

Issue 116

Thursday 7 February, 2013

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

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Drug treatment

Ophthalmology. 2013 Jan 23. pii: S0161-6420(12)00986-4. doi: 10.1016/j.ophtha.2012.10.014. [Epub ahead of print]

Twelve-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration.

Busbee BG, Ho AC, Brown DM, Heier JS, Suñer IJ, Li Z, Rubio RG, Lai P; HARBOR Study Group.

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OBJECTIVE: To evaluate the 12-month efficacy and safety of intravitreal ranibizumab 0.5 mg and 2.0 mg administered monthly and on an as-needed (PRN) basis in treatment-naïve patients with subfoveal neovascular age-related macular degeneration (wet AMD).

DESIGN: A 24-month, phase III, randomized, multicenter, double-masked, dose-response study.

PARTICIPANTS: Patients aged ≥50 years with subfoveal wet AMD.

METHODS: Patients (n = 1098) were randomized to receive ranibizumab 0.5 mg or 2.0 mg intravitreal injections administered monthly or on a PRN basis after 3 monthly loading doses.

MAIN OUTCOME MEASURES: The primary efficacy end point was the mean change from baseline in best-corrected visual acuity (BCVA) at month 12. Key secondary end points included the mean number of ranibizumab injections, the mean change from baseline in central foveal thickness (CFT) over time, and the proportion of patients who gained ≥15 letters of BCVA. Unless otherwise specified, end point analyses were performed using the last-observation-carried-forward method to impute missing data.

RESULTS: At month 12, the mean change from baseline in BCVA for the 4 groups was +10.1 letters (0.5 mg monthly), +8.2 letters (0.5 mg PRN), +9.2 letters (2.0 mg monthly), and +8.6 letters (2.0 mg PRN). The proportion of patients who gained ≥15 letters from baseline at month 12 in the 4 groups was 34.5%, 30.2%, 36.1%, and 33.0%, respectively. The mean change from baseline in CFT at month 12 in the 4 groups was -172.0 μm, -161.2 μm, -163.3 μm, and -172.4 μm, respectively. The mean number of injections was 7.7 and 6.9 for the 0.5-mg PRN and 2.0-mg PRN groups, respectively. Ocular and systemic safety profiles were consistent with previous ranibizumab trials in AMD and comparable between groups.

CONCLUSIONS: At month 12, the ranibizumab 2.0-mg monthly group did not meet the prespecified superiority comparison and the ranibizumab 0.5-mg and 2.0-mg PRN groups did not meet the prespecified noninferiority (NI) comparison. However, all treatment groups demonstrated clinically meaningful visual improvement (+8.2 to +10.1 letters) and improved anatomic outcomes, with the PRN groups requiring

approximately 4 fewer injections (6.9-7.7) than the monthly groups (11.2-11.3). No new safety events were observed despite a 4-fold dose escalation in the study. The pHase III, double-masked, multicenter, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis (PRN) in patients with subfoveal neOvasculaR age-related macular degeneration (HARBOR) study confirmed that ranibizumab 0.5 mg dosed monthly provides optimum results in patients with wet AMD.

PMID: 23352196 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2013 Jan 31;1-11. doi: 10.1001/jamaophthalmol.2013.2015. [Epub ahead of print]

Randomized Clinical Trial Evaluating Intravitreal Ranibizumab or Saline for Vitreous Hemorrhage From Proliferative Diabetic Retinopathy.

Diabetic Retinopathy Clinical Research Network*.

IMPORTANCE: Vascular endothelial growth factor plays a role in proliferative diabetic retinopathy (PDR). Intravitreal injection of saline has been shown potentially to lead to improved visual acuity compared with observation alone in eyes with vitreous hemorrhage. Therefore, it is important to determine if intravitreal anti-vascular endothelial growth factor can reduce vitrectomy rates (and risks associated with vitrectomy) compared with saline for vitreous hemorrhage from PDR that precludes placement or confirmation of complete panretinal photocoagulation.

OBJECTIVE: To evaluate intravitreal ranibizumab compared with intravitreal saline injections on vitrectomy rates for vitreous hemorrhage from PDR.

DESIGN: Phase 3, double-masked, randomized, multicenter clinical trial. Data reported were collected from June 2010 to March 2012 and include 16 weeks of follow-up.

SETTING: Community-based and academic-based ophthalmology practices specializing in retinal diseases.

PARTICIPANTS: Two hundred sixty-one eyes of 261 study participants, who were at least 18 years of age with type 1 or type 2 diabetes mellitus. Study eyes had vitreous hemorrhage from PDR precluding panretinal photocoagulation completion.

INTERVENTION: Eyes were randomly assigned to 0.5-mg intravitreal ranibizumab (n = 125) or intravitreal saline (n = 136) at baseline and 4 and 8 weeks.

MAIN OUTCOME MEASURE: Cumulative probability of vitrectomy within 16 weeks. **RESULTS** Cumulative probability of vitrectomy by 16 weeks was 12% with ranibizumab vs 17% with saline (difference, 4%; 95% CI, -4% to 13%) and of complete panretinal photocoagulation without vitrectomy by 16 weeks was 44% and 31%, respectively (P = .05). The mean (SD) visual acuity improvement from baseline to 12 weeks was 22 (23) letters and 16 (31) letters, respectively (P = .04). Recurrent vitreous hemorrhage occurred within 16 weeks in 6% and 17%, respectively (P = .01). One eye developed endophthalmitis after saline injection.

CONCLUSIONS AND RELEVANCE: Overall, the 16-week vitrectomy rates were lower than expected in both groups. This study suggests little likelihood of a clinically important difference between ranibizumab and saline on the rate of vitrectomy by 16 weeks in eyes with vitreous hemorrhage from PDR. Short-term secondary outcomes including visual acuity improvement, increased panretinal photocoagulation completion rates, and reduced recurrent vitreous hemorrhage rates suggest biologic activity of ranibizumab. Long-term benefits remain unknown. Whether vitrectomy rates after saline or ranibizumab injection are different than observation alone cannot be determined from this study.

PMID: 23370902 [PubMed - as supplied by publisher]

Digit J Ophthalmol. 2011;17(3):38-9. doi: 10.5693/djo.02.2011.02.004. Epub 2011 Aug 18.

Immediate loss of vision due to retinal pigment epithelial tear after anti-angiogenesis treatment of pigment epithelial detachment.

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Abstract: Intravitreal injection of ranibizumab, an antivascular endothelial growth factor (VEGF) drug, is currently the primary treatment for wet age-related macular degeneration (AMD) in the UK. Use of ranibizumab for the treatment of isolated pigment epithelial detachments (PEDs) without the presence of an occult choroidal neovascular membrane has not been studied in a randomized controlled fashion and is strictly off-label. One possible complication of intravitreal injection of the drug is retinal pigment epithelial (RPE) tear. To date, the etiology of RPE tear associated with intravitreal injection is unknown; it could be attributed to rapid contraction of the neovascular membrane by fibrosis, perhaps triggered by the drug. We report a case of an RPE tear occurring less than a minute after intravitreal injection of ranibizumab for a fibrovascular PED. To our knowledge, this is the first report of such a case.

PMID: 23362393 [PubMed]

Digit J Ophthalmol. 2011;17(3):23-30. doi: 10.5693/djo.01.2011.05.003. Epub 2011 Sep 30.

Combined intravitreal ranibizumab and verteporfin photodynamic therapy versus ranibizumab alone for the treatment of age-related macular degeneration.

Giustolisi R, Fantozzi N, Staltari M, Marchiori J, Mastrangelo O, Marcucci R, Mirra F, Mazzotta P, Gabrieli CB.

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PURPOSE: To compare same-day combined therapy of photodynamic therapy with verteporfin (PDT-V) and intravitreal ranibizumab versus monotherapy with ranibizumab for the treatment of choroidal neovascularization.

METHODS: IN THIS PROSPECTIVE STUDY, THE TOTAL NUMBER OF EYES WAS RANDOMIZED INTO TWO GROUPS: in the first, treatment consisted of a combined therapy of PDT-V and ranibizumab 0.5 mg on the same day; in the second, ranibizumab 0.5 mg in 3 monthly injections. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) on optical coherence tomography (OCT) were recorded before and 6 months after treatment.

RESULTS: A total of 47 eyes of 47 subjects were enrolled in the study. In the combined-therapy group (group 1), the mean baseline BCVA $\pm$ standard deviation (SD) was 32.65 ± 11.09 letters (Snellen equivalent, 20/59); in the ranibizumab-alone group (group 2), 29.13 ± 9.03 letters (20/70). At 6 months' follow-up, in group 1 the mean baseline BCVA was 39.06 ± 10.12 letters (20/42); in group 2, 33.87 ± 12.06 letters (20/57). Improvement was significant in both group 1 ($P = 0.03$) and group 2 ($P = 0.002$). In group 1, the mean CMT at baseline $\pm$ SD was 315 ± 95.49 μ m; in group 2, 306.33 ± 71.61 μ m. At 6 months' follow-up, in group 1 it was 202 ± 52.02 μ m; in group 2, 226 ± 65.58 μ m. Reduction was significant in both group 1 ($P = 0.0007$) and group 2 ($P = 0.00001$). After 6-months, the rate of retreated eyes was 29.4% in group 1 and 43.3% in group 2. The need for retreatment did not depend on the treatment protocol ($P = 0.34$).

CONCLUSIONS: From a functional and anatomic point of view, the two treatments showed equivalent efficacy, with fewer retreatments in group 1. No serious adverse events, such as retinal detachment, endophthalmitis, or ocular hypertension occurred in either group.

PMID: 23362390 [PubMed]

Invest Ophthalmol Vis Sci. 2013 Jan 29. pii: iovs.12-10260v1. doi: 10.1167/iovs.12-10260. [Epub ahead of print]

Pharmacokinetics of Ranibizumab in Patients With Neovascular Age-Related Macular Degeneration - A Population Approach.

Xu L, Lu T, Tuomi L, Jumbe N, Lu J, Eppler S, Kuebler P, Damico-Beyer LA, Joshi A.

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PURPOSE: To characterize ranibizumab pharmacokinetics in patients with age-related macular degeneration (AMD).

METHODS: A population approach of nonlinear mixed-effect pharmacokinetic modeling based on concentration-time data from 2993 serum samples from 674 AMD patients enrolled in 5 phase 1-3 clinical trials of single or multiple intravitreal (ITV) doses of ranibizumab (0.3-2.0 mg/eye) administered bi-weekly, monthly or quarterly for up to 24 months.

RESULTS: 696 concentration-time records from 229 subjects with ≥ 1 measurable serum ranibizumab concentration were analyzed. The systemic concentration-time data for ranibizumab was best described by a 1-compartment model with first-order absorption into and first-order elimination from the systemic circulation. Vitreous elimination half-life ($t(1/2)$) was calculated to be 9 days and the intrinsic systemic elimination $t(1/2)$ was calculated to be ~ 2 hours. Following ITV administration, ranibizumab egresses slowly into the systemic circulation resulting in an apparent serum $t(1/2)$ of 9 days. Systemic-to-vitreous exposure ratio was estimated to be 1:90,000. With monthly and quarterly ITV regimens, the serum concentrations of ranibizumab at steady-state for both the 0.3 and 0.5 mg/eye dose levels were estimated to be below the range needed to inhibit vascular endothelial growth factor A (VEGF)-induced endothelial cell proliferation in vitro by 50% at all times.

CONCLUSIONS: Systemic exposure to ranibizumab after ITV injection was very low due to rapid elimination upon reaching systemic circulation from the vitreous. Population pharmacokinetic analysis of data from a representative sample of AMD patients did not identify clinically significant sources or correlates of variability in ranibizumab exposure.

PMID: 23361508 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2012 Nov-Dec;128(6):3-5.

[Age-related macular degeneration and glaucoma: intraocular pressure monitoring after intravitreal injections]. [Article in Russian]

[No authors listed]

Abstract: In recent decades the problem of low vision and blindness in elderly people became major and socially significant issue. The number of patients having age-related macular degeneration (AMD) in association with glaucoma grows all over the world that attaches medical and social value to this problem. 102 patients with AMD were under follow-up, 7 of them had primary open-angle glaucoma (POAG). Three consecutive injections of ranibizumab resulted in visual acuity increase from 0.21 $\pm$ 0.17 till 0.37 $\pm$ 0.12. The mean retinal thickness in foveal zone decreased from 289.36 $\pm$ 88.73 till 230.47 $\pm$ 88.02 microm. Ocular hypertension within 12 hours after procedure was observed in 13 (12.7%) of 102 patients. In all cases intraocular pressure (IOP) returned to preoperative values in 3 days after hypotensive medical treatment. In one case trabeculectomy was performed simultaneously with ranibizumab intravitreal injection, the next two injections were performed in a month intervals. So the problem of IOP increase after intravitreal injections remains unsolved. Glaucoma is not an absolute contraindication to intravitreal injections in treatment of exudative AMD although patients with associated conditions need individual approach in terms of both IOP compensation and number of ranibizumab injections.

PMID: 23367753 [PubMed - in process]

Int J Inflam. 2013;2013:281981. doi: 10.1155/2013/281981. Epub 2013 Jan 14.

Nonsteroidal anti-inflammatory drugs for retinal disease.

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Abstract: Nonsteroidal anti-inflammatory drugs (NSAIDs) are used extensively in ophthalmology for pain and photophobia after photorefractive surgery and to reduce miosis, inflammation, and cystoid macular edema following cataract surgery. In recent years, the US Food and Drug Administration has approved new topical NSAIDs and previously approved NSAIDs have been reformulated. These changes may allow for greater drug penetration into the retina and thereby offer additional therapeutic advantages. For example, therapeutic effects on diabetic retinopathy and age-related macular degeneration may now be achievable. We provide an updated review on the scientific rationale and clinical use of NSAIDs for retinal disease.

PMID: 23365785 [PubMed] PMCID: PMC3556848

Br J Ophthalmol. 2013 Jan 26. [Epub ahead of print]

In vitro induction of protein complexes between bevacizumab, VEGF-A165 and heparin: explanation for deposits observed on endothelial veins in monkey eyes.

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PURPOSE: By investigating the effects of intravitreal bevacizumab on retinal vessels of monkeys, we found that bevacizumab accumulated locally at high concentration within individual blood vessels. It formed electron-dense fibrous deposits between endothelial cells and erythrocytes or granulocytes inducing retinal vein thrombosis. To better characterise the observed deposits, we investigated in vitro whether these deposits result from a complex between bevacizumab, vascular endothelial growth factor (VEGF)-A(165) and heparin.

METHODS: Cynomolgus monkeys were intravitreally injected with 1.25 mg bevacizumab. The eyes were enucleated between 1 and 14 days after injection and investigated by electron microscopy and immunohistochemistry. Human umbilical vein endothelial cells (HUVEC) were incubated with bevacizumab, VEGF-A(165) and heparin at different concentrations. Treatments with ranibizumab served as control. Bevacizumab and ranibizumab were detected immunohistochemically using Cy-3 or immunogold labelled antibodies.

RESULTS: Treated animals showed bevacizumab locally at high concentration within retinal blood vessels. Electron-dense deposits inside retinal vessels and between erythrocytes were detected in three out of four treated monkeys. In vitro, many globular aggregates heavily stained with anti-human IgG were only observed with equimolar amounts (240 nM) of bevacizumab and VEGF-A(165) and 0.2 U/ml heparin and not after ranibizumab treatment. The immunogold labelling specifically localised ultrastructurally the complexes formed between bevacizumab, VEGF-A(165) and heparin at the surfaces of HUVEC cells.

CONCLUSIONS: Heparin promotes bevacizumab immune complex deposition on to endothelial cells. Our in vitro results could explain the presence of deposits observed on endothelial veins in monkey eyes intravitreally injected with bevacizumab.

PMID: 23355530 [PubMed - as supplied by publisher]

Other treatment & diagnostics

Curr Genomics. 2012 Aug;13(5):350-62. doi: 10.2174/138920212801619214.

Prospectives for gene therapy of retinal degenerations.

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Abstract: Retinal degenerations encompass a large number of diseases in which the retina and associated retinal pigment epithelial (RPE) cells progressively degenerate leading to severe visual disorders or blindness. Retinal degenerations can be divided into two groups, a group in which the defect has been linked to a specific gene and a second group that has a complex etiology that includes environmental and genetic influences. The first group encompasses a number of relatively rare diseases with the most prevalent being Retinitis pigmentosa that affects approximately 1 million individuals worldwide. Attempts have been made to correct the defective gene by transfecting the appropriate cells with the wild-type gene and while these attempts have been successful in animal models, human gene therapy for these inherited retinal degenerations has only begun recently and the results are promising. To the second group belong glaucoma, age-related macular degeneration (AMD) and diabetic retinopathy (DR). These retinal degenerations have a genetic component since they occur more often in families with affected probands but they are also linked to environmental factors, specifically elevated intraocular pressure, age and high blood sugar levels respectively.

The economic and medical impact of these three diseases can be assessed by the number of individuals affected; AMD affects over 30 million, DR over 40 million and glaucoma over 65 million individuals worldwide. The basic defect in these diseases appears to be the relative lack of a neurogenic environment; the neovascularization that often accompanies these diseases has suggested that a decrease in pigment epithelium-derived factor (PEDF), at least in part, may be responsible for the neurodegeneration since PEDF is not only an effective neurogenic and neuroprotective agent but also a potent inhibitor of neovascularization. In the last few years inhibitors of vascularization, especially antibodies against vascular endothelial cell growth factors (VEGF), have been used to prevent the neovascularization that accompanies AMD and DR resulting in the amelioration of vision in a significant number of patients. In animal models it has been shown that transfection of RPE cells with the gene for PEDF and other growth factors can prevent or slow degeneration. A limited number of studies in humans have also shown that transfection of RPE cells in vivo with the gene for PEDF is effective in preventing degeneration and restore vision. Most of these studies have used virally mediated gene delivery with all its accompanying side effects and have not been widely used. New techniques using non-viral protocols that allow efficient delivery and permanent integration of the transgene into the host cell genome offer novel opportunities for effective treatment of retinal degenerations.

PMID: 23372421 [PubMed] PMCID: PMC3401892

Ophthalmic Surg Lasers Imaging. 2012 Nov 1;43(6):S32-7. doi: 10.3928/15428877-20121001-06.

Automated Detection of the Foveal Center Improves SD-OCT Measurements of Central Retinal Thickness.

Wang F, Gregori G, Rosenfeld PJ, Lujan BJ, Durbin MK, Bagherinia H.

BACKGROUND AND OBJECTIVE: To investigate the performance of an automated foveal center detection algorithm on spectral-domain optical coherence tomography (SD-OCT).

PATIENTS AND METHODS: Fifty normal eyes and 50 eyes with early stage dry age-related macular degeneration (AMD) were analyzed. The actual scan center (SC), automatically detected foveal center

(AF), and manually identified foveal center (MF) were compared.

RESULTS: The mean of the radial distances was $89 \pm 120 \mu\text{m}$ from MF to SC and $54 \pm 41 \mu\text{m}$ from MF to AF for normal eyes and $179 \pm 125 \mu\text{m}$ from SC to MF and $104 \pm 62 \mu\text{m}$ from AF to MF for eyes with AMD. The differences were statistically significant ($P < .001$).

CONCLUSION: The automated algorithm designed to detect the foveal center was more accurate in detecting the foveal center than relying on the fixation target of the SD-OCT instrument.

PMID: 23357322 [PubMed - in process]

Atheroscler Suppl. 2013 Jan;14(1):179-84. doi: 10.1016/j.atherosclerosissup.2012.10.023.

Rheohaemapheresis in the treatment of nonvascular age-related macular degeneration.

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PURPOSE: To evaluate the experience with rheohaemapheresis (RH) in the treatment of age-related macular degeneration (AMD).

METHODS: Thirty-eight patients were each treated with 8 procedures of RH (14 males, 24 females). The control group consisted of 34 random patients (30 females, 4 males) with the dry form of AMD but not treated by RH. Our modification of the cascade method (named rheohaemapheresis) was used for plasma separation. After plasma separation (blood cell separator, Cobe Spectra, Denver, CO, USA), the separated plasma was pumped through a rheofilter (Evaflux 4A, Kuraray, Osaka, Japan) to remove lipoproteins and other high-molecular-weight rheologic factors.

RESULTS: In treated patients, best-corrected visual acuity (BCVA) increased significantly from 0.61 (0.06-1.00) to 0.68 (0.35-1.00) after 2.5 years ($p = 0.035$). We found no significant changes or differences in scotopic activity, whereas cone response and paramacular activity in the more peripheral region between 14° and 22° of eccentricity were significantly higher in treated patients after 2.5 years.

CONCLUSION: RH therapy favourably influenced BCVA. During 2.5 years after the therapy, no progression of dry to wet AMD was observed in our patients. RH reduced the area of drusenoid retinal pigment epithelium detachment (which increased during the natural course of dry form AMD). RH influenced rheological markers and probably improved metabolism in the affected retinal areas which lead to the aforementioned positive results.

PMID: 23357162 [PubMed - in process]

J Vis Exp. 2013 Jan 15;(71). pii: 4390. doi: 10.3791/4390.

Integrated Photoacoustic Ophthalmoscopy and Spectral-domain Optical Coherence Tomography.

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Abstract: Both the clinical diagnosis and fundamental investigation of major ocular diseases greatly benefit from various non-invasive ophthalmic imaging technologies. Existing retinal imaging modalities, such as fundus photography(1), confocal scanning laser ophthalmoscopy (cSLO)(2), and optical coherence tomography (OCT)(3), have significant contributions in monitoring disease onsets and progressions, and developing new therapeutic strategies. However, they predominantly rely on the back-reflected photons

from the retina. As a consequence, the optical absorption properties of the retina, which are usually strongly associated with retinal pathophysiology status, are inaccessible by the traditional imaging technologies. Photoacoustic ophthalmoscopy (PAOM) is an emerging retinal imaging modality that permits the detection of the optical absorption contrasts in the eye with a high sensitivity(4-7) . In PAOM nanosecond laser pulses are delivered through the pupil and scanned across the posterior eye to induce photoacoustic (PA) signals, which are detected by an unfocused ultrasonic transducer attached to the eyelid. Because of the strong optical absorption of hemoglobin and melanin, PAOM is capable of non-invasively imaging the retinal and choroidal vasculatures, and the retinal pigment epithelium (RPE) melanin at high contrasts (6,7). More importantly, based on the well-developed spectroscopic photoacoustic imaging(5,8) , PAOM has the potential to map the hemoglobin oxygen saturation in retinal vessels, which can be critical in studying the physiology and pathology of several blinding diseases (9) such as diabetic retinopathy and neovascular age-related macular degeneration. Moreover, being the only existing optical-absorption-based ophthalmic imaging modality, PAOM can be integrated with well-established clinical ophthalmic imaging techniques to achieve more comprehensive anatomic and functional evaluations of the eye based on multiple optical contrasts(6,10) . In this work, we integrate PAOM and spectral-domain OCT (SD-OCT) for simultaneously in vivo retinal imaging of rat, where both optical absorption and scattering properties of the retina are revealed. The system configuration, system alignment and imaging acquisition are presented.

PMID: 23354081 [PubMed - in process]

Am J Ophthalmol. 2013 Jan 23. pii: S0002-9394(12)00832-X. doi: 10.1016/j.ajo.2012.11.021. [Epub ahead of print]

Angiographic and Optical Coherence Tomography Characteristics of Recent Myopic Choroidal Neovascularization.

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PURPOSE: To analyze the contribution of fluorescein angiography (FA) and spectral-domain optical coherence tomography (SD OCT) to the diagnosis of recent choroidal neovascularization (CNV) associated with high myopia.

DESIGN: Retrospective, observational case series.

METHODS: Ninety eyes of 73 highly myopic patients (refractive error ≥ -6 diopters) with CNV in 1 or both eyes were included. Epidemiologic features, refractive error, fundus examination, fluorescein angiography, and SD OCT findings at onset of CNV were analyzed.

RESULTS: Mean age at onset of CNV was 54.4 ± 14 years. CNV was bilateral in 17 of 73 cases. Mean refractive error was -13.9 ± 5.2 diopters. Myopic CNV was associated more frequently with patchy or geographic atrophy ($P = .019$). CNV was associated with exudative features on fluorescein angiography in 82% of cases (64/78), and on SD OCT in 48.6% of cases (36/74). There was no agreement about signs of active CNV between these 2 imaging methods ($\kappa = 25.7 \pm 10\%$; $P = .0044$). CNV area was significantly smaller in younger patients (<55 years) than in older patients (0.57 mm^2 vs 1.21 mm^2 , respectively; $P = .023$).

CONCLUSIONS: Exudative features of myopic CNV are more obvious on FA than on SD OCT, suggesting that fluorescein angiography should be performed when new-onset myopic CNV is suspected. Myopic CNV occurring in older patients (≥ 55 years) is larger than those seen in younger patients and resembles CNV

associated with age-related macular degeneration. This suggests an overlap between myopic CNV in older patients and age-related macular degeneration.

PMID: 23352343 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Jan 29. pii: iovs.12-11286v1. doi: 10.1167/iovs.12-11286. [Epub ahead of print]

Abnormal Thickening as well as Thinning of the Photoreceptor Layer in Intermediate Age-Related Macular Degeneration.

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PURPOSE: To investigate the relationship between photoreceptor layers overlying and adjacent to large drusen in intermediate non-neovascular age-related macular degeneration (AMD).

METHODS: Patients with AMD (n=41; ages 53-83 years) and elderly control subjects without eye disease (n=10; ages 51-79) were studied with SD-OCT (spectral-domain optical coherence tomography). Characteristics of large drusen (>125 µm) were measured and the thickness of photoreceptor laminae overlying drusen and in retinal regions neighboring the drusen were quantified.

RESULTS: There were 750 large drusen in 63 early AMD eyes studied. The width of the drusen sampled averaged 352 (SD=153) µm and the height averaged 78 (SD=31) µm. There was significant reduction of the photoreceptor outer nuclear layer (ONL) thickness overlying 92% of the drusen. The thickness of the layer corresponding to photoreceptor inner and outer segments above drusen was also reduced, and the reduction was proportional to ONL thickness. In a substantial fraction (~20%) of normally laminated paradrusen locations sampled within ~300 µm of peak drusen height, ONL thickness was significantly increased compared to age and retinal-location-matched normal values. Topographical analyses of the macula showed ONL thickening occurring in paradrusen regions as well as retinal locations distant from drusen.

CONCLUSIONS: Reductions in the photoreceptor laminae overlying drusen were detectable and this is consistent with histological studies revealing neuronal degeneration in AMD. ONL thickening in some macular areas of AMD eyes has not been previously reported and may be an early phenotypic marker for photoreceptor stress, as it has been speculated to be in hereditary retinal degenerations.

PMID: 23361506 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Jan 29. pii: iovs.12-10928v1. doi: 10.1167/iovs.12-10928. [Epub ahead of print]

Automated Classification of Severity of Age-related Macular Degeneration from Fundus Photographs.

Kankanahalli S, Burlina PM, Wolfson Y, Freund DE, Bressler NM.

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PURPOSE: To evaluate an automated analysis of retinal fundus photographs to detect and classify severity of age-related macular degeneration compared with grading by the Age-Related Eye Disease Study (AREDS) protocol.

Methods: Following approval by the Johns Hopkins University School of Medicine's Institution Review Board, digitized images (downloaded at <http://www.ncbi.nlm.nih.gov/gap/>) of field 2 (macular) fundus photographs from AREDS obtained over a 12 year longitudinal study were classified automatically using a visual words method to compare with severity by expert graders.

Results: Sensitivities and specificities, respectively, of automated imaging, when compared with expert fundus grading of 468 patients and 2145 fundus images are: 98.6% and 96.3% when classifying categories 1 and 2 vs. categories 3 and 4; 96.1% and 96.1% when classifying categories 1 and 2 vs. category 3; 98.6% and 95.7% when classifying category 1 vs. category 3; 96.0% and 94.7% when classifying category 1 vs. categories 3 and 4;

Conclusion: Development of an automated analysis for classification of AMD from digitized fundus photographs has high sensitivity and specificity when compared with expert graders and may have a role in screening or monitoring.

PMID: 23361512 [PubMed - as supplied by publisher]

Conf Proc IEEE Eng Med Biol Soc. 2012 Aug;2012:5967-70. doi: 10.1109/EMBC.2012.6347353.

Quantitative assessment of age-related macular degeneration using parametric modeling of the leakage transfer function: Preliminary results.

Eldeeb SM, Abdelmoula WM, Shah SM, Fahmy AS.

Abstract: Age-related macular degeneration (AMD) is a major cause of blindness and visual impairment in older adults. The wet form of the disease is characterized by abnormal blood vessels forming a choroidal neovascular membrane (CNV), that result in destruction of normal architecture of the retina. Current evaluation and follow up of wet AMD include subjective evaluation of Fluorescein Angiograms (FA) to determine the activity of the lesion and monitor the progression or regression of the disease. However, this subjective evaluation prevents accurate monitoring of the disease progression or regression in response to a pharmacologic agent. In this work, we present a method that allows objective assessment of the activity of a CNV lesion which can be statistically compared across different patient and time points. The method is based on a hypothesis that the discrepancy in the time-intensity signals among the diseased and normal retinal areas are due to an implicit transfer function whose parameters can be used to characterize the retina. The method begins with parametric modeling of the temporal variation of the lesion and background intensities. Then, the values of the model parameters are used to evaluate the change in the activity of the disease. Preliminary results on five datasets show that the calculated parameters are highly correlated with the Visual Acuity (VA) of the patients.

PMID: 23367288 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2012 Aug;2012:4954-7. doi: 10.1109/EMBC.2012.6347104.

Automatic localization of retinal landmarks.

Cheng X, Wong DW, Liu J, Lee BH, Tan NM, Zhang J, Cheng CY, Cheung G, Wong TY.

Abstract: Retinal landmark detection is a key step in retinal screening and computer-aided diagnosis for different types of eye diseases, such as glaucoma, age-related macular degeneration (AMD) and diabetic retinopathy. In this paper, we propose a semantic image transformation (SIT) approach for retinal representation and automatic landmark detection. The proposed SIT characterizes the local statistics of a fundus image and boosts the intrinsic retinal structures, such as optic disc (OD), macula. We propose our salient OD and macular models based on SIT for retinal landmark detection. Experiments on 5928 images show that our method achieves an accuracy of 99.44% in the detection of OD and an accuracy of 93.49%

in the detection of macula, while having an accuracy of 97.33% for left and right eye classification. The proposed SIT can automatically detect the retinal landmarks and be useful for further eye-disease screening and diagnosis.

PMID: 23367039 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2012 Aug;2012:3320-3. doi: 10.1109/EMBC.2012.6346675.

Dynamic image pre-compensation for computer access by individuals with ocular aberrations.

Huang J, Barreto A, Adjouadi M.

Abstract: Several image enhancement methods have been successfully used to improve the visual perception of patients with eye diseases, such as Age-related Macular Degeneration and Cataracts, on images displayed on TV and computers. However, few developments aim to enhance the visual performance of computer users with general ocular aberrations. This paper proposes an image enhancement approach based on dynamic pre-compensation for improving the visual performance of subjects with ocular aberrations, while interacting with computers. The degradation caused by ocular aberrations is counteracted through the pre-compensation performed on images displayed on the computer screen. As the ocular aberration initially measured as a priori information is related with a specific pupil size, real-time pupil size data are collected to recalculate and update the pre-compensation to match the corresponding aberrations. An icon recognition experiment, involving human subjects, was designed and implemented to evaluate the performance of the proposed method. The experimental results show that the proposed method significantly increased the number of icons correctly recognized, which confirmed that the dynamic pre-compensation is effective in improving the visual performance of computer users with ocular aberrations.

PMID: 23366636 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2012 Aug;2012:2985-8. doi: 10.1109/EMBC.2012.6346591.

Physiological response of normal and RD mouse retinal ganglion cells to electrical stimulation.

Cho AK, Sampath AP, Weiland JD.

Abstract: The epiretinal prosthesis aims to restore functional vision by stimulating electrically the retinal ganglion cells (RGCs) in patients afflicted with degenerative diseases that affect the photoreceptors, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). As degeneration progresses, photoreceptor death is followed by pronounced remodeling and rewiring of remaining inner retinal cells. Despite the loss of rods and cones, a considerable population of RGCs remain receptive to prosthetic stimulation. To stimulate effectively a localized population of RGCs, an improved understanding of the anatomical and physiological properties of these cells is required. Additionally, possible alterations in electrical excitability, produced by the effects of retinal degeneration, needs to be assessed. This study investigates the effect of RGC soma size on the threshold for action potential generation in normal and rd mice and its implications for the rescue of visual function.

PMID: 23366552 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2012 Aug;2012:2776-9. doi: 10.1109/EMBC.2012.6346540.

Efficacy of the hexpolar configuration in localizing the activation of retinal ganglion cells under electrical stimulation.

Habib AG, Cameron MA, Suaning GJ, Lovell NH, Morley JW.

Abstract: Retinal visual prostheses provide hope of restoring sight to patients suffering from retinal degeneration such as retinitis pigmentosa and age-related macular degeneration. Retinal prostheses are used to electrically stimulate residual neurons that are spared in these diseases, namely the retinal ganglion cells (RGCs), eliciting percepts of light termed 'phosphenes'. The elicitation of multiple phosphenes via an electrode array allows patterns to be produced, resulting in a rudimentary form of vision. For such patterns to be produced effectively, the prosthesis must generate well-defined phosphenes. To this end, the hexpolar configuration has been proposed as an alternative to the traditional monopolar or bipolar configurations. It utilizes six electrodes surrounding the stimulating electrode to serve as a combined return, or 'hex guard', purportedly localizing the activation to cells located within them. In this study, the efficacy of the hexpolar configuration in localizing activity was investigated by using patch-clamp electrophysiology to measure the activation thresholds of RGCs to electrical stimulation in isolated rabbit retina. Cells located outside the hex guard were found to have significantly higher relative hexpolar thresholds (>2 fold) as compared to cells located within the hex guard. This confirms the efficacy of the hexpolar configuration in localizing activity to within the hex guard. Furthermore, the effect of using cathodic-first versus anodic-first stimulation on hexpolar threshold and localization was investigated. No significant difference was observed between the two groups, in terms of lowering thresholds or improving localization.

PMID: 23366501 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2012 Aug;2012:1679-82. doi: 10.1109/EMBC.2012.6346270.

Implantable multilayer microstrip antenna for retinal prosthesis: Antenna testing.

Permana H, Fang Q, Rowe WS.

Abstract: Retinal prosthesis has come to a more mature stage and become a very strategic answer to Retinitis Pigmentosa (RP) and Age-related Macular Degeneration (AMD) diseases. In a retinal prosthesis system, wireless link holds a great importance for the continuity of the system. In this paper, an implantable multilayer microstrip antenna was proposed for the retinal prosthesis system. Simulations were performed in High Frequency Structure Simulator (HFSS) with the surrounding material of air and Vitreous Humor fluid. The fabricated antenna was measured for characteristic validation in free space. The results showed that the real antenna possessed similar return loss and radiation pattern, while there was discrepancy with the gain values.

PMID: 23366231 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2012 Aug;2012:292-5. doi: 10.1109/EMBC.2012.6345927.

ASIC design and data communications for the Boston retinal prosthesis.

Shire DB, Ellersick W, Kelly SK, Doyle P, Priplata A, Drohan W, Mendoza O, Gingerich M, McKee B, Wyatt JL, Rizzo JF.

Abstract: We report on the design and testing of a custom application-specific integrated circuit (ASIC) that has been developed as a key component of the Boston retinal prosthesis. This device has been designed for patients who are blind due to age-related macular degeneration or retinitis pigmentosa. Key safety and communication features of the low-power ASIC are described, as are the highly configurable neural stimulation current waveforms that are delivered to its greater than 256 output electrodes. The ASIC was created using an 0.18 micron Si fabrication process utilizing standard 1.8 volt CMOS transistors as well as 20 volt lightly doped drain FETs. The communication system receives frequency-shift keyed inputs at 6.78 MHz from an implanted secondary coil, and transmits data back to the control unit through a lower-bandwidth channel that employs load-shift keying. The design's safety is ensured by on-board electrode

voltage monitoring, stimulus charge limits, error checking of data transmitted to the implant, and comprehensive self-test and performance monitoring features. Each stimulus cycle is initiated by a transmitted word with a full 32-bit error check code. Taken together, these features allow researchers to safely and wirelessly tailor retinal stimulation and vision recovery for each patient.

PMID: 23365888 [PubMed - in process]

Pathogenesis

Ophthalmology. 2013 Jan 23. pii: S0161-6420(12)01005-6. doi: 10.1016/j.ophtha.2012.10.018. [Epub ahead of print]

Progression of Intermediate Age-related Macular Degeneration with Proliferation and Inner Retinal Migration of Hyperreflective Foci.

Christenbury JG, Folgar FA, O'Connell RV, Chiu SJ, Farsiu S, Toth CA; Age-Related Eye Disease Study 2 Ancillary Spectral Domain Optical Coherence Tomography Study Group(□).

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PURPOSE: Drusen and migrating retinal pigment epithelium have been associated with hyperreflective foci (HF) detected by spectral-domain optical coherence tomography (SD-OCT). This study sought to quantify the change in intraretinal HF distribution and its correlation with age-related macular degeneration (AMD) disease progression.

DESIGN: Prospective observational study from the multicenter Age-Related Eye Disease Study 2 (AREDS2) Ancillary SD-OCT Study.

PARTICIPANTS: Patients (n=299) with 1 enrolled eye with intermediate AMD and baseline SD-OCT, followed by SD-OCT imaging at 1-year and 2-year visits.

METHODS: The number and location of HF were scored in SD-OCT scans of all 299 eyes. The change in transverse (horizontal) and axial (vertical) distribution of HF in the macula were evaluated with pairwise signed-rank tests. Two-year inner retinal HF migration was determined by the change in HF-weighted axial distribution (AxD) score calculated for each eye. The correlation of HF with SD-OCT features of AMD progression was evaluated with logistic regression analysis.

MAIN OUTCOME MEASURES: The mean change in number of HF, transverse and axial distribution of HF in the macula, and AxD per eye.

RESULTS: In 299 study eyes, the 2-year increase in the number of HF ($P<0.001$) and the AxD ($P<0.001$) per eye represented longitudinal proliferation and shift to inner retinal layers, respectively. Eyes with geographic atrophy (GA) at 2 years were correlated with the presence of baseline HF ($P<0.001$; odds ratio [OR], 4.72; 95% confidence interval [CI], 2.43-9.80), greater number of baseline HF ($P<0.001$; OR, 1.61 per HF; 95% CI, 1.32-2.00), and greater baseline AxD ($P<0.001$; OR, 1.58 per AxD point; 95% CI, 1.29-1.95).

CONCLUSIONS: Proliferation and inner retinal migration of SD-OCT HF occurred during follow-up in eyes with intermediate AMD. These characteristics were associated with greater incidence of GA at year 2; therefore, SD-OCT HF proliferation and migration may serve as biomarkers for AMD progression.

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Hypoxia Increases the Yield of Photoreceptors Differentiating from Mouse Embryonic Stem Cells

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and Improves the Modeling of Retinogenesis in Vitro.

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CABIMER (Centro Andaluz de Biología Molecular y Medicina Regenerativa), Avda. Americo Vesputio s/n, Parque Científico y Tecnológico Cartuja, Sevilla, Spain.

Abstract: Retinitis pigmentosa (RP), a genetically heterogeneous group of diseases together with age-related macular degeneration (AMD), are the leading causes of permanent blindness and are characterized by the progressive dysfunction and death of the light sensing photoreceptors of the retina. Due to the limited regeneration capacity of the mammalian retina the scientific community has invested significantly in trying to obtain retinal progenitor cells from embryonic stem cells (ESC). These represent an unlimited source of retinal cells, but it has not yet been possible to achieve specific populations, such as photoreceptors, efficiently enough to allow them to be used safely in the future as cell therapy of RP or AMD. In this study we generated a high yield of photoreceptors from directed differentiation of mouse ESC (mESC) by recapitulating crucial phases of retinal development. We present a new protocol of differentiation, involving hypoxia and taking into account extrinsic and intrinsic cues. These include niche-specific conditions as well as the manipulation of the signaling pathways involved in retinal development. Our results show that hypoxia promotes and improves the differentiation of mESC towards photoreceptors. Different populations of retinal cells are increased in number under the hypoxic conditions applied, such as Crx positive cells, S-Opsin positive cells and double positive cells for Rhodopsin and Recoverin, as shown by immunofluorescence analysis. For the first time this manuscript reports the high efficiency of differentiation in vivo and the expression of mature rod photoreceptor markers in a large number of differentiated cells, transplanted in the sub-retinal space of wild type mice.

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PLoS One. 2013;8(1):e54339. doi: 10.1371/journal.pone.0054339. Epub 2013 Jan 24.

Mitochondrial DNA Variants Mediate Energy Production and Expression Levels for CFH, C3 and EFEMP1 Genes: Implications for Age-Related Macular Degeneration.

Kenney MC, Chwa M, Atilano SR, Pavlis JM, Falatoonzadeh P, Ramirez C, Malik D, Hsu T, Woo G, Soe K, Nesburn AB, Boyer DS, Kuppermann BD, Jazwinski SM, Miceli MV, Wallace DC, Udar N.

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BACKGROUND: Mitochondrial dysfunction is associated with the development and progression of age-related macular degeneration (AMD). Recent studies using populations from the United States and Australia have demonstrated that AMD is associated with mitochondrial (mt) DNA haplogroups (as defined by combinations of mtDNA polymorphisms) that represent Northern European Caucasians. The aim of this study was to use the cytoplasmic hybrid (cybrid) model to investigate the molecular and biological functional consequences that occur when comparing the mtDNA H haplogroup (protective for AMD) versus J haplogroup (high risk for AMD).

METHODOLOGY/PRINCIPAL FINDINGS: Cybrids were created by introducing mitochondria from individuals with either H or J haplogroups into a human retinal epithelial cell line (ARPE-19) that was devoid of mitochondrial DNA (Rho0). In cybrid lines, all of the cells carry the same nuclear genes but vary in mtDNA content. The J cybrids had significantly lower levels of ATP and reactive oxygen/nitrogen species production, but increased lactate levels and rates of growth. Q-PCR analyses showed J cybrids had decreased expressions for CFH, C3, and EFEMP1 genes, high risk genes for AMD, and higher expression for MYO7A, a gene associated with retinal degeneration in Usher type IB syndrome. The H and J cybrids also have comparatively altered expression of nuclear genes involved in pathways for cell signaling, inflammation, and metabolism.

CONCLUSION/SIGNIFICANCE: Our findings demonstrate that mtDNA haplogroup variants mediate not only energy production and cell growth, but also cell signaling for major molecular pathways. These data support the hypothesis that mtDNA variants play important roles in numerous cellular functions and disease processes, including AMD.

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Tissue-Specific Host Recognition by Complement Factor H Is Mediated by Differential Activities of Its Glycosaminoglycan-Binding Regions.

Clark SJ, Ridge LA, Herbert AP, Hakobyan S, Mulloy B, Lennon R, Würzner R, Morgan BP, Uhrin D, Bishop PN, Day AJ.

Wellcome Trust Centre for Cell-Matrix Research, Faculty of Life Sciences, University of Manchester, Manchester M13 9PT, United Kingdom;

Abstract: Complement factor H (CFH) regulates complement activation in host tissues through its recognition of polyanions, which mediate CFH binding to host cell surfaces and extracellular matrix, promoting the deactivation of deposited C3b. These polyanions include heparan sulfate (HS), a glycosaminoglycan with a highly diverse range of structures, for which two regions of CFH (CCP6-8 and CCP19-20) have been implicated in HS binding. Mutations/polymorphisms within these glycosaminoglycan-binding sites have been associated with age-related macular degeneration (AMD) and atypical hemolytic uremic syndrome. In this study, we demonstrate that CFH has tissue-specific binding properties mediated through its two HS-binding regions. Our data show that the CCP6-8 region of CFH binds more strongly to heparin (a highly sulfated form of HS) than CCP19-20, and that their sulfate specificities are different. Furthermore, the HS binding site in CCP6-8, which is affected by the AMD-associated Y402H polymorphism, plays the principal role in host tissue recognition in the human eye, whereas the CCP19-20 region makes the major contribution to the binding of CFH in the human kidney. This helps provide a biochemical explanation for the genetic basis of tissue-specific diseases such as AMD and atypical hemolytic uremic syndrome, and leads to a better understanding of the pathogenic mechanisms for these diseases of complement dysregulation.

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Invest Ophthalmol Vis Sci. 2013 Jan 30;54(1):871-80. doi: 10.1167/iovs.12-10827.

The aging eye: common degenerative mechanisms between the Alzheimer's brain and retinal disease.

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Abstract: Alzheimer's disease (AD) is a common, incurable, and progressive dementia, characterized by loss of learning and memory and the neuropathologic accumulation of amyloid plaques and neurofibrillary tangles in the brain. A number of similarities between AD pathology and several distinct retinal degenerations have been described, particularly with respect to either glaucoma or age-related macular degeneration (AMD), each a leading cause of vision loss and blindness worldwide. Although comparisons between these diseases may provide important new insights into their pathogenic mechanisms, glaucoma and AMD result in markedly different degenerations. Therefore, analyses of the differences and the similarities between these conditions may prove equally productive. Common mechanisms that appear to underlie all three diseases are explored here, as well as potential use of the retina as a biomarker for AD

diagnosis and progression. Based on this comparison, past and current efforts to transfer therapeutic strategies between diseases are discussed.

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PLoS One. 2013;8(1):e55079. doi: 10.1371/journal.pone.0055079. Epub 2013 Jan 24.

Comparative Analysis of Circulating Endothelial Progenitor Cells in Age-Related Macular Degeneration Patients Using Automated Rare Cell Analysis (ARCA) and Fluorescence Activated Cell Sorting (FACS).

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BACKGROUND: Patients with age-related macular degeneration (ARMD) begin with non-neovascular (NNV) phenotypes usually associated with good vision. Approximately 20% of NNV-ARMD patients will convert to vision debilitating neovascular (NV) ARMD, but precise timing of this event is unknown. Developing a clinical test predicting impending conversion to NV-ARMD is necessary to prevent vision loss. Endothelial progenitor cells (EPCs), defined as CD34(+)VEGR2(+) using traditional fluorescence activated cell sorting (FACS), are rare cell populations known to be elevated in patients with NV-ARMD compared to NNV-ARMD. FACS has high inter-observer variability and subjectivity when measuring rare cell populations precluding development into a diagnostic test. We hypothesized that automated rare cell analysis (ARCA), a validated and FDA-approved technology for reproducible rare cell identification, can enumerate EPCs in ARMD patients more reliably. This pilot study serves as the first step in developing methods for reproducibly predicting ARMD phenotype conversion.

METHODS: We obtained peripheral venous blood samples in 23 subjects with NNV-ARMD or treatment naïve NV-ARMD. Strict criteria were used to exclude subjects with known angiogenic diseases to minimize confounding results. Blood samples were analyzed in masked fashion in two separate laboratories. EPCs were independently enumerated using ARCA and FACS within 24 hours of blood sample collection, and $p < 0.2$ was considered indicative of a trend for this proof of concept study, while statistical significance was established at 0.05.

RESULTS: We measured levels of CD34(+)VEGFR2(+) EPCs suggestive of a trend with higher values in patients with NV compared to NNV-ARMD ($p = 0.17$) using ARCA. Interestingly, CD34(+)VEGR2(+) EPC analysis using FACS did not produce similar results ($p = 0.94$).

CONCLUSIONS: CD34(+)VEGR2(+) may have predictive value for EPC enumeration in future ARCA studies. EPC measurements in a small sample size were suggestive of a trend in ARMD using ARCA but not FACS. ARCA could be a helpful tool for developing a predictive test for ARMD phenotype conversion.

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Epidemiology

Ophthalmic Epidemiol. 2013;20(1):52-60. doi: 10.3109/09286586.2012.751429.

Lack of awareness of common eye conditions in the community.

Huang OS, Zheng Y, Tay WT, Chiang PP, Lamoureux EL, Wong TY.

Singapore Eye Research Institute, Singapore National Eye Centre , Singapore .

ABSTRACT Purpose: Awareness of eye conditions aids health promotion activities and leads to better outcomes. We examined factors influencing the lack of awareness of common eye conditions in a population.

Methods: The Singapore Malay Eye Study examined 3280 (78.7% response) Malays aged 40-80 years. We included 2112 (64.4%) participants with at least one of five eye conditions: 1504 (71.2%) with cataract, 1013 (47.8%) with myopia, 270 (12.8%) with diabetic retinopathy, 181 (8.6%) with age-related macular degeneration and 150 (7.1%) with glaucoma. Lack of awareness was defined in the questionnaire as not answering "yes" to previously being told by a doctor of having the eye condition.

Results: Among 2112 participants, 83.2% were unaware of at least one of their eye conditions. After controlling for age, sex and socioeconomic factors, participants unaware of their eye condition were older (odds ratio, OR, 1.03, per 1 year, $p < 0.001$), had better visual acuity (OR 1.32, $p = 0.04$), lower education (OR 1.89, $p < 0.001$), poorer literacy (OR 1.44, $p = 0.02$), lower income (OR 1.73, $p = 0.009$), higher blood glucose (OR 1.08, per 1 mmol/L, $p < 0.001$), higher serum cholesterol (OR 1.20, per 1 mmol/L, $p = 0.003$), lower annual eye examination attendance (OR 2.08, $p < 0.001$) and were less likely to wear glasses (OR 2.90, $p < 0.001$) than those who were aware of their condition.

Conclusions: In this community-based population, 80% of those with common eye conditions were unaware of their condition.

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Genetics

Ann Hum Genet. 2013 Jan 31. doi: 10.1111/ahg.12002. [Epub ahead of print]

Genotype-Based Association Analysis Using Discordant Pairs: A Penetrance Odds Ratio Approach.

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Abstract: Genotypic counts of paired relatives discordant for a complex late-onset disease are often used to test for genetic association. The power of the various statistical test options, when data on covariates are unavailable, has been the focus of recent research. Comparison of the Cochran-Armitage, Bhapkar, and McNemar tests indicates that none is superior to the others in all cases. Using an alternative approach, we found that the theoretical genotypic frequencies of the discordant pairs depend only on the penetrance odds ratios, after conditioning. These odds ratios can be estimated by maximizing a product binomial likelihood and provide insight into the mode of inheritance. We identified cases where exact maximum likelihood (ML) estimates can be explicitly obtained. This approach led us to two tests for association which depend on likelihood ratio (LR) or score statistics. We quantified the power of these tests analytically and examined their performance through simulation. We explored the utility of these tests with an example from the literature-the association between complement factor H (CFH) polymorphisms and age-related macular degeneration. The LR and Score tests serve as simple and effective ways of interpreting paired case-control data sets.

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Association of Single Nucleotide Polymorphisms in CFH, ARMS2 and HTRA1 Genes with Risk of Age-related Macular Degeneration in Egyptian Patients.

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Department of Chemistry, The American University in Cairo , New Cairo , Egypt and.

ABSTRACT Background: Age-related macular degeneration (AMD) is one of the leading causes of blindness in the elderly worldwide. Several single nucleotide polymorphisms (SNPs) have been linked to the risk of developing AMD. We aimed to examine the association between AMD and SNPs on CFH, ARMS2 and HTRA1 in Egyptians, a previously unstudied population.

Materials and methods: Genomic DNA was extracted from 26 AMD patients and 20 controls. Genotyping was performed using PCR followed by allele-specific restriction digestion and direct sequencing.

Results: CFH rs1061170 was significantly associated with AMD with the frequency of the risk C allele being 0.53 in patients and 0.17 in controls ($p < 0.017$). The odds ratio (OR) for the TC genotype was 5.5 (95% CI: 1.1-26.4) and for combined TC + CC genotypes was 8 (95% CI: 1.7-37.1). ARMS2 rs10490924 was also significantly associated with the risk allele T found at a frequency of 0.5 in AMD and 0.15 in controls ($p < 0.017$, χ^2 test). The OR for the TG genotype was 4.667 (95% CI: 1.2-18.4) and for combined TG + TT genotypes was 7 (95% CI: 1.8-26.5). HTRA1 rs11200638 also was significantly associated, with the risk allele A found at a frequency of 0.44 in patients and 0.17 in controls ($p < 0.017$, χ^2 test). OR for GA genotype was 5 (95% CI: 1.2-20.9) and for the combined GA + AA genotypes was 6 (95% CI: 1.4-24.7).

Conclusions: Our data demonstrates significant association between AMD and rs1061170 on CFH, rs10490924 on ARMS2 and rs11200638 on HTRA1 in Egyptian patients. These findings are in agreement with previous findings in Caucasians.

PMID: 23362846 [PubMed - as supplied by publisher]

Diet

Nutrients. 2012 Nov 27;4(12):1812-27. doi: 10.3390/nu4121812.

Retinal Spectral Domain Optical Coherence Tomography in Early Atrophic Age-Related Macular Degeneration (AMD) and a New Metric for Objective Evaluation of the Efficacy of Ocular Nutrition.

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PURPOSE: A challenge in ocular preventive medicine is identification of patients with early pathological retinal damage that might benefit from nutritional intervention. The purpose of this study is to evaluate retinal thinning (RT) in early atrophic age-related macular degeneration (AMD) against visual function data from the Zeaxanthin and Visual Function (ZVF) randomized double masked placebo controlled clinical trial (FDA IND #78973).

METHODS: Retrospective, observational case series of medical center veterans with minimal visible AMD retinopathy (AREDS Report #18 simplified grading 1.4/4.0 bilateral retinopathy). Foveal and extra-foveal four quadrant SDOCT RT measurements were evaluated in $n = 54$ clinical and ZVF AMD patients. RT by age was determined and compared to the OptoVue SD OCT normative database. RT by quadrant in a subset of $n = 29$ ZVF patients was correlated with contrast sensitivity and parafoveal blue cone increment thresholds.

RESULTS: Foveal RT in AMD patients and non-AMD patients was preserved with age. Extrafoveal regions, however, showed significant slope differences between AMD patients and non-AMD patients, with the superior and nasal quadrants most vulnerable to retinal thinning (sup quad: $-5.5 \mu\text{m/decade}$ thinning vs. Non-AMD: $-1.1 \mu\text{m/decade}$, $P < 0.02$; nasal quad: $-5.0 \mu\text{m/decade}$ thinning vs. Non-AMD: $-1.0 \mu\text{m/decade}$,

$P < 0.04$). Two measures of extrafoveal visual deterioration were correlated: A significant inverse correlation between % RT and contrast sensitivity ($r = -0.33$, $P = 0.01$, 2 Tailed Paired T) and an elevated extrafoveal increment blue cone threshold ($r = +0.34$, $P = 0.01$, 2 Tailed T). Additional SD OCT RT data for the non-AMD oldest age group (ages 82-91) is needed to fully substantiate the model.

CONCLUSION: A simple new SD OCT clinical metric called "% extra-foveal RT" correlates well with functional visual loss in early AMD patients having minimal visible retinopathy. This metric can be used to follow the effect of repleting ocular nutrients, such as zinc, antioxidants, carotenoids, n-3 essential fats, resveratrol and vitamin D.

PMID: 23363992[PubMed - in process] PMCID: PMC3546609

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