

Issue 105

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Drug treatment

Clin Ophthalmol. 2012;6:1633-8. doi: 10.2147/OPTH.S37252. Epub 2012 Oct 8.

Two-year follow-up of ranibizumab combined with photodynamic therapy for polypoidal choroidal vasculopathy.

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PURPOSE: We evaluated the 2-year efficacy of combined intravitreal ranibizumab (IVR) treatment and photodynamic therapy (PDT) for treatment-naïve polypoidal choroidal vasculopathy (PCV).

PATIENTS AND METHODS: Twenty-two eyes of 22 Japanese patients with treatment-naïve PCV were prospectively recruited. All eyes had angiographic features of PCV according to indocyanine green angiography. The initial combination treatment regimen included a session of PDT with IVR. A total of three consecutive IVR treatments were given at 4-week intervals. Eyes were retreated with IVR or PDT at specific times. We evaluated the mean visual acuity and mean central retinal thickness (CRT) at 3, 6, 9, 12, 18, and 24 months after initial treatment.

RESULTS: At month 9, visual acuity had improved by 5.7 letters ($P = 0.10$). Subsequently, mean visual acuity gradually decreased, and the difference from baseline was diminished to 2.9 letters at 24 months ($P = 0.43$). Mean CRT was significantly decreased from baseline over the 24-month follow-up ($P < 0.05$).

CONCLUSION: With PDT combined with IVR for PCV, visual acuity improved during year 1, but the benefit decreased in year 2.

PMID: 23109800 [PubMed] PMCID: PMC3474272

Clin Ophthalmol. 2012;6:1595-9. doi: 10.2147/OPTH.S35795. Epub 2012 Oct 9.

Topical azithromycin or ofloxacin for endophthalmitis prophylaxis after intravitreal injection.

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BACKGROUND: The number of patients who have undergone intravitreal injections has increased

enormously in recent years, but a consensus is still lacking on prophylaxis for endophthalmitis. The aim of this prospective, observational study was to evaluate the prophylactic effect of azithromycin eye drops versus ofloxacin eye drops.

METHODS: The study was conducted in five hospitals in Spain and included all patients undergoing intravitreal injections of triamcinolone, bevacizumab, ranibizumab, or pegaptanib over one year. Patients received azithromycin 15 mg/g eye drops (twice daily on the day prior to injection and for another 2 days) or ofloxacin 3 mg/g eye drops (every 6 hours on the day prior to injection and for another 7 days).

RESULTS: In the azithromycin group, there were 4045 injections in 972 eyes of 701 patients. In the ofloxacin group, there were 4151 injections in 944 eyes of 682 patients. There were two cases of endophthalmitis (0.049%) in the azithromycin group and five (0.12%) in the ofloxacin group. The odds ratio of presenting with endophthalmitis in the ofloxacin group compared with the azithromycin group was 2.37 (95% confidence interval [CI] 1.32-3.72, $P < 0.001$). There were two cases of noninfectious uveitis after triamcinolone injection in the azithromycin group (0.049%) and two (0.048%) in the ofloxacin group; no significant differences were observed (odds ratio 0.902, 95% CI 0.622-1.407, $P = 0.407$). Conjunctival hyperemia was observed in 12 cases in the azithromycin group and none in the ofloxacin group.

CONCLUSION: The risk of endophthalmitis was significantly greater with ofloxacin than with azithromycin. These findings provide a valuable addition to the ever-increasing pool of information on endophthalmitis prophylaxis after intravitreal injection, although further large-scale studies are required to provide definitive conclusions.

PMID: 23109798 [PubMed] PMCID: PMC3474266

Other treatment & diagnosis

Am J Ophthalmol. 2012 Oct 27. pii: S0002-9394(12)00559-4. doi: 10.1016/j.ajo.2012.07.030. [Epub ahead of print]

Computerized Assessment of Intraretinal and Subretinal Fluid Regions in Spectral-Domain Optical Coherence Tomography Images of the Retina.

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PURPOSE: To evaluate a new computerized segmentation technique for the quantification of intraretinal and subretinal fluid in spectral-domain optical coherence tomography (SD OCT) images of the retina.

DESIGN: Prospective, cross-sectional study.

METHODS: Thirty-seven B-scan images of 37 patients with exudative age-related macular degeneration were chosen randomly from SD OCT volume scans (1 per volume scan). All hyporeflective areas in the image first were segmented automatically as candidate regions by the program. Researchers who were masked to the candidate region information selected each fluid region from the original image using a single mouse click. The program then delineated the boundary of each region selected and calculated quantitative parameters, including total area of fluid regions if multiple regions were selected. The performance of our technique was validated by comparing the results with the measurements obtained from boundaries manually delineated by 2 masked observers. Time efficiency, agreement with manual delineation, and intraobserver and interobserver agreement of using the program were evaluated.

RESULTS: The proposed technique reduced the average processing time per image approximately 6-fold (15 seconds for computerized segmentation vs 90 seconds for manual delineation). There was good

agreement between computerized segmentation and manual delineation measured by intraclass correlation coefficient (range, 0.897 to 0.979) and the Dice coefficient (range, 0.721 to 0.785). The proposed technique has excellent intraobserver and interobserver agreement (intraclass correlation coefficient range, 0.998 to 0.999; Dice coefficient range, 0.959 to 0.981).

CONCLUSIONS: This computerized segmentation method allows for accurate and fast quantification of fluid in retinal SD OCT images and could assist in monitoring disease progression and evaluating therapeutic intervention.

PMID: 23111180 [PubMed - as supplied by publisher]

Clin Exp Optom. 2012 Oct 28. doi: 10.1111/j.1444-0938.2012.00813.x. [Epub ahead of print]

Clinical applicability of the Macular Degeneration Detection Device (MDD-2): a novel photostress recovery measurement device.

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BACKGROUND: Diseases affecting the macula, such as age-related macular degeneration (AMD), diabetic retinopathy and central serous retinopathy can result in impaired photostress recovery time (PSRT) despite normal visual acuity and fundoscopic appearance. The MDD-2 Macular Degeneration Detection Device is a novel flash photostress recovery device. In this study, we examine the repeatability of the MDD-2 in a normal population and its suitability for incorporation into routine clinical practice.

METHODS: One hundred (60 female) subjects (mean age 35 ± 8 years; range 18 to 66 years) were recruited to partake in this study. The photostress recovery time was measured using the MDD-2 on three occasions in the dominant eye and one final occasion in the non-dominant eye to assess measurement repeatability. All subjects were in good ocular health. Visual acuity and iris colour were recorded for each participant.

RESULTS: Repeated measures analysis of variance revealed a statistically significant learning effect on intra-measurement repeatability ($p < 0.01$). Although paired t-test analysis revealed statistically significant differences between repeated measures both within and between eyes ($p < 0.05$ for all) the correlation between repeat measurements is statistically significant ($p < 0.05$ for all), and the coefficient of repeatability reaches clinically acceptable levels once the initial photostress recovery time, which demonstrated increased variability and latency compared to all subsequent measures, is excluded.

CONCLUSION: The MDD-2 provides highly repeatable measurements of photostress recovery time among young naïve subjects, following verbal explanation of the task and only one 'practise' measurement. The measurement is also highly repeatable between eyes, providing a potential immediate clinical biomarker of ocular health.

PMID: 23106424 [PubMed - as supplied by publisher]

Australas Med J. 2012;5(9):507-12. doi: 10.4066/AMJ.2012.1364.. Epub 2012 Oct 14.

Retinal image registration and comparison for clinical decision support.

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BACKGROUND: For eye diseases, such as glaucoma and age-related macular degeneration (ARMD), involved in long-term degeneration procedure, longitudinal comparison of retinal images is a common step for reliable diagnosis of these kinds of diseases.

AIMS: To provide a retinal image registration approach for longitudinal retinal image alignment and comparison.

METHOD: Two image registration solutions were proposed for facing different image qualities of retinal images to make the registration methods more robust and feasible in a clinical application system.

RESULTS: Thirty pairs of longitudinal retinal images were used for the registration test. The experiments showed both solutions provided good performance for the accurate image registrations with efficiency.

CONCLUSION: We proposed a set of retinal image registration solutions for longitudinal retinal image observation and comparison targeting a clinical application environment.

PMID: 23115586 [PubMed]

Pathogenesis

Photochem Photobiol. 2012 Nov;88(6):1303-8. doi: 10.1111/j.1751-1097.2012.01240.x.

Light-Induced Damage to the Retina: Current Understanding of the Mechanisms and Unresolved Questions: A Symposium-in-Print.

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Abstract: Light-induced injury to the retina resembles many features of several retinal degenerative diseases, particularly age-related macular degeneration. This Symposium-in-Print on Retinal Photodamage discusses the mechanisms involved and protective strategies to increase the retinal resistance to damage and/or to counteract its deleterious effects. Recent results help explaining the wavelength dependence of susceptibility of the retina to photodamage and different sites of the initial injury for shorter- and longer-wavelength light. Still, there are many unanswered questions pointing toward next directions in research so as to increase the understanding of the responses of the retina to photodamage and help to develop effective therapeutic approaches for retinal degenerations.

PMID: 23106541 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2012 Oct 30. pii: iovs.12-9805v1. doi: 10.1167/iov.12-9805. [Epub ahead of print]

Dynamic Contrast Enhanced MRI for Assessing Therapeutic Response of Choroidal Neovascularization in a Rat Model.

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PURPOSE: To evaluate the potential of dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) as a non-invasive biomarker of choroidal neovascularization (CNV) and its utility as a tool for monitoring therapeutic response in a laser-induced rat CNV models..

METHODS: CNV was induced in the right eyes of 14 rats using a laser. Rats (n=7) were treated daily for 14

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days with a candidate drug (KR-31831, 50 mg/kg of body weight) having anti-angiogenic effects whereas control rats (n = 7) were treated with the vehicle alone (10% cremophor, 10% absolute ethyl alcohol, and 80% saline). DCE-MRI examinations were performed on the day before surgery (D-1), 3, 7 and 14 days after surgery (D+3, D+7 and D+14), from which pharmacokinetic parameters (Ktrans, ve, vp) were calculated. Angiography was performed to visualize CNV using FITC-labeled high molecular-weight dextran after MRI on D+14. The Paired Wilcoxon test and Mann-Whitney U test were performed for statistical analysis.

Results: The Ktrans and ve values of the CNV induced right eyes were significantly higher than those of the intact eyes in control rats at D+14 ($p < 0.05$). In the CNV induced eyes, the relative Ktrans and ve values of the KR-31831 treated group were significantly lower than those of non-treated group at D+14 ($p < 0.05$). The angiography showed that decreased CNV was observed in rats treated with KR-31831.

Conclusions: Quantitative DCE-MRI produces non-invasive biomarker of CNV thus allowing monitoring of therapeutic response of anti-angiogenic drugs in neovascular age-related macular degeneration (AMD).

PMID: 23111615 [PubMed - as supplied by publisher]

Genetics

Eur J Med Genet. 2012 Oct 25. pii: S1769-7212(12)00283-2. doi: 10.1016/j.ejmg.2012.10.005. [Epub ahead of print]

Age-related macular degeneration and coronary heart disease: evaluation of genetic and environmental associations.

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Abstract: An association between coronary heart disease (CHD) and age-related macular degeneration (AMD) has long been postulated but results from epidemiological case-control studies, and genetic analyses have been ambiguous. In this study we illuminate the association between AMD and CHD with respect to genetic and environmental risk factors, age of disease onset and AMD subgroups. AMD patients (n=1,036) and age-matched control subjects (n=412) between 68 and 95 years of age were included in the case-control study. A medical history of CHD, cerebral stroke and arterial hypertension was determined for each individual. The assessment of interacting factors included the current use of systemic medications and smoking habits. Analysis of AMD associated genetic variants included frequent polymorphisms at the complement factor H (CFH, MIM 134370) gene (rs1061170 [p.Y402H], rs800292 [p.I62V]), the complement factor H-related 3 (CFHR3, MIM 605336) / complement factor H-related 1 (CFHR1, MIM 134371) locus (rs6677604; proxy for Δ CFHR3/CFHR1; $r^2 = 0.97$) as well as the age-related maculopathy susceptibility 2 (ARMS2, MIM 611313) gene (rs10490924 [p.A69S]).

Logistic regression identified a significant positive association of AMD with AMD-risk variants in CFH, ARMS2, and smoking ≥ 20 pack/years. A history of CHD and the current use of antihyperuricemic agents were inversely associated with the disease. Significantly fewer patients with rs6677604 nonrisk genotype A/A regularly used statins. ARMS2:p.A69S risk variant was significantly associated with exudative AMD. AMD patients with risk variants at rs1061170 (CFH:p.Y402H) and ARMS2 and smokers (≥ 20 pack/years) were significantly earlier affected by AMD than those carrying the non-risk variants at each locus. Our data support three major conclusions. First, the age of AMD onset is significantly influenced by genetic and environmental risk factors. Second, in support of previous reports we also show that the ARMS2 rs10490924:T allele is significantly linked to exudative AMD. And finally, a self-reported history of CHD was inversely associated with AMD in this study. Novel therapeutic strategies aiming at preventing the development of AMD may considerably differ from those that have been developed to treat cardiovascular disorders as both common disorders likely underlie different pathomechanisms.

PMID: 23103884 [PubMed - as supplied by publisher]

Mol Vis. 2012;18:2578-85. Epub 2012 Oct 20.

Suggestive association between PLA2G12A single nucleotide polymorphism rs2285714 and response to anti-vascular endothelial growth factor therapy in patients with exudative age-related macular degeneration.

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PURPOSE: The use of anti-vascular endothelial growth factor (anti-VEGF) therapy, with drugs such as ranibizumab and bevacizumab, to treat neovascular age-related macular degeneration (nAMD) produces an effective but widely variable response. Identifying markers that predict differentiated response could serve as a valuable assay in developing more personalized medicine. This study aimed to identify single nucleotide polymorphisms (SNPs) that influence the outcome of treatment with anti-VEGF therapy for AMD.

METHODS: One hundred six patients with nAMD were treated with either ranibizumab or bevacizumab as needed over a period of 12 months. Visual acuity and the presence of macular fluid were measured with optical coherence tomography at baseline, six months, and 12 months. Patients were then classified as good or poor responders based on change in visual acuity and macular fluid on follow-up visits. DNA extracted from blood was genotyped with a TaqMan-based allelic discrimination SNP assay for 21 SNPs in six candidate genes (PLA2G12A, IL23R, STAT3, VEGFA, KDR, and HIF1A). The SNPs were primarily selected based on previously reported associations with AMD and functional involvement in angiogenesis pathways. SNPs shown to be promising for association with anti-VEGF therapy were then assessed in an independent AMD case-control cohort.

RESULTS: Of the 106 patients with nAMD, 77 were classified as good responders and 29 as poor responders. For rs2285714 (PLA2G12A), the frequency of minor allele T was 40.1% for good responders compared to 51.7% for poor responders (odds ratio: 1.60, 95% confidence interval of odds ratio: 0.87-2.94, $p=0.13$). Genetic model analysis of rs2285714 (PLA2G12A) demonstrated an association between rs2285714 (PLA2G12A) and therapy response in a dominant genotypic model. Patients carrying at least one T allele of rs2285714 were 2.79 times (95% confidence interval=1.02-7.69, $p<0.05$) more likely to be poor responders (79.3% of poor responders) than good responders (57.3% of good responders). However, after adjusting for multiple testing by the false discovery rate or Bonferroni correction, the initially observed association was no longer statistically significant. No association was identified between the remaining SNPs and response status. The SNP rs2285714 of PLA2G12A was not significantly associated with AMD in an independent AMD case-control cohort.

CONCLUSIONS: Data suggest a possible weak association between rs2285714 (PLA2G12A) and response to anti-VEGF therapy, but the association must be confirmed in additional cohorts with larger patient samples. Identifying factors that predict the differentiated response could provide a valuable assay for developing approaches in personalized medicine.

PMID: 23112570 [PubMed - in process] PMCID: PMC3482167

Mol Vis. 2012;18:2518-25. Epub 2012 Oct 11.

Susceptibility to advanced age-related macular degeneration and alleles of complement factor H, complement factor B, complement component 2, complement component 3, and age-related maculopathy susceptibility 2 genes in a Mexican population.

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PURPOSE: To investigate the association of age-related macular degeneration (AMD)-high risk alleles of the complement factor H (CFH), complement factor B (CFB), complement component 2 (C2), complement component 3 (C3), and age-related maculopathy susceptibility 2 (ARMS2) genes in a Mexican population for the first time.

METHODS: Genotyping was performed for the Y402H variant of CFH, for the L9H, R32Q, and K565E variants of CFB, the E318D variant of C2, the A69S variant of ARMS2, and the R102G variant of C3 in 159 Mexican mestizo patients at advanced stages of AMD, i.e., CARMS (Clinical Age-Related Maculopathy Staging System) grade 4 or 5. The frequency of these variants was also investigated in a group of 152 control subjects without AMD. Genomic DNA was extracted from blood leukocytes, and genotyping was performed using PCR followed by direct sequencing. Allele-specific restriction enzyme digestion was used to detect the R102G polymorphism in C3.

RESULTS: There were significant differences in the allelic distribution between the two groups for CFH Y402H ($p=1 \times 10^{-5}$), ARMS A69S ($p=4 \times 10^{-7}$), and CFB R32Q ($p=0.01$). The odds ratios (95% confidence interval) obtained for the risk alleles of these three variants were 3.8 (2.4-5.9), 3.04 (2.2-4.3), and 2.5 (1.1-5.7), respectively. Haplotype analysis including the two most significantly associated alleles (CFH Y402H and ARMS A69S) indicated that the C-T combination conferred an odds ratio (95% confidence interval) of 6.9 (3.2-14.8). The exposed attributable risk for this particular haplotype was 85.5%.

CONCLUSIONS: This is the first case-control investigation of AMD-high risk alleles in a Latino population. Our results support that CFH, ARMS2, and CFB AMD-risk alleles are consistently associated with the disease, even in ethnic groups with a complex admixture of ancestral populations such as Mexican mestizos.

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Epidemiology

Am J Ophthalmol. 2012 Oct 27. pii: S0002-9394(12)00582-X. doi: 10.1016/j.ajo.2012.08.011. [Epub ahead of print]

Prevalence and Genomic Association of Reticular Pseudodrusen in Age-Related Macular Degeneration.

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PURPOSE: To survey the prevalence of reticular pseudodrusen in late age-related macular degeneration (AMD) using multiple imaging methods, and to investigate the association between reticular pseudodrusen and polymorphisms in complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) genes.

DESIGN: Retrospective case series.

METHODS: This study included 216 consecutive patients with late AMD (typical AMD, polypoidal choroidal vasculopathy [PCV], retinal angiomatous proliferation [RAP], or geographic atrophy). Eyes were assessed for reticular pseudodrusen using the blue channel of color fundus photography, infrared reflectance, fundus autofluorescence, and spectral-domain optical coherence tomography. The major AMD-associated single nucleotide polymorphisms (CFH Y402 rs1061170, CFH I62V rs800292, and ARMS2 A69S rs10490924) were genotyped.

RESULTS: Forty-nine eyes of 30 patients had a reticular pattern in ≥ 2 imaging modalities and were diagnosed with reticular pseudodrusen. Of these, 16 had bilateral late AMD, whereas 32 of 186 patients without reticular pseudodrusen had bilateral late AMD ($P < .001$). The prevalence of reticular pseudodrusen was 83% in RAP, 50% in geographic atrophy, 9% in typical AMD, and 2% in PCV. The frequency of the T allele in ARMS2 A69S in patients with and without reticular pseudodrusen was 78.6% and 59.9%, respectively ($P=.007$).

CONCLUSIONS: The prevalence of reticular pseudodrusen was low in PCV cases. About 50% of patients with reticular pseudodrusen had bilateral late AMD. The connection of ARMS2 risk allele and reticular pseudodrusen was confirmed in a Japanese population.

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Diet

Invest Ophthalmol Vis Sci. 2012 Oct 30. pii: iovs.11-9367v1. doi: 10.1167/iov.11-9367. [Epub ahead of print]

Education is positively associated with macular pigment: the Irish Longitudinal Study on Ageing (TILDA).

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PURPOSE: The three carotenoids lutein, zeaxanthin, and meso-zeaxanthin, are found at the macula and referred to as macular pigment (MP). This study was undertaken to investigate determinants of MP in a large randomly selected sample from the Republic of Ireland (as part of The Irish Longitudinal Study on Ageing [TILDA]).

METHODS: MP optical density (MPOD) was measured using customized heterochromatic flicker photometry in 4,373. Socio-demographic and self-reported health data was obtained using computer assisted personal interview (CAPI).

RESULTS: Mean (SD) MPOD for the study group was 0.203 (0.156) with a range of 0 to 1.01. MPOD was higher for participants with secondary education [mean (SD) = 0.205 (0.148)] than for those with only primary education or no education [mean (SD) = 0.183 (0.113); $p < 0.001$]. MPOD was also higher for those with tertiary education [mean (SD) = 0.232 (0.231)] compared with primary/no education or secondary education ($p < 0.001$ for both comparisons).

CONCLUSIONS: We report that MP is lower amongst those participants of a population-representative study who did not have secondary or third level education when compared to participants who had such education. Given the emerging evidence that MP is important for visual performance and comfort, and given the putative protection that this pigment confers against age-related macular degeneration (especially important in the context of increased risk of AMD in this social group), public health measures aimed at improving diet for this at-risk population need to be considered.

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Indian J Clin Biochem. 2001 Jan;16(1):9-14. doi: 10.1007/BF02867562.

Antioxidants: Basis concepts in relation to the eye.

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Abstract: Antioxidants are a small group of substances that protect living cells from the destructive consequences of powerful oxidizing intermediates that can be formed from oxygen. Situations in which pro-oxidant mechanisms within the body are more active than the antioxidant mechanisms (oxidative stress) predispose and contribute to the pathogenesis of several ailments in various organs of the body. In the eye, pro-oxidant factors have been blamed for the causation of diseases such as age related macular degeneration and senile cataract. The role of pro-oxidants in the genesis of certain diseases is well established however, the effectivity of antioxidants provided to the body by dietary supplementation is inconclusive. In this article we provide a review on the basic concepts of antioxidant-pro-oxidant interaction in relation to its effects on the eye.

PMID: 23105286 [PubMed]

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