okamoto S, Sakai N, Suga A, Sugita S, Kiryu J, Takahashi M.

Abstract: Age-related macular degeneration (AMD) causes severe visual impairment due in part to age-dependent impairment of retinal pigment epithelium (RPE). It has been suggested that autologous human induced pluripotent stem cells (hiPSCs) may represent a useful cell source for the generation of graft RPE. We generated hiPSC-derived RPE (hiPSC-RPE) cell sheets optimized to meet clinical use requirements, including quality, quantity, consistency, and safety. These cell sheets are generated as a monolayer of cells without any artificial scaffolds, express typical RPE markers, form tight junctions that exhibit polarized secretion of growth factors, and show phagocytotic ability and gene-expression patterns similar to those of native RPE. Additionally, upon transplantation, autologous nonhuman primate iPSC-RPE cell sheets showed no immune rejection or tumor formation. These results suggest that autologous hiPSC-RPE cell

sheets may serve as a useful form of graft for use in tissue replacement therapy for AMD.

PMID: 24527394 [PubMed]

Stem Cell Reports. 2014 Jan 2;2(1):64-77. doi: 10.1016/j.stemcr.2013.11.005. eCollection 2014.

Human RPE Stem Cells Grown into Polarized RPE Monolayers on a Polyester Matrix Are Maintained after Grafting into Rabbit Subretinal Space.

Stanzel BV, Liu Z, Somboonthanakij S, Wongsawad W, Brinken R, Eter N, Corneo B, Holz FG, Temple S, Stern JH, Blenkinsop TA.

Abstract: Transplantation of the retinal pigment epithelium (RPE) is being developed as a cell-replacement therapy for age-related macular degeneration. Human embryonic stem cell (hESC) and induced pluripotent stem cell (iPSC)-derived RPE are currently translating toward clinic. We introduce the adult human RPE stem cell (hRPESC) as an alternative RPE source. Polarized monolayers of adult hRPESC-derived RPE grown on polyester (PET) membranes had near-native characteristics. Trephined pieces of RPE monolayers on PET were transplanted subretinally in the rabbit, a large-eyed animal model. After 4 days, retinal edema was observed above the implant, detected by spectral domain optical coherence tomography (SD-OCT) and fundoscopy. At 1 week, retinal atrophy overlying the fetal or adult transplant was observed, remaining stable thereafter. Histology obtained 4 weeks after implantation confirmed a continuous polarized human RPE monolayer on PET. Taken together, the xeno-RPE survived with retained characteristics in the subretinal space. These experiments support that adult hRPESC-derived RPE are a potential source for transplantation therapies.

PMID: 24511471 [PubMed] PMCID: PMC3916756

Med Phys. 2014 Feb;41(2):021729. doi: 10.1118/1.4863482.

ITAR: A modified TAR method to determine depth dose distribution for an ophthalmic device that performs kilovoltage x-ray pencil-beam stereotaxy.

Hanlon J, Chell E, Firpo M, Koruga I.

PURPOSE: New technology has been developed to treat age-related macular degeneration (AMD) using 100 kVp pencil-beams that enter the patient through the radio-resistant sclera with a depth of interest between 1.6 and 2.6 cm. Measurement of reference and relative dose in a kilovoltage x-ray beam with a 0.42 cm diameter field size and a 15 cm source to axis distance (SAD) is a challenge that is not fully addressed in current guidelines to medical physicists. AAPM's TG-61 gives dosimetry recommendations for low and medium energy x-rays, but not all of them are feasible to follow for this modality.

METHODS: An investigation was conducted to select appropriate equipment for the application. PTW's Type 34013 Soft X-Ray Chamber (Freiburg, Germany) and CIRS's Plastic Water LR (Norfolk, VA) were found to be the best available options. Attenuation curves were measured with minimal scatter contribution and thus called Low Scatter Tissue Air Ratio (LSTAR). A scatter conversion coefficient (Cscat) was derived through Monte Carlo radiation transport simulation using MCNPX (LANL, Los Alamos, NM) to quantify the difference between a traditional TAR curve and the LSTAR curve. A material conversion coefficient (Cmat) was determined through experimentation to evaluate the difference in attenuation properties between water and Plastic Water LR. Validity of performing direct dosimetry measurements with a source to detector distance other than the treatment distance, and therefore a different field size due to a fixed collimator, was explored. A method-Integrated Tissue Air Ratio (ITAR)-has been developed that isolates each of the three main radiological effects (distance from source, attenuation, and scatter) during measurement, and integrates them to determine the dose rate to the macula during treatment.

RESULTS: LSTAR curves were determined to be field size independent within the range explored, indicating that direct dosimetry measurements may be performed with a source to detector distance of 20 cm even though the SAD is 15 cm during treatment. Cscat varied from 1.102 to 1.106 within the range of depths of interest. The experimental variance among repeated measurements of Cmat was larger than depth dependence, so Cmat was estimated as1.019 for all depths of interest.

CONCLUSIONS: Equipment selection, measurement techniques, and formalism for the determination of dose rate to the macula during stereotaxy for AMD have been determined and are strongly recommended by the authors of this paper to be used by clinical medical physicists.

PMID: 24506620 [PubMed - in process]

Pathogenesis

Exp Eye Res. 2013 Oct 26. pii: S0014-4835(13)00302-3. doi: 10.1016/j.exer.2013.10.014. [Epub ahead of print]

Autophagy of iron-binding proteins may contribute to the oxidative stress resistance of ARPE-19 cells.

Karlsson M, Frennesson C, Gustafsson T, Brunk UT, Nilsson SE, Kurz T.

Abstract: The objective of this study was to elucidate possible reasons for the remarkable resistance of human retinal pigment epithelial (RPE) cells to oxidative stress. Much oxidative damage is due to hydrogen peroxide meeting redox-active iron in the acidic and reducing lysosomal environment, resulting in the production of toxic hydroxyl radicals that may oxidize intralysosomal content, leading to lipofuscin (LF) formation or, if more extensive, to permeabilization of lysosomal membranes. Formation of LF is a risk factor for age-related macular degeneration (AMD) and known to jeopardize normal autophagic rejuvenation of vital cellular biomolecules. Lysosomal membrane permeabilization causes release of lysosomal content (redox-active iron, lytic enzymes), which may then cause cell death. Total cellular and lysosomal low-mass iron of cultured, immortalized human RPE (ARPE-19) cells was compared to that of another professional scavenger cell line, J774, using atomic absorption spectroscopy and the cytochemical sulfide-silver method (SSM). It was found that both cell lines contained comparable levels of total as well as intralysosomal iron, suggesting that the latter is mainly kept in a non-redox-active state in ARPE-19 cells. Basal levels and capacity for upregulation of the iron-binding proteins ferritin, metallothionein and heat shock protein 70 were tested in both cell lines using immunoblotting. Compared to J774 cells, ARPE-19 cells were found to contain very high basal levels of all these proteins, which could be even further upregulated following appropriate stimulation. These findings suggest that a high basal expression of iron-binding stress proteins, which during their normal autophagic turnover in lysosomes may temporarily bind iron prior to their degradation, could contribute to the unusual oxidative stress-resistance of ARPE-19 cells. A high steady state influx of such proteins into lysosomes would keep the level of lysosomal redox-active iron permanently low. This, in turn, should delay intralysosomal accumulation of LF in RPE cells, which is known to reduce autophagic turnover as well as uptake and degradation of worn out photoreceptor tips. This may explain why severe LF accumulation and AMD normally do not develop until fairly late in life, in spite of RPE cells being continuously exposed to high levels of oxygen and light, as well as large amounts of lipid-rich material.

PMID: 24512774 [PubMed - as supplied by publisher]

J Cell Physiol. 2014 Feb 10. doi: 10.1002/jcp.24575. [Epub ahead of print]

Interleukin-18 has Antipermeablity and Antiangiogenic Activities in the Eye; Reciprocal Suppression with VEGF.

Shen J, Choy DF, Yoshida T, Iwase T, Hafiz G, Xie B, Hackett SF, Arron JR, Campochiaro PA.

Abstract: Interleukin-18 (IL-18) is increased along with IL-1β by activation of the inflammasome and has been implicated in inflammatory and autoimmune diseases, but its role in the eye is uncertain. In patients with macular edema due to retinal vein occlusion, intraocular IL-18 levels increased significantly ($p < 0.001$) after treatment with ranibizumab particularly in patients with high baseline IL-18 which correlated with good visual outcome ($p < 0.05$). In mice with ischemic retinopathy, suppression of VEGF caused an increase in IL18 mRNA due to an increase in IL-18-positive myeloid cells. VEGF significantly and specifically inhibited IL-18 production by myeloid cells stimulated with lipopolysaccharide ($p < 0.001$). Intraocular injection of IL-18 reduced VEGF-induced leakage and neovascularization, and reversed VEGF-induced suppression of Claudin5 expression and Claudin 5 labeling of vascular tight junctions. Injection of IL-18 also increased expression of Thrombospondin 1 and reduced ischemia-induced retinal neovascularization relevant to diabetic retinopathy and subretinal neovascularization relevant to neovascular age-related macular degeneration. Thus, VEGF and IL-18 suppress each other's production and effects on the vasculature suggesting that IL-18 may provide benefit in multiple retinal/choroidal vascular diseases. J. Cell. Physiol. © 2014 Wiley Periodicals, Inc.

PMID: 24515951 [PubMed - as supplied by publisher]

J Biol Chem. 2014 Feb 11. [Epub ahead of print]

Cytochrome P450 2C Epoxygenases Mediate Photochemical Stress-induced Death of Photoreceptors.

Chang Q, Berdyshev E, Bogaard J, White JJ, Chen S, Shah R, Mu W, Grantner R, Bettis S, Grassi MA.

Abstract: Degenerative loss of photoreceptors occurs in inherited and age-related retinal degenerative diseases. Chemical screen facilitates development of new testing routes for neuroprotection and mechanistic investigation. Herein, we conducted a mouse-derived photoreceptor (661W cells)-based high throughput screen of the FDA-approved Prestwick drug library to identify putative cytoprotective compounds against light-induced, synthetic visual chromophore-precipitated cell death. Different classes of hit compounds were identified, some of which target to known genes or pathways pathologically associated with retinitis pigmentosa. Sulfaphenazole (SFZ), a selective inhibitor of human cytochrome P450 (CYP) 2C9 isozyme, was identified as a novel and leading cytoprotective compound. Expression of CYP2C proteins was induced by light. Gene-targeted knockdown of CYP2C55, the homologous gene of CYP2C9, demonstrated viability rescue to light-induced cell death while stable expression of functional CYP2C9-GFP fusion protein further exacerbated light-induced cell death. Mechanistically, SFZ inhibited light-induced necrosis and mitochondrial stress-initiated apoptosis. Light elicited calcium influx, which was mitigated by SFZ. Light provoked release of arachidonic acid (AA) from membrane phospholipids and production of non-epoxyeicosatrienoic acid (EET) metabolites. Administration of SFZ further stimulated the production of non-EET metabolites, suggesting a metabolic shift of AA under inhibition of the CYP2C pathway. Together, our findings indicate that CYP 2C genes play a direct causative role in photochemical stress-induced death of photoreceptors and suggest that the CYP monooxygenase system is a risk factor for retinal photo damage, especially in individuals with Stargardt disease or age-related macular degeneration that deposit condensation products of retinoids.

PMID: 24519941 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Feb 7. pii: S0014-4835(14)00006-2. doi: 10.1016/j.exer.2013.12.019. [Epub ahead of print]

N-Nitroso-N-methylurea-induced retinal degeneration in mice.

Chen YY, Liu SL, Hu DP, Xing YQ, Shen Y.

Abstract: Mouse retinal degeneration models have been investigated for many years in the hope of understanding the mechanism of photoreceptor cell death. N-Nitroso-N-methylurea (MNU) has been previously shown to induce outer retinal degeneration in mice. After MNU was intraperitoneally injected in C57/BL mice, we observed a gradual decrease in the outer nuclear layer (ONL) thickness associated with photoreceptor outer segment loss, bipolar cell dendritic retraction and reactive gliosis. Reactive gliosis was confirmed by increased GFAP protein levels. More serious damage to the central retina as opposed to the peripheral retina was found in the MNU-induced retinal degeneration model. Retinal ganglion cells (RGC) appear to be spared for at least two months after MNU treatment. Following retinal vessel labelling, we observed vascular complexes in the distal vessels, indicating retinal vessel damage. In the remnant retinal photoreceptor of the MNU-treated mouse, concentrated colouring nuclei were detected by electron microscopy, together with the loss of mitochondria and displaced remnant synaptic ribbons in the photoreceptor. We also observed decreased mitochondrial protein levels and increased amounts of nitrosylation/nitration in the photoreceptors. The mechanism of MNU-induced apoptosis may result from oxidative stress or the loss of retinal blood supply. MNU-induced mouse retinal degeneration in the outer retina is a useful animal model for photoreceptor degeneration diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP).

PMID: 24509257 [PubMed - as supplied by publisher]

Epidemiology

Invest Ophthalmol Vis Sci. 2014 Feb 7. pii: iovs.13-13206v1. doi: 10.1167/iovs.13-13206. [Epub ahead of print]

Association Between Aspirin Use and Age-Related Macular Degeneration;A Meta-Analysis.

Ye J, Xu Y, He J, Lou L.

Purpose: We conducted a meta-analysis of randomized controlled trials (RCTs) and observational studies to evaluate the association between aspirin use and age-related macular degeneration (AMD).

Methods: The pertinent studies were identified via literature search through four databases (Medline, Web of Science, Cochrane Library, Embase) and reference lists of retrieved studies. RCTs and cohort and case-control studies meeting the predefined criteria were included. We extracted relative risk (RR) or odds ratio (OR) or hazard ratio (HR) and 95% confidence interval (CI) from each study. Overall and study-specific risk estimates were pooled using fixed-effects and random-effects models, respectively. Subgroup analyses based on several stratified factors were also performed.

Results: In total, two RCTs, three cohort studies, and four case-control studies involving 177,683 subjects were included. The pooled effect of all nine studies showed no significant association between aspirin use and occurrence of AMD (RR, 1.00; 95% CI 0.96-1.04), and no significant association was observed in any specific study design (RR, 0.93; 95% CI 0.71-1.22 for RCT; RR, 1.02; 95% CI 0.87-1.20 for cohort study; RR, 1.00; 95% CI 0.96-1.04 for case-control study). However, subgroup analysis showed aspirin use to be significantly associated with an increased risk of neovascular AMD (RR, 1.59; 95% CI 1.09-2.31).

Conclusions: The pooled effects from current literatures suggest that aspirin use is not associated with AMD, but it increased the risk of the neovascular form of AMD.

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Aspirin use and early age-related macular degeneration: a meta-analysis.

Kahawita SK, Casson RJ.

OBJECTIVE: The aim of this review was to evaluate the evidence for an association between Aspirin use and early age-related macular degeneration (ARMD).

METHODS: A literature search was performed in 5 databases with no restrictions on language or date of publication. Four studies involving 10292 individuals examining the association between aspirin and ARMD met the inclusion criteria. Meta-analysis was carried out by Cochrane Collaboration Review Manager 5.2 software (Cochrane Collaboration, Copenhagen, Denmark).

RESULTS: The pooled odd ratios showed that Aspirin use was associated with early ARMD (pooled odds ratio 1.43, 95% CI 1.09-1.88).

CONCLUSIONS: There is a small but statistically significant association between Aspirin use and early ARMD, which may warrant further investigation.

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Br J Ophthalmol. 2014 Feb 11. doi: 10.1136/bjophthalmol-2013-304013. [Epub ahead of print]

Prevalence and causes of vision loss in Latin America and the Caribbean: 1990-2010.

Leasher JL, Lansingh V, Flaxman SR, Jonas JB, Keeffe J, Naidoo K, Pesudovs K, Price H, Silva JC, White RA, Wong TY, Resnikoff S, Taylor HR, Bourne RR; on behalf of the Vision Loss Expert Group of the Global Burden of Disease Study.

OBJECTIVE: To present regional estimates of the magnitude and temporal trends in the prevalence and causes of blindness and moderate/severe visual impairment (MSVI) in Latin America and the Caribbean (LAC).

METHODS: A systematic review of cross-sectional population-representative data from published literature and unpublished studies was accessed and extracted to model the estimated prevalence of vision loss by region, country and globally, and the attributable cause fraction by region.

RESULTS: In the LAC combined region, estimated all-age both-gender age-standardised prevalence of blindness halved from 0.8% (0.6 to 1.1) in 1990 to 0.4% (0.4 to 0.6) in 2010 and MSVI decreased from 4.3% (3.1 to 5.3) to 2.7% (2.2 to 3.4). In the Caribbean, estimated all-age both-gender age-standardised prevalence of blindness decreased from 0.6% (0.4 to 0.8) in 1990 to 0.5% (0.4 to 0.6) in 2010 and MSVI decreased from 3.3% (1.3 to 4.1) in 1990 to 2.9% (1.8 to 3.8). In the LAC regions combined, there was an estimated 2.3 million blind and 14.1 million with MSVI in 2010. In 2010, cataract continues to contribute the largest proportion of blindness, except in Southern Latin America where macular degeneration is most common. In 2010, uncorrected refractive error was the most common cause of MSVI.

CONCLUSIONS: While models suggest a decrease in age-standardised prevalence estimates, better data are needed to evaluate the disparities in the region. The increasing numbers of older people, coupled with the increase in vision loss associated with older age, will require further intervention to continue to reduce prevalence rates and to prevent a rise in absolute numbers of blind.

PMID: 24518073 [PubMed - as supplied by publisher]

Genetics

Medicina (Kaunas). 2013;49(8):386-91.

Stargardt disease caused by a rare combination of double homozygous mutations.

Serapinas D, Obrikytė V, Sakalauskas R.

Abstract: Stargardt disease is a juvenile macular degeneration most often inherited in an autosomal recessive pattern, characterized by decreased vision in the first 2 decades of life. This report presents a clinical case of Stargardt disease: a 10-year-old female patient complained of blurry vision, and in a 4-year period, her visual acuity was reduced from OD=0.3 and OS=0.3 to OD=0.08 and OS=0.1, respectively. A genetic analysis revealed a rare combination of 2 homozygous recessive mutations in the ABCA4 gene, which caused Stargardt disease. The presence of different genetic mechanisms leading to a severe disease phenotype can challenge molecular geneticists, ophthalmologists, and genetic counselors.

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Age (Dordr). 2014 Feb 14. [Epub ahead of print]

In-depth analyses unveil the association and possible functional involvement of novel RAD51B polymorphisms in age-related macular degeneration.

Chu XK, Meyerle CB, Liang X, Chew EY, Chan CC, Tuo J.

Abstract: The contribution of DNA damage to the pathogenesis of age-related macular degeneration (AMD) has been reported. Recently, a genomewide association study detected the association of a single-nucleotide polymorphism (SNP) in RAD51B (rs8017304 A>G) with AMD. RAD51B is involved in recombinational repair of DNA double-strand breaks. We analyzed RAD51B influence on AMD using two cohorts from Caucasian and Han Chinese populations. The Caucasian set replicated the rs8017304 A>G association and revealed two novel AMD-associated SNPs in RAD51B, rs17105278 T>C and rs4902566 C>T. Under the dominant model, these two SNPs exhibit highly significant disease risk. SNP-SNP interaction analysis on rs17105278 T>C and rs4902566 C>T homozygous demonstrated a synergistic effect on AMD risk, reaching an odds ratio multifold higher than well-established AMD susceptibility loci in genes such as CFH, HTRA1, and ARMS2. Functional study revealed lower RAD51B mRNA expression in cultured primary human fetal retinal pigment epithelium (hfRPE) carrying rs17105278 T>C variants than in hfRPE carrying rs17105278 wild type. We concluded that the risk of developing AMD exhibits dose dependency as well as an epistatic combined effect in rs17105278 T>C and rs4902566 C>T carriers and that the elevated risk for rs17105278 T>C carriers may be due to decreased transcription of RAD51B. This study further confirms the role of DNA damage/DNA repair in AMD pathogenesis.

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Complement C3, C2, and factor B gene polymorphisms and age-related macular degeneration in a Greek cohort study.

Havvas I, Marioli DI, Deli A, Zarkadis IK, Pharmakakis N.

Purpose: To elucidate whether polymorphisms of C2, C3, and CFB genes are major genetic determinants of age-related macular degeneration (AMD) in a Greek population.

Methods: This was a case-control association study comprising 120 Greek patients with early and late-stage AMD and 140 independent controls of Caucasian origin. All participants were genotyped for

rs547154, rs2230199, rs641153, and rs12614 polymorphisms by a combination of PCR and direct DNA sequencing assays.

Results: The frequency of the rs2230199 G allele (minor allele) was significantly higher in patients with AMD in comparison with controls (0.34 vs 0.22, p = 0.0031) and similar to the frequency of other reported populations. There was a significant difference in the frequencies of the rs2230199 genotypes among cases and controls (p = 0.0055). rs2230199 was found to be a significant predictor of advanced AMD status (odds ratio 6.41, confidence interval [CI] 2.72-15.09, p<0.0001; area under the curve 0.706, CI 0.61-0.78, p<0.0001]). For the other single nucleotide polymorphism (SNP) loci, the allele and genotype frequencies did not reach statistical significance. The minor allele frequencies in controls and cases were similar and still much lower than the frequencies reported in other populations.

Conclusions: The rs547154, rs641153, and rs12614 SNPs were not associated with AMD development in Greek patients. However, this finding should be viewed with caution as the particular polymorphisms presented with very low frequencies in the Greek population. Finally, the replication of the reported associations of C3 with AMD suggests that the presence of the C3 G allele could serve as a high-risk genetic marker for the development of AMD and the progression of the disease to the advanced clinical stage.

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PLoS One. 2014 Feb 10;9(2):e88324. doi: 10.1371/journal.pone.0088324. eCollection 2014.

Systematic Review and Meta-Analysis of the Association between Complement Factor H I62V Polymorphism and Risk of Polypoidal Choroidal Vasculopathy in Asian Populations.

Wang ZY, Zhao K, Zheng J, Rossmiller B, Ildefonso C, Biswal M, Zhao PQ.

PURPOSE:To investigate whether the polymorphism rs800292 (184G>A, I62V) in the complement factor H gene is associated with polypoidal choroidal vasculopathy (PCV) and the genetic difference between PCV and neovascular age-related macular degeneration (nAMD), in Asian populations.

METHODS:A comprehensive literature search was performed in PubMed, Medline, Web of Science, and reference lists. A system review and meta-analysis of the association between I62V and PCV and/or nAMD were performed from 8 studies involving 5,062 subjects. The following data from individual studies were extracted and analyzed: 1) comparison of I62V polymorphisms between PCV and controls; 2) comparison of I62V polymorphisms between PCV and nAMD. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using fixed-effects models. The Q-statistic test was used to assess heterogeneity, and Egger's test was used to evaluate publication bias. Sensitivity analysis and cumulative meta-analysis were also performed.

RESULTS:The I62V polymorphism showed a significant summary OR1 for genotype GA+GG versus homozygous genotype AA was 3.18 (95% CI, 2.51-4.04, P<0.00001), the OR2 of heterozygous genotype GA versus AA was 2.29 (95% CI: 1.79-2.94, P<0.00001), the OR3 of homozygous genotype GG versus AA was 4.42 (95% CI: 3.45-5.67, P<0.00001), and the OR4 of allele G versus A was 2.04 (95% CI: 1.85-2.26, P<0.00001). Sensitivity analysis indicated the robustness of our findings, and evidence of publication bias was not observed in our meta-analysis. Cumulative meta-analysis revealed that the summary ORs were stable. There was no significant difference in every genetic model between PCV and nAMD (n=5, OR1= 0.92, OR2=0.96, OR3=0.90, OR4=0.94).

CONCLUSIONS:Our analysis provides evidence that the I62V polymorphism is associated with an increased risk of PCV. The variant of I62V could be a promising genetic biomarker of PCV in Asian populations.

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Diet & lifestyle

JAMA Ophthalmol. 2014 Feb 1;132(2):231-2. doi: 10.1001/jamaophthalmol.2013.6340.

Regarding Macular Xanthophylls and ω-3 Long-Chain Polyunsaturated Fatty Acids in Age-Related Macular Degeneration-Reply.

Arnold C, Jentsch S, Schweitzer D, Böhm V.

PMID: 24525936 [PubMed - in process]

JAMA Ophthalmol. 2014 Feb 1;132(2):230-1. doi: 10.1001/jamaophthalmol.2013.6667.

Regarding Macular Xanthophylls and ω-3 Long-Chain Polyunsaturated Fatty Acids in Age-Related Macular Degeneration.

Meagher KA, Nolan JM, Beatty S.

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Neurobiol Aging. 2013 Dec 27. pii: S0197-4580(13)00666-0. doi: 10.1016/ j.neurobiolaging.2013.12.024. [Epub ahead of print]

Relationships between macular pigment optical density and cognitive function in unimpaired and mildly cognitively impaired older adults.

Renzi LM, Dengler MJ, Puente A, Miller LS, Hammond BR Jr.

Abstract: Low carotenoid status (especially of the xanthophylls, lutein [L], and zeaxanthin [Z]) is common in older adults and has been associated with a number of degenerative diseases of the central nervous system ranging from retina (e.g., macular degeneration) to brain (e.g., Alzheimer's disease). In this study, we tested whether retinal measures of L + Z (macular pigment optical density [MPOD]), used as a surrogate for brain L + Z levels, were related to cognitive function when comparing healthy older adults with mildly cognitively impaired older adults. Twenty-four subjects with mild cognitive impairment were compared with 24 matched controls. Subjects were matched with respect to age, body mass index, ethnicity, sex, and smoking status. Degree of cognitive impairment and cognitive ability was determined via structured clinical interview. MPOD was measured psychophysically. In healthy older adults, MPOD was only related to visual-spatial and constructional abilities ($p = 0.04$). For subjects with mild cognitive impairment (MCI), however, MPOD was broadly related to cognition including the composite score on the mini-mental state examination ($p = 0.02$), visual-spatial and constructional abilities ($p = 0.04$), language ability ($p = 0.05$), attention ($p = 0.03$), and the total scale on the Repeatable Battery for the Assessment of Neuropsychological Status ($p = 0.03$). It is possible that L/Z status may be more strongly related to cognition when individuals are considered with established onset of cognitive decline.

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