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MD Research News

Issue 42

Monday August 15 , 2011

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Drug treatment

Retina. 2011 Jun;31(6):1036-42.

AGE-RELATED MACULAR DEGENERATION, ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR AGENTS, AND SHORT-TERM MORTALITY: A Postmarketing Medication Safety and Surveillance Study.

French DD, Margo CE.

From the *VA Center of Excellence on Implementing Evidence Based Practice, Regenstrief Institute, Inc, Department of General Internal Medicine and Geriatrics, Indiana University School of Medicine, Indianapolis; and †Departments of Ophthalmology and Pathology, University of South Florida, College of Medicine; James A. Haley Veterans Hospital, Tampa, Florida.

PURPOSE: To compare short-term (1 year) survival of subjects treated for exudative age-related macular degeneration (AMD) with those with AMD who received no treatment.

METHODS: This was a case-control study. Beneficiaries of the Veterans Health Administration aged ≥55 years with a diagnosis of AMD in fiscal years 2007-2009 were included in this study. Veterans Health Administration clinical and pharmacy data sets were linked with a national Veterans Health Administration mortality registry. Anti-vascular endothelial growth factor exposure was identified through pharmacy records, coupled to procedure code for intravitreous injection and diagnosis code of exudative AMD. Control group consisted of patients with coded diagnosis of dry AMD and no pharmacy claims for case-defining medications. Cox proportional hazard model was adjusted for age, gender, number of injections, and ocular and medical comorbidities. The main outcome measure was hazard of death according to medication exposure.

RESULTS: A total of 3,210 patients received intravitreous injections for exudative AMD. There were 117,364 nonexposed patients with dry AMD. Twelve-month all-cause mortality in the exposed and control groups were 3.9% and 4.5%, respectively. When adjusted for age, gender, and ocular and medical comorbidities, the death hazard was 0.89 (95% confidence interval, 0.74-1.06). The risk of all-cause mortality was similar for patients receiving bevacizumab and ranibizumab.

CONCLUSION: Twelve-month all-cause mortality in a population of predominately men with exudative AMD and a high prevalence of medical comorbidities was unaffected by exposure to therapeutic levels of vitreous bevacizumab and ranibizumab. Commonly used anti-vascular endothelial growth factor agents for exudative AMD do not adversely impact short-term survival in men.

PMID: 21836410 [PubMed - in process]

Retina. 2011 Jun;31(6):1028-35.

Sustained elevated intraocular pressures after intravitreal injection of bevacizumab, ranibizumab, and pegaptanib.

Choi DY, Ortube MC, McCannel CA, Sarraf D, Hubschman JP, McCannel TA, Gorin MB.

From the *David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California; and †Jules Stein Eye Institute, David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles, California.

PURPOSE: To investigate elevated intraocular pressures (IOP) (defined by a measurement >25 mmHg at a follow-up visit) after an intravitreal injection of anti-vascular endothelial growth factor agents for age-related macular degeneration.

METHODS: Retrospective review of medical records.

RESULTS: A total of 127 patients (155 eyes) received an intravitreal injection of anti-vascular endothelial growth factor agents (bevacizumab, ranibizumab, or pegaptanib) ranging from 1 to 39 injections for more than a period of 30 to 1759 days. Among this population, 12 patients (14 eyes; 9.4%) developed elevated IOP >25 mmHg. Of these, 7 patients (5.5%) developed sustained elevated IOP (IOP >25 mmHg on 2 separate visits requiring glaucoma medication or surgery), of which 8 eyes required topical medications and 1 eye underwent glaucoma surgery. Mean IOP of injected eyes receiving intravitreal injection was 15.2 ± 2.4 mmHg, and the mean IOP was 14.9 ± 2.6 mmHg for noninjected eyes. Among eyes that had elevated IOPs, there was no association with injection frequency, number of injections, or anti-vascular endothelial growth factor agent used.

CONCLUSION: Elevated IOP, sustained or unsustained, after intravitreal injection is not uncommon. No association with patient demographics or injection history was identified in the authors' study population.

PMID: 21836409 [PubMed - in process]

Retina. 2011 Apr;31(4):662-8.

ENDOPHTHALMITIS AFTER INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR ANTAGONISTS: A Six-Year Experience at a University Referral Center.

Moshfeghi AA, Rosenfeld PJ, Flynn HW Jr, Schwartz SG, Davis JL, Murray TG, Smiddy WE, Berrocal AM, Dubovy SR, Lee WH, Albini TA, Lalwani GA, Kovach JL, Puliafito CA.

From the Bascom Palmer Eye Institute, Department of Ophthalmology, University of Miami Miller School of Medicine, Miami, Florida. Dr. Puliafito is currently also affiliated with the Keck School of Medicine, University of Southern California, Los Angeles, California.

PURPOSE: To assess the rate of infectious endophthalmitis and to describe the clinical and microbiological features of eyes that develop clinically suspected endophthalmitis after an intravitreal injection of vascular endothelial growth factor antagonists.

METHODS: The medical records of patients undergoing intravitreal injections of anti-vascular endothelial growth factor agents from January 1, 2005, through December 31, 2010, at a single university referral center and associated satellite clinics were retrospectively analyzed to determine the rate of infectious endophthalmitis after intravitreal anti-vascular endothelial growth factor injections.

RESULTS: Twelve cases (11 patients) of clinically suspected endophthalmitis were identified after a total of 60,322 injections (0.02%; 95% confidence interval, 0.0114%-0.0348%). Of the 12 cases, 11 presented within 3 days of the injection. Of the 7 culture-positive cases, 5 were because of Streptococcus species. In 4 of the 5 Streptococcus cases, final visual acuity was hand

motions or worse. The rate of clinically suspected endophthalmitis was 0.018% after bevacizumab and 0.027% after ranibizumab injections.

CONCLUSION: A very low rate of endophthalmitis after intravitreal injections of anti-vascular endothelial growth factor agents was observed. Patients typically presented within 3 days of injection. Streptococcus species was the most common bacteria isolated, and it was generally associated with poor visual outcomes.

PMID: 21836400 [PubMed - in process]

J Ocul Pharmacol Ther. 2011 Aug 10. [Epub ahead of print]

Influence of Ranibizumab on Vascular Endothelial Growth Factor Plasma Level and Endothelial Progenitor Cell Mobilization in Age-Related Macular Degeneration Patients: Safety of Intravitreal Treatment for Vascular Homeostasis.

Machalińska A, Paczkowska E, Pabin T, Safranow K, Karczewicz D, Machaliński B.

Department of Histology and Embryology, Pomeranian Medical University , Szczecin, Poland .

Purpose: Intravitreal ranibizumab, which neutralizes vascular endothelial growth factor (VEGF), nowadays constitutes the first-line treatment in neovascular age-related macular degeneration (AMD). However, its potential systemic effect on vascular homeostasis as the consequence of such therapy has not been extensively investigated.

Methods: Peripheral blood (PB) samples from 12 patients with newly diagnosed neovascular AMD were analyzed before as well as 1 and 4 weeks after intravitreal treatment with ranibizumab. VEGF plasma levels, the number of circulating endothelial progenitor cells (EPCs), and the intracellular expression of hypoxia-inducible factor (HIF) in PB cells were determined by enzyme-linked immunosorbent assay, flow cytometry, and real-time quantitative reverse transcriptase-polymerase chain reaction assays, respectively.

Results: No significant changes within the analyzed parameters were found in the first or fourth weeks after ranibizumab injection compared with the primary, basic values before treatment. Based on our findings, intravitreal ranibizumab does not induce significant systemic effects or vascular impairment.

Conclusions: Evaluation of the VEGF plasma level, the PB EPC concentration, and intracellular HIF expression may be supportive indicators of drug safety for ranibizumab.

PMID: 21830945 [PubMed - as supplied by publisher]

Retina. 2011 Aug 4. [Epub ahead of print]

RANDOMIZED CLINICAL TRIAL FRANCE DMLA2: Effect of Trimetazidine on Exudative and Nonexudative Age-Related Macular Degeneration.

Cohen SY, Bourgeois H, Corbe C, Chaine G, Espinasse-Berrod MA, Garcia-Sanchez J, Gaudric A, Hullo A, Leys A, Soubrane G, Sahel JA.

From the *Ophthalmic Center for Imaging and Laser, Paris, France; †Val de Gràce Hospital, Paris, France; ‡Invalids Hospital, Paris, France; §Avicenne Hospital, Bobigny, France; Necker Hospital, Paris, France; **San Carlos Clinical Hospital, Complutense University of Madrid, Madrid, Spain; ††Lariboisiere Hospital, Paris, France; ‡‡Lyon-Sud Hospital, France; §§University of Leuven, Belgium; University Eye Clinic, Creteil, France; and ***XV-XX Hospital, Paris, France.

PURPOSE: To evaluate the effect of trimetazidine (TMZ) in a randomized, double-blind, placebo-controlled

clinical trial on the occurrence of choroidal neovascularization or geographic atrophy in age-related macular degeneration.

METHODS: A total of 1,086 patients from France, Belgium, and Spain with soft drusen and/or retinal pigment epithelium abnormalities in the study eye and choroidal neovascularization in the contralateral eye were randomly assigned to receive orally placebo or TMZ 70 mg daily (35 mg × 2) and followed-up for 3 years to 5 years.

RESULTS: Treatment duration ranged between 0.4 months and 67.8 months with a mean ± SD of 38 ± 16 months. Three hundred and fifty-eight patients developed choroidal neovascularization (incidence per 100 patient-years: TMZ 10.86; placebo 11.13). Trimetazidine did not prevent the choroidal neovascularization (hazard ratio = 0.97; 95% confidence interval, 0.77-1.20; P = 0.781). However, there was a trend favoring TMZ for retinal atrophy, a secondary endpoint (HR = 0.76; 95% confidence interval, 0.56-1.02; P = 0.069). Overall, the difference in atrophy incidence between TMZ and placebo was not statistically different. Differences within some prespecified subgroups of patients showed superiority of TMZ in men (HR = 0.50; 95% confidence interval, 0.28-0.89; p = 0.016), in patients aged ≤75 years (HR = 0.58; 95% confidence interval, 0.38-0.88; p = 0.010), or in patients presenting with isolated pigmentary changes (HR = 0.19; 95% confidence interval, 0.05-0.70; p = 0.005).

CONCLUSION: Trimetazidine failed to prevent choroidal neovascularization. Subgroup analyses suggest that this drug could be tested as preventive therapy for geographic atrophy, although the overall comparison showed no statistically significant differences in the progression of geographic atrophy.

PMID: 21822162 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging. 2011 Aug 11:1-6. doi: 10.3928/15428877-20110804-01. [Epub ahead of print]

16-Gy Low-Voltage X-ray Irradiation With Ranibizumab Therapy for AMD: 6-Month Safety and Functional Outcomes.

Canton VM, Quiroz-Mercado H, Velez-Montoya R, Lopez-Miranda MJ, Moshfeghi AA, Shusterman EM, Kaiser PK, Sanislo SR, Gertner M, Moshfeghi DM.

BACKGROUND AND OBJECTIVE: To describe the 6-month safety and preliminary efficacy outcomes of the use of 16-Gy radiation with intravitreal ranibizumab for patients with neovascular age-related macular degeneration (AMD).

PATIENTS AND METHODS: A single treatment of a non-invasive, externally delivered low-voltage 16-Gy x-ray irradiation was administered in one session through three locations in the inferior pars plana. Optical coherence tomography (OCT) and Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (VA) examinations were performed at 1 week, 1 month, and monthly thereafter, with quarterly fluorescein angiography (FA). After the two initial ranibizumab injections, subsequent injections were administered according to the following criteria: VA decline of 10 ETDRS letters compared with baseline, increase of 100-µm central foveal thickness on OCT compared with baseline, the development of new submacular hemorrhage, and the development of a new area of classic choroidal neovascularization on FA.

RESULTS: Twenty-six patients completed a 6-month follow-up. There was no evidence of radiation retinopathy, optic neuropathy, or cataract. The mean baseline ETDRS score was 46.6 letters (range: 5 to 80; standard deviation [SD]: 21.5). At 6 months, the corresponding ETDRS score was 55.6 letters (range: 25 to 80; SD: 18.9) and the mean change in VA was 9.5 ETDRS letters (SD: 10.3). On responder analysis, 96% lost 15 or fewer ETDRS letters, 81% gained 0 or more ETDRS letters, and 50% gained 15 or more ETDRS letters. Patients received a total of 13 ranibizumab injections following two initial injections. At 6 months, patients received an average of 0.5 additional injections following the initial two mandated injections.

CONCLUSION: A single treatment of externally applied, non-invasive 16-Gy low-voltage x-ray therapy in conjunction with ranibizumab demonstrated an overall improvement of VA in patients with neovascular AMD at 6 months with no radiation-related adverse effects.

PMID: 21830747 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging. 2011 Aug 11:1-8. doi: 10.3928/15428877-20110804-03. [Epub ahead of print]

16-Gy Low-Voltage X-ray Irradiation Followed by As-Needed Ranibizumab Therapy for AMD: 6-Month Outcomes of a "Radiation-First" Strategy.

Moshfeghi AA, Canton VM, Quiroz-Mercado H, Velez-Montoya R, Lopez-Miranda MJ, Shusterman EM, Kaiser PK, Sanislo SR, Gertner M, Moshfeghi DM.

BACKGROUND AND OBJECTIVE: To describe the effect of a "radiation-first" combination treatment strategy for neovascular age-related macular degeneration (AMD) with ranibizumab rescue therapy.

PATIENTS AND METHODS: Non-invasive, externally delivered low-voltage x-ray irradiation at a dose of 16 Gy was given in a single session through three locations in the inferior pars plana in a consecutive series of patients with neovascular AMD. Ranibizumab was administered according to prospectively determined criteria.

RESULTS: Thirteen patients completed a 6-month follow-up. All patients lost 15 or fewer ETDRS letters, 7 gained 0 or more ETDRS letters, and 0 gained more than 15 ETDRS letters. Patients received a total of 15 ranibizumab injections following x-ray irradiation at baseline. Two patients received no ranibizumab injections, seven patients received 1 injection, and four patients received 2 injections.

CONCLUSION: Low-voltage x-ray treatment followed by ranibizumab rescue demonstrates an independent visual acuity stabilizing effect for patients with wet AMD.

PMID: 21830745 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging. 2011 Aug 11:1-11. doi: 10.3928/15428877-20110804-04. [Epub ahead of print]

Angiographic Regression Patterns After Intravitreal Ranibizumab Injections for Neovascular Age-Related Macular Degeneration.

Tran TH, Querques G, Forzy G, Souied EH.

BACKGROUND AND OBJECTIVE: To investigate the relation between visual gain, injection frequency, and the angiographic regression patterns after intravitreal ranibizumab on an as-needed basis in exudative age-related macular degeneration (AMD).

PATIENTS AND METHODS: Fifty-nine treatment-naïve patients (68 eyes) were retrospectively analyzed. All patients received three consecutive monthly injections (induction phase) of ranibizumab (0.5 mg/0.05 mL). Based on fluorescein angiography (FA), the choroidal neovascularization (CNV) was judged to present either complete regression (pattern 1), partial regression (pattern 2), stabilization of the lesion size without leakage (pattern 3), stabilization of the lesion size with persistence of leakage (pattern 4), or increased angiographic size (pattern 5).

RESULTS: Mean visual acuity (VA) significantly improved from 48 to 54.3 letters at 1 year after a mean of 5.5 injections ($P < .001$). Multiple linear regression revealed baseline VA as a predictor of visual gain and the angiographic pattern as a predictor of number of injections. Analysis of variance revealed a significant

interaction (F-test [1.67] = 25, P < .001) between the number of injections at 12 months and the regression patterns, as evaluated by FA 1 month after the induction phase. Eyes showing complete CNV regression needed significantly fewer injections than eyes without any angiographic sign of CNV regression (3.4 injections in pattern 1 vs 5.6 injections in pattern 3 [P = .03], and 7 injections in pattern 4 [P < .001], 4.4 injections in pattern 2 vs 7 injections in pattern 4 [P < .001]).

CONCLUSION: FA may represent a useful tool to adapt the rhythm of visits and intravitreal anti-vascular endothelial growth factor injections in exudative AMD.

PMID: 21830744 [PubMed - as supplied by publisher]

Case Report Med. 2011;2011:747648. Epub 2011 Aug 3.

The use of intravitreal ranibizumab for choroidal neovascularization associated with vogt-koyanagi-harada syndrome.

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Purpose: To describe the use of intravitreal ranibizumab for choroidal neovascular membrane (CNVM) secondary to Vogt-Koyanagi-Harada (VKH) syndrome.

Methods. Interventional case report.

Results: A 50-year-old woman presented with conjunctival injection and bilateral eye pain. Vision was 20/400 and 20/80 in the right and left eyes, respectively. Bilateral iritis, vitritis, and choroidal thickening were evident. Exudative retinal detachment was present in the left eye. Corticosteroid treatment improved vision to 20/40 bilaterally. Methotrexate (MTX) was initiated and vision remained stable for 3 months. After a 5-month loss to follow-up, vision in the left eye decreased to finger counting (CF) and a parafoveal CNVM was identified. After 3 intravitreal ranibizumab injections, vision improved to 20/40. Twelve months later, despite inflammation control, vision decrease to CF due to recurrent CNVM. A fourth ranibizumab injection was given. Twenty months later, best-corrected vision was 20/400, and an inactive CNVM was present in the left eye.

Conclusion: After initial CNVM regression and visual acuity improvement due to ranibizumab, the CNVM recurred and became refractory to treatment. Despite control of inflammation and neovascularization, VKH chronicity lead to permanent vision loss in our patient. A combinational treatment approach may be required in such patients.

PMID: 21826150 [PubMed - in process]

PMCID: PMC3151517

Indian J Ophthalmol. 2011 Sep-Oct;59(5):394-6.

Combination therapy of low-fluence photodynamic therapy and intravitreal ranibizumab for choroidal neovascular membrane in choroidal osteoma.

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Abstract

Choroidal osteoma is an unusual form of intraocular calcification seen in otherwise healthy eyes. It is a benign idiopathic osseous tumor of the choroid, typically seen in young females. Choroidal neovascular membrane (CNVM) is a complication seen in one-third of these patients and carries a poor visual outcome. We report a case of a 25-year-old hyperthyroid female with choroidal osteoma and subfoveal CNVM in her left eye which was successfully treated using low-fluence photodynamic therapy (PDT) with verteporfin followed by a single injection of intravitreal ranibizumab.

PMID: 21836351 [PubMed - in process]

Arch Soc Esp Oftalmol. 2011 Aug;86(8):254-259. Epub 2011 Jul 22.

Treatment of wet age-related macular degeneration with ranibizumab in clinical practice: results and prognostic factors.

[Article in English, Spanish]

Muriel MA, Fatela B, Valdivia A, Clement F.

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OBJECTIVES: To evaluate the efficacy of ranibizumab in wet age-related macular degeneration (ARMD), and to identify prognostic factors.

METHODS: A retrospective longitudinal study of 79 eyes treated with intravitreal Ranibizumab in our hospital due to wet ARMD, with an initial regimen of three consecutive monthly injections, followed by injections on demand based on the exploratory findings. We conducted a descriptive study of the baseline examination (n=79), and 3 (n=79), 6 (n=67) and 12 months (n=49) after starting treatment. The characteristics of the baseline examination and annual examination results were compared using univariate and multivariate analysis.

RESULTS: After the three initial injections, the 93.67% of patients lost fewer than 15 letters, and 19% gained 15 points or more. This result remained similar at 1 year (83.67% and 20.40%, respectively). After 1 year of treatment 40.82% had a VA ≥ 0.3 and 22'45% had a VA ≤ 0.1. We used a median of 5 injections per year. The increased AV at the beginning and the persistence of large intraretinal cysts at 3 months (P=.0013), as well as the development of fibrosis during evolution (P=.0005), are associated with visual deterioration.

CONCLUSIONS: The guidelines used here stabilised or improved visual acuity in most patients. The most favourable cases are those with initially lower VA or large intraretinal cysts resolved after the loading phase. The appearance of fibrosis implies a poor long-term visual prognosis.

PMID: 21821192 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2011 Apr;31(4):779-84.

IDIOPATHIC AND SECONDARY EPIRETINAL MEMBRANES: Do They Differ in Terms of Morphology? An Optical Coherence Tomography-Based Study.

Yazici AT, Alagöz N, Celik HU, Bozkurt E, Alagöz C, Cakir M, Cekiç O, Yilmaz OF.

From the *Beyoğlu Eye Training and Research Hospital, İstanbul, Turkey; and †Vakıf Guraba Training and Research Hospital, İstanbul, Turkey.

PURPOSE: The purpose of this study was to define the morphologic differences in idiopathic and secondary epiretinal membranes (ERMs) using a time domain optical coherence tomography.

METHODS: The medical records and optical coherence tomography images of 293 eyes of 236 consecutive patients diagnosed to have ERM were evaluated retrospectively. Demographic features, best-corrected visual acuities, central macular thickness, membrane attachment patterns, macular changes, and the presence of posterior retinal detachment at the time of diagnosis were compared between the groups (idiopathic group, n = 125 eyes; secondary group, n = 168 eyes).

RESULTS: The mean age was higher among idiopathic ERMs (67 ± 9 vs. 62 ± 10 years, P = 0.001). In the secondary group, best-corrected visual acuity was estimated to be worse (P < 0.001) and central macular thickness higher (P = 0.02) than the idiopathic group. In both groups, ERMs were mostly diagnosed at Grade 1 level. Diffuse attachment was more common in both of the groups. Among macular changes, only cystoid macular degeneration differed significantly between the groups (P = 0.0001).

CONCLUSION: Idiopathic and secondary ERMs were estimated to differ significantly at the time of diagnosis in terms of age, visual acuities, macular thickness, presence of cystoid macular degeneration, and posterior vitreous detachment. These parameters may assist the retinal surgeon in the treatment process of ERM.

PMID: 21836405 [PubMed - in process]

Epidemiology & pathogenesis

Clin Experiment Ophthalmol. 2011 Aug;39(6):494-500. doi: 10.1111/j.1442-9071.2011.02509.x. Epub 2011 Mar 24.

Assessing the diagnostic validity of a blind register.

Crewe JM, Morgan WH, Morlet N, Spilsbury K, Mukhtar A, Clark A, Ng JQ, Crowley M, Semmens JB.

Centre for Population Health Research, Curtin Health Innovation Research Institute, Curtin University Centre for Ophthalmology and Visual Science, Lions Eye Institute, University of Western Australia Association for the Blind of Western Australia, Perth, Western Australia, Australia.

Background: To validate the accuracy of clinical ophthalmic information held on the West Australian blind register.

Design: Community-based cross-sectional study.

Participants: Legally blind or severely vision-impaired people were selected randomly from the Association for the Blind of Western Australia register.

Methods: Individuals were reviewed by one of two consultant ophthalmologists.

Main Outcome Measures: The positive predictive value (ppv), sensitivity and specificity for legal blindness status and diagnostic causes of vision loss were calculated using data extracted from the Association for the Blind of Western Australia blind register.

Results: 273 blind or near blind people were reviewed from the register total of 4271 individuals. There were more women (57%) than men, median age 81 years. For legal blindness status the ppv was 0.88 (95% confidence interval [CI] 0.82-0.92), sensitivity 0.75 (95% CI 0.74-0.84) and specificity 0.6 (95% CI 0.46-0.73). The ppv for the diagnostic causes of blindness were: age-related macular degeneration = 0.95 (95% CI 0.91-0.97), retinitis pigmentosa ppv = 1 (95% CI 0.81-1.0), diabetic retinopathy ppv = 0.9 (95% CI 0.57-0.99), optic neuropathies ppv = 0.77 (95% CI 0.51-0.92) and glaucoma ppv = 0.87 (95% CI 0.7-0.96). Forty individuals (15%) had treatable conditions contributing to their vision loss.

Conclusions: The blind register diagnoses and legal blindness status are of high accuracy. This information allows useful linkages to other databases for studies of blindness interactions. A regular updating mechanism would improve the future accuracy of this valuable regional asset. The presence of untreated cataract suggests that regular follow up and appropriate treatment may help optimize vision in blind patients.

PMID: 21819503 [PubMed - in process]

Ophthalmologica. 2011 Aug 3. [Epub ahead of print]

Age-Related Macular Degeneration and Risk Factors for the Development of Choroidal Neovascularisation in the Fellow Eye: A 3-Year Follow-Up Study.

Silva R, Cachulo ML, Fonseca P, Bernardes R, Nunes S, Vilhena N, Faria de Abreu JR.

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Introduction: The presence of large-sized drusen (≥125 μm), soft indistinct drusen, pigmentary changes, a large area of drusen and a choroidal neovascular membrane in one eye have been found to be predictive risk factors of late exudative age-related macular degeneration (AMD). Multimodal imaging potentially increases the possibility of indentifying further potential risk factors of developing wet AMD. Purpose: To identify morphological and/or functional baseline risk factors for the development of choroidal neovascularization (CNV) in a multimodal set of images from fellow eyes of patients with exudative AMD.

Methods: Single-center, prospective, observational, longitudinal 2-year plus 1-year extension study of 62 patients with neovascular AMD in one eye (the nonstudy eye) and early age-related maculopathy (ARM) in the fellow eye (study eye). Best-corrected ETDRS visual acuity, fluorescein angiography (FA) and indocyanine green angiography (ICG), fundus photography, retinal leakage analysis, fundus autofluorescence imaging and optical coherence tomography (OCT Stratus 4.0.2, Carl Zeiss Meditech Inc.) were performed at baseline and every 6 months in order to identify both conversion to CNV as well as possible predictive features present before conversion. A semiautomated computer-assisted grading system was used for classifying fundus color images. Only eyes with 3 years of follow-up were considered for statistical analysis.

Results: Fifty-two patients completed the 3-year study follow-up: 26 men and 26 women aged from 56 to 92 years (mean ± SD: 76 ± 6 years). CNV confirmed with FA developed in 46% of the 52 study eyes during the 3-year follow-up (24 converted eyes: 7 in the first year, 11 in the second and 6 in the third). A significantly higher risk for conversion to wet AMD was found only for leakage on a retinal leakage analyzer (odds ratio, OR = 5.0; 95% confidence interval, CI = 1.5-16.4; p = 0.006) detected at least in one visit before the onset of exudative lesions, for baseline ICG hot spots (OR = 7.2; 95% CI = 2.0-25.7; p = 0.002), baseline late ICG hot spots (OR = 4.7; 95% CI = 1.4-15.4; p = 0.009) and baseline early ICG hypofluorescent spots (OR = 3.7; 95% CI = 1.2-12.1; p = 0.025). The total area of drusen, the area of drusen in subfield 1, inner circle or outer circle, the total number of drusen and the number of drusen ≥125 μm, fundus autofluorescence patterns, OCT findings and the severity of ARM at baseline did not show any correlation with an increased risk of conversion to wet AMD.

Conclusion: At 3 years, progression from early to late exudative AMD was superior to the expected rate (44%). ICG early and late hyperfluorescent spots or areas, ICG early hypofluorescent spots or areas and early leakage detected with the retinal leakage analyzer, but not pigmentary changes, large drusen, number and area of drusen at any location or a greater severity of ARM at baseline, showed to be a predictive parameter of conversion to wet AMD.

PMID: 21822000 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2011 Aug 8. [Epub ahead of print]

Risk Assessment Model for Development of Advanced Age-Related Macular Degeneration.

Klein ML, Francis PJ, Ferris FL 3rd, Hamon SC, Clemons TE.

Casey Eye Institute, Oregon Health & Science University and Devers Eye Institute, Legacy Good Samaritan Hospital and Medical Center, Portland (Drs Klein and Francis); National Eye Institute, National Institutes of Health, US Department of Health and Human Services, Bethesda (Dr Ferris), and The EMMES Corp, Rockville (Dr Clemons), Maryland; and Laboratory of Statistical Genetics, Rockefeller University, New York, New York (Dr Hamon).

OBJECTIVE: To design a risk assessment model for development of advanced age-related macular degeneration (AMD) incorporating phenotypic, demographic, environmental, and genetic risk factors.

METHODS: We evaluated longitudinal data from 2846 participants in the Age-Related Eye Disease Study. At baseline, these individuals had all levels of AMD, ranging from none to unilateral advanced AMD (neovascular or geographic atrophy). Follow-up averaged 9.3 years. We performed a Cox proportional hazards analysis with demographic, environmental, phenotypic, and genetic covariates and constructed a risk assessment model for development of advanced AMD. Performance of the model was evaluated using the C statistic and the Brier score and externally validated in participants in the Complications of Age-Related Macular Degeneration Prevention Trial.

RESULTS: The final model included the following independent variables: age, smoking history, family history of AMD (first-degree member), phenotype based on a modified Age-Related Eye Disease Study simple scale score, and genetic variants CFH Y402H and ARMS2 A69S. The model did well on performance measures, with very good discrimination (C statistic = 0.872) and excellent calibration and overall performance (Brier score at 5 years = 0.08). Successful external validation was performed, and a risk assessment tool was designed for use with or without the genetic component.

CONCLUSIONS: We constructed a risk assessment model for development of advanced AMD. The model performed well on measures of discrimination, calibration, and overall performance and was successfully externally validated. This risk assessment tool is available for online use.

PMID: 21825180 [PubMed - as supplied by publisher]

Neuron. 2011 Aug 11;71(3):389-405.

Regulated reprogramming in the regeneration of sensory receptor cells.

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Abstract

Vision, olfaction, hearing, and balance are mediated by receptors that reside in specialized sensory epithelial organs. Age-related degeneration of the photoreceptors in the retina and the hair cells in the cochlea, caused by macular degeneration and sensorineural hearing loss, respectively, affect a growing number of individuals. Although sensory receptor cells in the mammalian retina and inner ear show only limited or no regeneration, in many nonmammalian vertebrates, these sensory epithelia show remarkable regenerative potential. We summarize the current state of knowledge of regeneration in the specialized sense organs in both nonmammalian vertebrates and mammals and discuss possible areas where new advances in regenerative medicine might provide approaches to successfully stimulate sensory receptor cell regeneration. The field of regenerative medicine is still in its infancy, but new approaches using stem cells and repro-

gramming suggest ways in which the potential for regeneration may be restored in individuals suffering from sensory loss.

PMID: 21835338 [PubMed - in process]

Genetics

Arch Ophthalmol. 2011 Aug;129(8):1061-6.

Complement Factor H 402H Variant and Reticular Macular Disease.

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OBJECTIVE: To determine the association of high-risk alleles in the complement factor H (CFH; Y402H, rs1061170) and age-related maculopathy susceptibility (ARMS2; A69S, rs10490924) genes with reticular macular disease (RMD), a major clinical subphenotype of age-related macular degeneration (AMD).

METHODS: Using retinal images from the Columbia Macular Genetics Study, we identified 67 subject individuals with RMD. A comparison group of 64 subjects with AMD without RMD was matched by ethnicity, age, sex, and AMD clinical stage.

RESULTS: In the RMD group, 53 of 67 subjects (79.1%) were female, the mean age was 83 years, and 47 of 67 (70.1%) had late AMD, with closely matched values in the non-RMD group. The frequencies of the CFH 402H allele were 39.6% in the RMD group (53 of 134 individuals) and 58.6% in the non-RMD group (75 of 128 individuals) ($\chi(2) = 8.8$; $P = .003$; odds ratio, 0.46 [95% confidence interval, 0.28-0.76]). The corresponding frequencies of the risk allele for ARMS2 were 44.0% (40 of 128 individuals) and 31.3% (40 of 128 individuals), respectively ($\chi(2) = 4.0$; $P = .045$; odds ratio, 1.73 [95% confidence interval, 1.04-2.90]). Homozygosity for 402H was particularly associated with the absence of RMD, occurring in 8 of 67 subjects (11.9%) with RMD vs 24 of 64 subjects (37.5%) without RMD ($P < .001$). Retinal macular disease also was associated with hypertension among male patients.

CONCLUSIONS: The AMD-associated CFH 402H risk variant is significantly associated with the absence of RMD but enhanced risk for RMD is conferred by the ARMS2 69S AMD risk allele. These results are consistent with the hypothesis that 402H may confer a survival benefit against certain infections, some of which may cause RMD. Clinical Relevance Reticular macular disease may be genetically distinct from the rest of AMD.

PMID: 21825189 [PubMed - in process]

PLoS One. 2011;6(8):e22959. Epub 2011 Aug 2.

Overexpression of HTRA1 Leads to Ultrastructural Changes in the Elastic Layer of Bruch's Membrane via Cleavage of Extracellular Matrix Components.

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Abstract

Variants in the chromosomal region 10q26 are strongly associated with an increased risk for age-related

macular degeneration (AMD). Two potential AMD genes are located in this region: ARMS2 and HTRA1 (high-temperature requirement A1). Previous studies have suggested that polymorphisms in the promotor region of HTRA1 result in overexpression of HTRA1 protein. This study investigated the role of HTRA1 overexpression in the pathogenesis of AMD. Transgenic Htra1 mice overexpressing the murine protein in the retinal pigment epithelium (RPE) layer of the retina were generated and characterized by transmission electron microscopy, immunofluorescence staining and Western Blot analysis. The elastic layer of Bruch's membrane (BM) in the Htra1 transgenic mice was fragmented and less continuous than in wild type (WT) controls. Recombinant HTRA1 lacking the N-terminal domain cleaved various extracellular matrix (ECM) proteins. Subsequent Western Blot analysis revealed an overexpression of fibronectin fragments and a reduction of fibulin 5 and tropoelastin in the RPE/choroid layer in transgenic mice compared to WT. Fibulin 5 is essential for elastogenesis by promoting elastic fiber assembly and maturation. Taken together, our data implicate that HTRA1 overexpression leads to an altered elastogenesis in BM through fibulin 5 cleavage. It highlights the importance of ECM related proteins in the development of AMD and links HTRA1 to other AMD risk genes such as fibulin 5, fibulin 6, ARMS2 and TIMP3.

PMID: 21829675 [PubMed - in process]

Pre-clinical

Arch Ophthalmol. 2011 Aug;129(8):1042-52.

Prevention of experimental choroidal neovascularization and resolution of active lesions by VEGF trap in nonhuman primates.

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OBJECTIVE: To evaluate the efficacy of systemic and intravitreous administration of VEGF Trap (aflibercept) in a nonhuman primate model of choroidal neovascularization (CNV).

METHODS: VEGF Trap treatment on laser-induced CNV was evaluated in 48 adult cynomolgus monkeys. In the prevention arms of the study, VEGF Trap was administered by intravenous injection (3 or 10 mg/kg weekly) or intravitreous injection (50, 250, or 500 µg/eye every 2 weeks) beginning before laser injury. In the treatment arm, a single intravitreous injection (500 µg) was given 2 weeks following laser injury. Laser-induced lesions were scored from grade 1 (no hyperfluorescence) to grade 4 (clinically relevant leakage). Representative lesions were evaluated histologically.

RESULTS: Grade 4 leakage developed at 32.4% and 45.4% of the laser sites in animals receiving intravitreous or intravenous administration of placebo at 2 weeks following laser injury, respectively. In contrast, the development of grade 4 lesions was completely or nearly completely prevented in all groups receiving intravenous or intravitreous injections of VEGF Trap. A single intravitreous injection of VEGF Trap (500 µg) administered following the development of CNV reduced the frequency of grade 4 lesions from 44.4% to 0% within 14 days of treatment. Intravitreous VEGF Trap was well tolerated with either no or only mild ocular inflammation. Histological evaluation showed decreased scores for morphologic features of tissue proliferation in the VEGF Trap prevention groups.

CONCLUSIONS: VEGF Trap prevented the development of clinically relevant CNV leakage when administered at the lowest doses tested. Moreover, a single intravitreous injection induced inhibition of active CNV leakage. Clinical Relevance The animal model used in this study has an established track record as a predictor of pharmacologic efficacy of antineovascular drugs in humans having the neovascular, or wet, form of age-related macular degeneration.

PMID: 21825187 [PubMed - in process]

Diet

Free Radic Biol Med. 2011 Jul 23. [Epub ahead of print]

Zinc-desferrioxamine attenuates retinal degeneration in the rd10 mouse model of retinitis pigmentosa.

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Abstract

Iron-associated oxidative injury plays a role in retinal degeneration such as age-related macular degeneration and retinitis pigmentosa. The metallo-complex zinc-desferrioxamine (Zn/DFO) may ameliorate such injury by chelation of labile iron in combination with release of zinc. We explored whether Zn/DFO can affect the course of retinal degeneration in the rd10 mouse model of retinitis pigmentosa. Zn/DFO-treated animals showed significantly higher electroretinographic responses at 3 and 4.5weeks of age compared with saline-injected controls. Corresponding retinal (photoreceptor) structural rescue was observed by quantitative histological and immunohistochemical techniques. When administered alone, the components of the complex, Zn and DFO, showed a lesser, partial effect. TBARS, a marker of lipid peroxidation, and levels of oxidative DNA damage as quantified by 8-OHdG immunostaining were significantly lower in Zn/DFO-treated retinas compared with saline-injected controls. Reduced levels of retinal ferritin as well as reduced iron content within ferritin molecules were measured in Zn/DFO-treated retinas. The data, taken together, suggest that the protective effects of the Zn/DFO complex are mediated through modulation of iron bioavailability, leading to attenuation of oxidative injury. Reducing iron-associated oxidative stress using complexes such as Zn/DFO may serve as a "common pathway" therapeutic approach to attenuate injury in retinal degeneration.

PMID: 21824515 [PubMed - as supplied by publisher]

J Lipids. 2011;2011:802059. Epub 2011 Jul 28.

Lipids, lipoproteins, and age-related macular degeneration.

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Abstract

Age-related macular degeneration (AMD) is the leading cause of blindness among the elderly. While excellent treatment has emerged for neovascular disease, treatment for early AMD is lacking due to an incomplete understanding of the early molecular events. A prominent age-related change is the accumulation of neutral lipid in normal Bruch's membrane (BrM) throughout adulthood and also disease-related BrM accumulations called basal deposits and drusen. AMD lesion formation has thus been conceptualized as sharing mechanisms with atherosclerotic plaque formation, where low-density lipoprotein (LDL) retention within the arterial wall initiates a cascade of pathologic events. However, we do not yet understand how lipoproteins contribute to AMD. This paper explores how systemic and local production of lipoproteins might contribute to the pathogenesis of AMD.

PMID: 21822496 [PubMed - in process]

PMCID: PMC3147126

Exp Eye Res. 2011 Aug 2. [Epub ahead of print]

Decreasing dietary linoleic acid promotes long chain omega-3 fatty acid incorporation into rat retina and modifies gene expression.

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Abstract

Age-related macular degeneration (AMD) may be partially prevented by dietary habits privileging the consumption of ω3 long chain polyunsaturated fatty acids (ω3s) while lowering linoleic acid (LA) intake. The present study aimed to document whether following these epidemiological guidelines would enrich the neurosensory retina and RPE with ω3s and modulate gene expression in the neurosensory retina. Rat progenitors and pups were fed with diets containing low or high LA, and low or high ω3s. After scotopic single flash and 8-Hz-Flicker electroretinography, rat pups were euthanized at adulthood. The fatty acid profile of the neurosensory retina, RPE, liver, adipose tissue and plasma was analyzed using gas chromatography. Gene expression was analyzed with real-time PCR in the neurosensory retina. Diets rich in ω3s efficiently improved the incorporation of ω3s into the organs and tissues. This raising effect was magnified by lowering LA intake. Compared to a diet with high LA and low ω3s, low LA diets significantly upregulated LDL-receptor gene expression. Similar but not significant upregulation of CD36, ABCA1, ALOX5 and ALOX12 gene expression was observed in rats fed with low LA. No effect was observed on retinal function. Increasing the intake in ω3s and lowering LA improved the enrichment with ω3s of the tissues, including the neurosensory retina and RPE, and upregulated genes involved in lipid trafficking in the neurosensory retina. Those results consistently reinforced the beneficial role of ω3s in the prevention of AMD, especially when the diet contained low levels of LA, as suggested from epidemiological data.

PMID: 21821023 [PubMed - as supplied by publisher]