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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

Retina. 2012 Dec 21. [Epub ahead of print]

CHANGES IN VISUAL ACUITY IN PATIENTS WITH WET AGE-RELATED MACULAR DEGENERATION TREATED WITH INTRAVITREAL RANIBIZUMAB IN DAILY CLINICAL PRACTICE: The Lumiere Study.

Cohen SY, Mimoun G, Oubraham H, Zourdani A, Malbrel C, Queré S, Schneider V; for the LUMIERE Study Group.

*Centre Ophtalmologique d'Imagerie et de Laser, Paris, France †Centre d'Imagerie de l'Ecole Militaire, Paris, France ‡Departement of Ophthalmology, Centre Hospitalier, Orleans, France §Private Practice, Nice, France ¶Clinique Courlancy, Reims, France **Novartis Pharma SAS, Rueil Malmaison, France.

PURPOSE: To survey compliance with recommended intravitreal ranibizumab treatment protocols in daily clinical practice in France, with reference to outcomes.

METHODS: A retrospective, descriptive, observational study in patients with subfoveal wet age-related macular degeneration treated with ranibizumab. All historical data for the study period, including demographic, treatment, and disease details and visual acuity measurements (baseline, Month 3, and Month 12), were recorded retrospectively at least 12 months after the beginning of treatment.

RESULTS: In 551 patients followed by 16 ophthalmologists, 12 months of intravitreal ranibizumab treatment induced a mean visual acuity gain of 3.2 ± 14.8 Early Treatment Diabetic Retinopathy Study-equivalent letters. Fewer than 40% of patients received the recommended treatment of initial 3 monthly injections. More than 50% had to wait >8 days between diagnosis and treatment. At Month 3, visual acuity gain was greater in patients who had received recommended induction and in whom treatment was initiated quickly. At Month 12, the induction-related effect had largely disappeared but the time-to-treatment effect persisted. Patients had an average of 5.1 injections (2.6 during induction period). No patients were monitored monthly as stipulated in the guidelines.

CONCLUSION:: Although poor compliance with recommendations has been reflected in mediocre outcomes, there is evidence that practice is improving.

PMID: 23266880 [PubMed - as supplied by publisher]

Arq Bras Oftalmol. 2012 Aug;75(4):273-6.

Intravitreal ranibizumab and bevacizumab therapy for choroidal neovascularization in age-related

macular degeneration with extensive pre-existing geographic atrophy.

Amaro MH, Roller AB.

Instituto de Olhos e Laser de Belém, Belém, PA, Brazil.

PURPOSE: To report the response of choroidal neovascularization to intravitreal ranibizumab or bevacizumab treatment in the setting of age-related macular degeneration with extensive pre-existing geographic atrophy of the retinal pigment epithelium.

METHODS: This is a retrospective case series of 11 eyes in ten consecutive patients retrieved from a photographic database. The patients were treated with ranibizumab or bevacizumab for neovascular age-related macular degeneration with pre-existing geographic atrophy. Patients were included if they had geographic atrophy at or adjacent to the foveal center of at least 1 disc area in size that was present before the development of choroidal neovascularization. The best corrected visual acuity and optical coherence tomography analysis of the central macular thickness were recorded for each visit. Serial injections of ranibizumab or bevacizumab were administered until there was complete resolution of subretinal fluid on optical coherence tomography. Data over the entire follow-up period were analyzed for overall visual and optical coherence tomography changes.

RESULTS: The patients received an average of 7 ± 3 intravitreal injections over the treatment period. Seven of 11 eyes had reduced retinal thickening on optical coherence tomography. On average, the central macular thickness was reduced by 72 ± 115 μm. Six of these 7 eyes had improvement of one or more lines of vision and one had no change. The average acuity change for all patients was -0.04 ± 0.46 logMAR units, which corresponded to a gain of 0.2 ± 4.4 lines of Snellen acuity. The treatment resulted in a good anatomic response with resolution of the subretinal fluid and overall stable visual acuity.

CONCLUSIONS: The results of this case series suggest that the use of an intravitreal anti-vascular endothelial growth factor (VEGF) agent (ranibizumab or bevacizumab) for choroidal neovascularization in age-related macular degeneration with pre-existing geographic atrophy is effective. Our results are not as striking as published results from large-scale trials of anti-vascular endothelial growth factor therapy for subfoveal choroidal neovascularization, presumably due to the limitation in the baseline visual acuity caused by the underlying geographic atrophy. The favorable anatomic response with the resolution of subretinal fluid and stable acuity were consistent with other ranibizumab and bevacizumab studies.

PMID: 23258660 [PubMed - in process]

Retina. 2012 Dec 21. [Epub ahead of print]

THE EFFECTS OF AFLIBERCEPT ON THE VIABILITY AND METABOLISM OF OCULAR CELLS IN VITRO.

Ammar DA, Mandava N, Kahook MY.

Department of Ophthalmology, University of Colorado School of Medicine, Aurora, Colorado.

PURPOSE: To investigate the effects of the vascular endothelial growth factor-neutralizing agent aflibercept on primary cultures of human trabecular meshwork cells (hTMC), human scleral fibroblasts (hFibro), and a retinal pigment epithelial cell line (ARPE-19).

METHODS:: Various concentrations of aflibercept were incubated with confluent cell cultures for 24 hours. Ranibizumab was used as an active control for comparison. Assays of cellular metabolism (MTT assay) and cell viability (calcein dye uptake) were performed.

RESULTS: Compared with untreated controls (100% live), a 24-hour exposure to 1 mg/mL aflibercept had no significant effect on cell viability in hTMC (100.1 ± 1.7%), hFibro (102.4 ± 2.4%), or ARPE-19 (99.3 ±

3.9%) cells. Aflibercept vehicle controls also had no detrimental effect. Aflibercept (1 mg/mL) had no statistically significant effect on metabolic activity in hTMC (84.3 ± 10.2%), hFibro (102.7 ± 4.3%), and ARPE-19 (104.6 ± 12.6%) cells. When compared side-by-side in ARPE-19 cells, aflibercept and the anti-vascular endothelial growth factor agent ranibizumab had no toxicity at the highest concentration tested (1 mg/mL).

CONCLUSION: The authors' data reveal that concentrations of aflibercept in the range expected to occur in the human vitreous after intraocular injection are not harmful in an in vitro cell assay.

PMID: 23266881 [PubMed - as supplied by publisher]

Ophthalmologica. 2012 Dec 14. [Epub ahead of print]

Intravitreal Ranibizumab for Acute Central Serous Chorioretinopathy.

Kim M, Lee SC, Lee SJ.

Department of Ophthalmology, School of Medicine, Kangwon National University, Chuncheon, Republic of Korea.

Background/Aims: To evaluate the effectiveness of intravitreal ranibizumab injection (IVRI) for acute central serous chorioretinopathy (CSC).

Methods: Patients with symptomatic CSC of less than 3 months were prospectively recruited. Patients (n = 20/group) were randomly assigned to IVRI (0.5 mg/0.05 ml) or observation and followed for 6 months. logMAR best-corrected visual acuity (BCVA), fluorescein angiography, indocyanine angiography, and central foveal thickness (CFT) were assessed at baseline and at regular follow-ups.

Results: All patients had increased BCVA, decreased CFT, and resolution of the neurosensory detachment. Complete resolution of neurosensory retinal detachment required more time in the observation group (13.0 ± 3.1 vs. 4.2 ± 0.9 weeks; $p < 0.001$). Mean BCVA and mean CFT improved significantly in both groups, but the changes were not significantly different between groups at 6 months.

Conclusions: IVRI for acute CSC might hasten resolution of neurosensory detachment compared to observation alone. At 6 months, BCVA and CFT did not differ between IVRI and observation groups. Further studies are required to determine the long-term benefits of IVRI.

PMID: 23257663 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Dec 14. doi: 10.1111/aos.12018. [Epub ahead of print]

Comparison of Ranibizumab monotherapy versus combination of Ranibizumab with photodynamic therapy with neovascular age-related macular degeneration.

Krebs I, Vécsei Marlovits V, Bodenstorfer J, Glittenberg C, Ansari Shahrezaei S, Ristl R, Binder S.

The Ludwig Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery, Vienna, Austria Department of Ophthalmology, Rudolph Foundation Clinic, Vienna, Austria Department of Ophthalmology, Hospital Hietzing, Vienna, Austria Department of Ophthalmology, Medical Center East, Vienna, Austria Center for Medical Statistics, Informatics, and Intelligent Systems, Section for Medical Statistics, Medical University, Vienna, Austria.

Purpose: Modern therapy of neovascular age-related macular degeneration consists in intravitreal injections of inhibitors of the vascular endothelial growth factor. An increasing number of these injections is required not only in monthly but also in as-needed treatment regimen. In this study, it should be examined whether an additional administered photodynamic therapy (PDT) can considerably reduce the number of

injection.

Methods: In this prospective, randomized study carried out in three large hospitals of Vienna eyes with neovascular age-related macula degeneration were included. Patients were randomized to either Ranibizumab monotherapy or combined standard fluence PDT and Ranibizumab therapy. All patients received a loading dose of three intravitreal Ranibizumab injections and were thereafter treated in an as-needed regimen based on distance acuity and retinal thickness values. In the combined treatment group, PDT was administered 1 day after the first Ranibizumab injection.

Results: Fifty-one patients were randomized, 44 were finally included (four screening failures and three withdrawals). Twenty-four patients were assigned to the monotherapy and 20 patients to the combined treatment group. Fewer injections were required in the combined treatment group (4.7 versus 6.3). Overall the patients lost 0.5 letters; in the combined treatment group, the patients lost mean 7.1 letters; in the monotherapy group, they gained mean 5.1 letters. Retinal thickness decreased significantly in both groups.

Conclusion: A significant reduction of the number of required intravitreal injections could be achieved by the additional PDT treatment, but was accompanied by a worse functional outcome in this group.

PMID: 23241227 [PubMed - as supplied by publisher]

J Korean Med Sci. 2012 Dec;27(12):1580-5. doi: 10.3346/jkms.2012.27.12.1580. Epub 2012 Dec 7.

Comparison of Systemic Adverse Events Associated with Intravitreal Anti-VEGF Injection: Ranibizumab versus Bevacizumab.

Hwang DJ, Kim YW, Woo SJ, Park KH.

Department of Ophthalmology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea.

Abstract: The aim of this study was to compare the incidence of systemic adverse events in patients treated with intravitreal injections of bevacizumab or ranibizumab, and to evaluate whether compared to ranibizumab administration, bevacizumab constitutes a higher risk for systemic adverse events. A retrospective review was conducted for 916 consecutive patients treated with at least 1 intravitreal injection of bevacizumab or ranibizumab. Cox regression was performed to assess whether a variable had predictive value for occurrence of new systemic adverse events and to account for different follow-up times. A total of 702 patients were analyzed; 503 patients received bevacizumab alone, and 199 patients received ranibizumab alone. Systemic adverse events occurred in 10 of 702 patients (1.4%): 7 in the bevacizumab group (7/503; 1.4%) and 3 in the ranibizumab group (3/199; 1.5%). This difference was not statistically significant (Fisher's exact test, P = 0.573). Cox proportional hazards analysis of 4 models did not reveal a covariate that significantly changed the hazard for systemic adverse events. In conclusion, compared to ranibizumab, bevacizumab may not increase the risk of systemic adverse events in patients receiving intravitreal injections.

PMID: 23255862 [PubMed - in process] PMCID: PMC3524442

J Ophthalmol. 2012;2012:690641. doi: 10.1155/2012/690641. Epub 2012 Nov 28.

Fixed Monthly versus Less Frequent Ranibizumab Dosing and Predictors of Visual Response in Exudative Age-Related Macular Degeneration.

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Purpose: To examine temporal patterns of visual acuity (VA) response to pooled 0.3 mg/0.5 mg ranibizumab treatment in patients with age-related macular degeneration and identify potential baseline predictors of response.

Design: Retrospective analysis. Methods. Results from 1824 ranibizumab-treated patients receiving fixed monthly, quarterly, or as-needed dosing after three monthly loading doses in four phase III/IIIb trials (ANCHOR, MARINA, PIER, and SAILOR) were analyzed.

Results: At month 3, 14.9% to 29.4% of patients had gained ≥15 letters. Not all patients achieved peak gains at month 3; many continued to have VA increases throughout treatment. After three monthly loading doses, continued monthly dosing resulted in further gains, as there were more delayed 15-letter responders at month 12 (14.7-16.1%) than with less frequent dosing (5.0-6.0%). Monthly dosing also resulted in more patients maintaining VA gains at later time points. Early 15-letter responders had lower baseline mean VA than delayed 15-letter responders in ANCHOR and MARINA; no other differences in baseline characteristics were noted.

Conclusions: Although some patients have rapid improvements in VA, others do not experience peak VA until later during treatment. Continued monthly dosing resulted in a greater percentage of patients gaining ≥15 letters than with switching to less frequent dosing regimens.

PMID: 23251787 [PubMed] PMCID: PMC3515919

Ther Adv Chronic Dis. 2011 Sep;2(5):325-31. doi: 10.1177/2040622311415895.

Age-related macular degeneration: current treatment and future options.

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Abstract: Age-related macular degeneration is the leading cause of visual impairment among older adults in the developed world. Epidemiological studies have revealed a number of genetic, ocular and environmental risk factors for this condition, which can be addressed by disease reduction strategies. We discuss the various treatment options for dry and exudative age-related macular degeneration available and explain how the recommended treatment depends on the exact type, location and extent of the degeneration. Currently, vascular endothelial growth factor (VEGF) inhibition therapy is the best available treatment for exudative age-related macular degeneration but is limited by the need for repeated intravitreal injections. The current treatment regime is being refined through research on optimal treatment frequency and duration and type of anti-VEGF drug. Different modes of drug delivery are being developed and in the future other methods of VEGF inhibition may be used.

PMID: 23251758 [PubMed] PMCID: PMC3513889

Clinicoecon Outcomes Res. 2012;4:361-74. doi: 10.2147/CEOR.S37458. Epub 2012 Dec 6.

The use of comparative effectiveness research to inform policy decisions on the inclusion of bevacizumab for the treatment of macular diseases in Thailand's pharmaceutical benefit package.

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Abstract: There is increasing impetus to use pharmaceutical interventions, ie, ranibizumab or bevacizumab, for the treatment of particular macular diseases. This paper describes the evidence and decision-making of the National List of Essential Medicines Committee that recently announced the inclusion of bevacizumab for the treatment of macular diseases in its pharmaceutical benefit package. The findings of a systematic review and meta-analysis in this paper indicate that the intravitreal administration of bevacizumab is superior to nonpharmaceutical treatments for age-related macular degeneration (AMD) and diabetic macular edema (DME), but inconclusive for retinal vein occlusion, given the limited evidence. The study also failed to distinguish among the differences in terms of visual acuity improvement, reduction of central macular thickness, and response to treatment between AMD and DME patients treated with bevacizumab and those treated with ranibizumab. Although bevacizumab was not licensed for AMD and DME, the committee decided to include bevacizumab in the National List of Essential Medicines. It is expected that many patients who are in need of treatment but who are unable to afford the expensive alternative drug, ranibizumab, will be able to receive this effective treatment instead and be prevented from suffering irreversible loss of vision. At the same time, this policy will help generate evidence about the real-life effectiveness and safety profiles of the drug for future policy development in Thailand and other settings.

PMID: 23248574 [PubMed] PMCID: PMC3520463

Case Report Ophthalmol. 2012 Sep;3(3):298-303. doi: 10.1159/000342848. Epub 2012 Sep 12.

Intravitreal ranibizumab and laser photocoagulation in the management of idiopathic juxtafoveolar retinal telangiectasia type 1: a case report.

Ciarnella A, Verrilli S, Fenicia V, Mannino C, Cutini A, Perdicchi A, Recupero SM.

Ophthalmology Unit, NESMOS Department, S. Andrea Hospital, Faculty of Medicine and Psychology, 'Sapienza' University of Rome, Rome, Italy.

BACKGROUND: Idiopathic juxtafoveolar retinal telangiectasia (IJRT) type 1 represents an uncommon cause of congenital unilateral visual loss and it typically affects males. Decrease in visual acuity is caused by serous and lipid exudation into the fovea with cystoid macular edema. In some cases, spontaneous resolution may be observed, but when there is a progressive loss of visual acuity, laser photocoagulation is often necessary. This treatment is not always successful and therapy for this condition is still controversial.

CASE PRESENTATION: A 57-year-old man referred a 2-month history of blurred and distorted vision in the right eye. Best-corrected visual acuity was 20/50 in the right eye and 20/20 in the left eye. Fundus examination showed temporal macular edema, confirmed by optical coherence tomography. Fluorescein angiography showed a localized area of hyperfluorescence probably due to telangiectasia type 1 located below the inferior temporal area of the fovea. A combined therapy of intravitreal ranibizumab injection and laser photocoagulation was performed. Visual acuity improved from 20/50 to 20/32 and the therapy was well tolerated by the patient. After 3 years of follow-up, both visual acuity and fundus examination were stable.

CONCLUSIONS: This case suggests that the combined use of ranibizumab and laser photocoagulation may be considered an effective treatment for JRT type 1, leading to an improvement in both visual acuity and macular edema. We believe that intravitreal ranibizumab injection associated with laser photocoagulation should be considered as treatment for IJRT type 1.

PMID: 23275792 [PubMed] PMCID:PMC3530150

Case Report Ophthalmol. 2012 Sep;3(3):283-5. doi: 10.1159/000342693. Epub 2012 Sep 5.

Rhizobium radiobacter Endophthalmitis following Intravitreal Ranibizumab Injection.

Joshi L, Morarji J, Tomkins-Netzer O, Lightman S, Taylor SR.

Royal Surrey County Hospital NHS Foundation Trust, Guildford ; UCL Institute of Ophthalmology.

Abstract: We present the first reported case of acute endophthalmitis due to Rhizobium radiobacter after an intravitreal injection of ranibizumab for neovascular age-related macular degeneration.

PMID: 23275789 [PubMed] PMCID: PMC3530142

Acta Ophthalmol. 2012 Dec 31. doi: 10.1111/aos.12014. [Epub ahead of print]

Intravitreal ranibizumab for diabetic macular oedema: 1-year experiences in a clinical setting.

Brynskov T, Laugesen CS, Sørensen TL.

Clinical Eye Research Unit, Department of Ophthalmology, Copenhagen University Hospital, Roskilde, Denmark The University of Copenhagen, Copenhagen, Denmark.

PMID: 23280048 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Jan;120(1):221. doi: 10.1016/j.ophtha.2012.07.069.

Ranibizumab for diabetic macular edema.

Mayor R, Agarwal M, Singh S, Venkatesh R.

Vitreo Retina Services, Dr. Shroff's Charity Eye Hospital, Delhi, India.

PMID: 23283200 [PubMed - in process]

Other treatment & diagnosis

Aging (Albany NY). 2012 Dec 20. [Epub ahead of print]

Chronic oxidative stress upregulates Drusen-related protein expression in adult human RPE stem cell-derived RPE cells: A novel culture model for dry AMD.

Rabin DM, Rabin RL, Blenkinsop TA, Temple S, Stern JH.

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Purpose: The goal of this study was to examine changes in the expression of transcripts and proteins associated with drusen in Age-related Macular Degeneration (AMD) after exposing human retinal pigment epithelium (hRPE) cells to chronic oxidative stress.

Methods: Primary adult human RPE cells were isolated from cadaveric donor eyes. The subpopulation of RPE stem cells (RPESCs) was activated, expanded, and then differentiated into RPE progeny. Confluent cultures of RPESC-derived hRPE and ARPE-19 cells were exposed to a regimen of tert-butylhydroperoxide (TBHP) for 1-5 days. After treatment, gene expression was measured by quantitative PCR (qPCR), protein expression was assessed by immunocytochemistry and transepithelial resistance and cell toxicity were measured.

Results: hRPE cells exposed to a regimen of TBHP for 5 days upregulate expression of several molecules identified in drusen, including molecular chaperones and pro-angiogenic factors. 5-day TBHP treatment was significantly more effective than 1-day treatment at eliciting these effects. The extent of hRPE re-

sponse to 5-day treatment varied significantly between individual donors, nevertheless, 6 transcripts were reliably significantly upregulated. ARPE-19 cells treated with the same 5-day stress regime did not show the same pattern of response and did not upregulate this group of transcripts.

Conclusions: RPESC-derived hRPE cells change significantly when exposed to repeated oxidative stress conditions, upregulating expression of several drusen-related proteins and transcripts. This is consistent with the hypothesis that hRPE cells are competent to be a source of proteins found in drusen deposits. Our results suggest that donor-specific genetic and environmental factors influence the RPE stress response. ARPE-19 cells appear to be less representative of AMD-like changes than RPESC-derived hRPE. This adult stem cell-based system using chronic TBHP treatment of hRPE represents a novel in vitro model useful for the study of drusen formation and dry AMD pathophysiology.

PMID: 23257616 [PubMed - as supplied by publisher]

Retina. 2012 Dec 21. [Epub ahead of print]

SUBRETINAL DRUSENOID DEPOSITS IN NON-NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: Morphology, Prevalence, Topography, and Biogenesis Model.

Curcio CA, Messinger JD, Sloan KR, McGwin G, Medeiros NE, Spaide RF.

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PURPOSE: To characterize the morphology, prevalence, and topography of subretinal drusenoid deposits, a candidate histological correlate of reticular pseudodrusen, with reference to basal linear deposit (BlinD), a specific lesion of age-related macular degeneration, and to propose a biogenesis model for both lesion.

METHODS: Donor eyes with median death-to-preservation of 2:40 hours were postfixed in osmium tannic acid paraphenylenediamine and prepared for macula-wide high-resolution digital sections. Annotated thicknesses of 21 chorioretinal layers were determined at standard locations in sections through the fovea and the superior perifovea.

RESULTS: In 22 eyes of 20 white donors (83.1 ± 7.7 years), SDD appeared as isolated or confluent drusenoid dollops punctuated by tufts of retinal pigment epithelium apical processes and associated with photoreceptor perturbation. Subretinal drusenoid deposits and BlinD were detected in 85 and 90% of non-neovascular age-related macular degeneration donors, respectively. Subretinal drusenoid deposit was thick (median, 9.4 μm) and more abundant in the perifovea than in the fovea ($P < 0.0001$). BlinD was thin (median, 2.1 μm) and more abundant in the fovea than in the perifovea ($P < 0.0001$).

CONCLUSION: Subretinal drusenoid deposits and BlinD prevalence in age-related macular degeneration eyes are high. Subretinal drusenoid deposits organized morphology, topography, and impact on surrounding photoreceptors imply specific processes of biogenesis. Contrasting topographies of subretinal drusenoid deposits and BlinD suggest relationships with differentiable aspects of rod and cone physiology, respectively. A 2-lesion 2-compartment biogenesis model incorporating outer retinal lipid homeostasis is presented.

PMID: 23266879 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2012 Dec 21. [Epub ahead of print]

Drusen detection by confocal aperture-modulated infrared scanning laser ophthalmoscopy.

Diniz B, Ribeiro RM, Rodger DC, Maia M, Sadda S.

Doheny Eye Institute, Los Angeles, California, USA.

AIM: To evaluate the efficiency of drusen detection by scanning laser ophthalmoscopy (SLO) using various infrared confocal apertures and differential contrast (DC) strategies.

METHODS: 11 eyes with non-neovascular age-related macular degeneration (AMD) underwent infrared imaging with a Nidek F-10 confocal SLO using multiple confocal apertures: central, ring, aperture on the right side (AR) and left side (AL), with and without use of the DC. A conventional colour fundus photograph was also obtained. Images were exported into a certified grading tool and all visible drusen were manually outlined by two graders. For each image type, the number of drusen and total drusen area were calculated, and the measurements obtained by the two graders were averaged. Intergrader reliability was evaluated, and paired t tests compared measurements between the various aperture/DC modes and the colour image.

RESULTS:Agreement between graders was high (r=0.93-0.98). Drusen number values obtained with the AR (121.0, p=0.01) mode were higher than for the colour photographs (69.1). Area measurements were also significantly higher in the AR (1.93 mm(2); p=0.04) and AL modes (1.41 mm(2); p=0.03) when compared with the colour photographs (1.24 mm(2)). The addition of the DC did not seem to improve drusen detection compared with the unmodified infrared images.

CONCLUSIONS:In this pilot study, drusen number and area grades were significantly higher using the AR and AL in which the laterally scattered light is captured (retromode). Use of the lateral confocal aperture may highlight subclinical drusen and aid in monitoring disease progression and response to emerging non-neovascular AMD therapies.

PMID: 23264545 [PubMed - as supplied by publisher]

Regen Med. 2012 Nov;7(6 Suppl):136-8. doi: 10.2217/rme.12.73.

Global Update: UK.

Culme-Seymour EJ.

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Abstract: 2012 has been an exciting year in the UK with substantial development on every front - research, clinical, industry and government. In particular, the focus has now moved to encompass far more post-research activities, with the continued enrolment of patients onto two pioneering Phase I clinical trials: ReNeuron's ReN001 stem cell therapy for stroke (PISCES) in Southern General Hospital, Greater Glasgow and Advanced Cell Technology's retinal pigment epithelial cells derived from human embryonic stem cells for Stargardts macular dystrophy and dry age-related macular degeneration at Moorfields Eye Hospital, London. The funding landscape for the sector has evolved from previous years to more fully embrace development and translation, including the provision of £180 million available for biomedical research via the Biomedical Catalyst Fund (joint Technology Strategy Board and Medical Research Council [MRC] funding) and a further £25 million through the UK Research Council's UK Regenerative Medicine Platform initiative, as well as ongoing developments with the Cell Therapy Catapult, which all act to further encourage a pan-UK collaborative environment. Overall, the UK cell therapy community continues to thrive and impact heavily upon the worldwide sector, with an established research base, a solid approach to translation and a small but growing commercial sector that is going from strength to strength.

PMID: 23210827 [PubMed - in process]

Regen Med. 2012 Nov;7(6 Suppl):32-9. doi: 10.2217/rme.12.77.

Ophthalmologic stem cell transplantation therapies.

Blenkinsop TA, Corneo B, Temple S, Stern JH.

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Abstract: Vision loss is a major social issue, with more than 20 million people over the age of 18 years affected in the USA alone. Loss of vision is feared more than premature death or cardiovascular disease, according to a recent Society for Consumer Research group survey. The annual direct cost of medical care for the most prevalent eye disease, age-related macular degeneration, was estimated at US$255 billion in 2010 with an additional economic impact of US$88 billion due to lost productivity and the burden of family and community care for visual disability. With the blossoming of human stem cell research, regenerative treatments are now being developed that can help reduce this burden. Positive results from animal studies demonstrate that stem cell-based transplants can preserve and potentially improve vision. This has led to new clinical trials for several eye diseases that are yielding encouraging results. In the next few years, additional trials and longer-term results are anticipated to further develop ocular regenerative therapies, with the potential to revolutionize our approach to ophthalmic disease and damage.

PMID: 23210809 [PubMed - in process]

Sensors (Basel). 2012 Dec 27;13(1):334-66. doi: 10.3390/s130100334.

Adaptive optics technology for high-resolution retinal imaging.

Lombardo M, Serrao S, Devaney N, Parravano M, Lombardo G.

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Abstract: Adaptive optics (AO) is a technology used to improve the performance of optical systems by reducing the effects of optical aberrations. The direct visualization of the photoreceptor cells, capillaries and nerve fiber bundles represents the major benefit of adding AO to retinal imaging. Adaptive optics is opening a new frontier for clinical research in ophthalmology, providing new information on the early pathological changes of the retinal microstructures in various retinal diseases. We have reviewed AO technology for retinal imaging, providing information on the core components of an AO retinal camera. The most commonly used wavefront sensing and correcting elements are discussed. Furthermore, we discuss current applications of AO imaging to a population of healthy adults and to the most frequent causes of blindness, including diabetic retinopathy, age-related macular degeneration and glaucoma. We conclude our work with a discussion on future clinical prospects for AO retinal imaging.

PMID: 23271600 [PubMed - in process]

Retina. 2013 Jan;33(1):56-62. doi: 10.1097/IAE.0b013e3182641875.

Prospective study of peripheral panretinal photocoagulation of areas of nonperfusion in central retinal vein occlusion.

Spaide RF.

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PURPOSE: To investigate the effect that panretinal photocoagulation to peripheral areas of retinal vascular

nonperfusion has on the visual acuity and injection frequency of ranibizumab in eyes with previous central retinal vein occlusion.

METHODS: Patients enrolled in a prospective study of ranibizumab for central retinal vein occlusion were imaged with wide-field angiography using the Optos P200 system. Laser photocoagulation was carried out and the extent of laser photocoagulation was evaluated with repeat wide-field angiography. Injection of ranibizumab was based on an as needed strategy throughout the study. The injection frequency in the 6 months before laser was compared with a 6-month period starting 2 months after the laser photocoagulation. The visual acuity was measured by Early Treatment Diabetic Retinopathy Study protocol refraction at both the end of the 6-month follow-up period and at the time of laser photocoagulation.

RESULTS: There were 10 patients treated in this study with a mean number of 1,757 spots of laser photocoagulation in the peripheral retina. The injection frequency in the 6-month lead-in period was 3.4 and in the 6-month follow-up period was 3.1, a difference that was not significant (P = 0.26). The visual acuity at the time of laser photocoagulation was 54.2 letters (approximate Snellen equivalent of 20/80) and at the end of the observation period was 51.4 letters, a difference that was not significant (P = 0.33).

CONCLUSION: In this small study, laser photocoagulation to peripheral areas of nonperfusion as visualized by wide-field angiography did not result in either decreased injection frequency or improved visual acuity in eyes with central retinal vein occlusion treated with ranibizumab.

PMID:23269405 [PubMed - in process]

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Repair of the degenerate retina by photoreceptor transplantation.

Barber AC, Hippert C, Duran Y, West EL, Bainbridge JW, Warre-Cornish K, Luhmann UF, Lakowski J, Sowden JC, Ali RR,Pearson RA.

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Abstract: Despite different aetiologies, age-related macular degeneration and most inherited retinal disorders culminate in the same final common pathway, the loss of photoreceptors. There are few treatments and none reverse the loss of vision. Photoreceptor replacement by transplantation is proposed as a broad treatment strategy applicable to all degenerations. Recently, we demonstrated restoration of vision following rod-photoreceptor transplantation into a mouse model of stationary night-blindness, raising the critical question of whether photoreceptor replacement is equally effective in different types and stages of degeneration. We present a comprehensive assessment of rod-photoreceptor transplantation across six murine models of inherited photoreceptor degeneration. Transplantation is feasible in all models examined but disease type has a major impact on outcome, as assessed both by the morphology and number of integrated rod-photoreceptors. Integration can increase (Prph2(+/Δ307)), decrease (Crb1(rd8/rd8), Gnat1(-/-), Rho(-/-)), or remain constant (PDE6β(rd1/rd1), Prph2(rd2/rd2)) with disease progression, depending upon the gene defect, with no correlation with severity. Robust integration is possible even in late-stage disease. Glial scarring and outer limiting membrane integrity, features that change with degeneration, significantly affect transplanted photoreceptor integration. Combined breakdown of these barriers markedly increases integration in a model with an intact outer limiting membrane, strong gliotic response, and otherwise poor transplantation outcome (Rho(-/-)), leading to an eightfold increase in integration and restoration of visual function. Thus, it is possible to achieve robust integration across a broad range of inherited retinopathies. Moreover, transplantation outcome can be improved by administering appropriate, tailored manipulations of the recipient environment.

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Int J Ophthalmol. 2012;5(6):708-13. doi: 10.3980/j.issn.2222-3959.2012.06.11. Epub 2012 Dec 18.

Effects of major ozonated autohemotherapy in the treatment of dry age related macular degeneration: a randomized controlled clinical study.

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AIM: To evaluate the effect of systemic ozonated major autohaemotherapy (O(3)-AHT) in patients affected by dry age related macular degeneration (AMD).

METHODS: This study was a randomized, controlled clinical study. One hundred and forty patients with the diagnosis of AMD in both eyes, with the study eye presenting dry AMD and soft drusen, were randomly assigned in a 1:1 ratio to either receive 27 major ozonated autohemotherapy treatments during 12-month period, or a standardized multi-vitamin therapy. Primary outcome was the change in best corrected visual acuity (mean logMar change) between the baseline and 6 and 12 months, end point of the study. In addition, to investigate the safety of prolonged ozonated autohaemotherapy, we measured the routine haematochemical parameters and biochemical oxidative stress values at baseline and after 12 months treatment time.

RESULTS: The mean baseline best corrected visual acuity in study eyes was 0.36 in the treatment group and 0.38 in the control group (difference not statistically significant). At the primary endpoint, 6 months post -baseline, the mean logMAR change in the treated group improved by 0.1 and the values of the control group at the same time impaired by 0.2 respect to the baseline. Four percent and twenty-five percent of eyes in the group treated with O(3)-AHT gained 1 or more lines after 6 and 12 months respectively compared to 0% in the eyes which received no treatment ($P<0.05$ at 12 months). None of the treated patients experienced a loss in visual acuity in their study eye at 6 and 12 months, compared to 16% and 40 % of patients in the control group who lost 2 lines or more at 6 months and 12 months respectively ($P<0.05$ treated vs control group)). Major ozonated autohemotherapy was shown to be safe and well- tolerated by the patients. Moreover, the haematochemical parameters showed a decrease in the Reactive Oxygen Metabolites (300±10.1 UCARR at 12 months compared to a baseline value of 380±10.4 UCARR, $P<0.05$) and an increase in Biological Antioxidant Potential plasma values (2100±34.8 micromoles/ C vitamin after 12 months compared to the baseline value of 1610±36.2, $P<0.05$) in the treated patients when compared to the control group. This data suggests that major ozonated autohaemotherapy may exert a role in reducing oxidative stress by endogenously stimulating the production of antioxidant molecules.

CONCLUSION: The results of this study suggests that major ozonated autohaemotherapy could be a safe and effective therapeutic option for high-risk patients with dry AMD, and that a series of such treatments could improve the natural course of AMD.

PMID: 23275905 [PubMed] PMCID: PMC3530813

Wideochir Inne Tech Malo Inwazyjne. 2012 Aug;7(3):220-3. doi: 10.5114/wiitm.2011.28910. Epub 2012 Jun 22.

A pedicled autologous choroid RPE patch: a technique to preserve perfusion.

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Abstract: The aim of the study is to report a technique of a pedicled autologous choroid retinal pigment epithelium (RPE) patch that aims to preserve perfusion of the transplanted tissue. A case report of a patient with sudden vision deterioration due to submacular hemorrhage in age-related macular degeneration. The surgery involved a 180-degree peripheral retinectomy and the creation of a pedicled graft instead of an isolated one. Outcome measures included preoperative and postoperative visual acuity and optical coherence

tomography scans at 1, 3, 6, 12 months and patch vascularization on postoperative indocyanine green angiography. Postoperatively the patch was positioned under the fovea with an intact pedicle. Indocyanine green angiography showed perfusion through the pedicle and patch vasculature on the third postoperative day. Best corrected visual acuity improved from 0.5/50 to 5/50 at 1 month and remained stable over 1 year follow-up. No choroidal neovascularization recurrence was observed. This case report demonstrates the feasibility of a pedicled RPE-choroid graft that is an alternative to a free isolated graft. Our modification of patch surgery, by demonstrating early perfusion, offers an advantage, similar to macular translocation, when photoreceptors are embedded in RPE and choroid with blood circulation immediately after the surgery.

PMID: 23256032 [PubMed] PMCID: PMC3516983

Nihon Ganka Gakkai Zasshi. 2012 Oct;116(10):937-45.

[Five-year visual outcomes of typical age-related macular degeneration and/or polypoidal choroidal vasculopathy patients who received photodynamic therapy (PDT) as initial treatment in comparison with patients prior to the PDT era]. [Article in Japanese]

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PURPOSE: To evaluate five-year visual outcomes of typical age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) in patients who received photodynamic therapy (PDT) as initial treatment compared with the outcomes of patients prior to the PDT era.

SUBJECTS AND METHODS: Twenty-three eyes observed for 5 years before PDT was available (group A: typical AMD/PCV 16 eyes/7 eyes) and 61 eyes which had been observed for 5 years after PDT with additional treatment as needed (group B: typical AMD/PCV 25 eyes/36 eyes). The visual changes in these groups were retrospectively compared.

RESULTS: In group A of typical AMD patients, the mean visual acuity (VA, logMAR) was significantly worse at the 3-year visit and later. In group B of typical AMD patients, the VA was stabilized after 2 years and no significant mean VA deterioration was observed for 5 years. More patients in group B retained a logMAR of less than 1.0 (43% vs. 25%) than in group A. Those patients in group B with PCV, maintained the VA for one year, but it gradually worsened thereafter.

CONCLUSION: The PDT shortened the duration of VA deterioration in typical AMD patients from 5 to 2 years with no significant VA decrease for 5 years. The positive effect of PDT on PCV eyes was temporary.

PMID: 23285841 [PubMed - in process]

Med Image Comput Comput Assist Interv. 2012;15(Pt 3):599-606.

Pathology hinting as the combination of automatic segmentation with a statistical shape model.

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Abstract: With improvements in acquisition speed and quality, the amount of medical image data to be screened by clinicians is starting to become challenging in the daily clinical practice. To quickly visualize and find abnormalities in medical images, we propose a new method combining segmentation algorithms

with statistical shape models. A statistical shape model built from a healthy population will have a close fit in healthy regions. The model will however not fit to morphological abnormalities often present in the areas of pathologies. Using the residual fitting error of the statistical shape model, pathologies can be visualized very quickly. This idea is applied to finding drusen in the retinal pigment epithelium (RPE) of optical coherence tomography (OCT) volumes. A segmentation technique able to accurately segment drusen in patients with age-related macular degeneration (AMD) is applied. The segmentation is then analyzed with a statistical shape model to visualize potentially pathological areas. An extensive evaluation is performed to validate the segmentation algorithm, as well as the quality and sensitivity of the hinting system. Most of the drusen with a height of 85.5 microm were detected, and all drusen at least 93.6 microm high were detected.

PMID: 23286180 [PubMed - in process]

Eye (Lond). 2013 Jan 4. doi: 10.1038/eye.2012.274. [Epub ahead of print]

Retinal angiomatous proliferation occurring after radiotherapy.

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Purpose: To describe two cases of retinal angiomatous proliferation (RAP)-like lesion following radiation therapy for primary tumor.

Patients and methods: Retrospective evaluation of two patients with previous irradiation treatment for a pleomorphic adenoma of the lacrimal gland and a vocal cord carcinoma, respectively. Visual acuity (VA), fluorescein angiography and optical coherence tomography were performed and demonstrated a RAP-like lesion in both cases. Treatment with intravitreal injections of Ranibizumab was performed with a follow-up of 19 and 10 months, respectively.

Results: Both the patients had a positive response to the treatment with improvement in VA and reduction of intraretinal fluid.

Conclusion: RAP-like lesions can develop following radiation treatment for a primary tumor. In patients presenting with idiopathic RAP, a history of prior radiotherapy should be considered.Eye advance online publication, 4 January 2013; doi:10.1038/eye.2012.274.

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Reversal of end-stage retinal degeneration and restoration of visual function by photoreceptor transplantation.

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Abstract: One strategy to restore vision in retinitis pigmentosa and age-related macular degeneration is cell replacement. Typically, patients lose vision when the outer retinal photoreceptor layer is lost, and so the therapeutic goal would be to restore vision at this stage of disease. It is not currently known if a degenerate retina lacking the outer nuclear layer of photoreceptor cells would allow the survival, maturation, and reconnection of replacement photoreceptors, as prior studies used hosts with a preexisting outer nuclear layer at the time of treatment. Here, using a murine model of severe human retinitis pigmentosa at a stage when no host rod cells remain, we show that transplanted rod precursors can reform an anatomically distinct and

appropriately polarized outer nuclear layer. A trilaminar organization was returned to rd1 hosts that had only two retinal layers before treatment. The newly introduced precursors were able to resume their developmental program in the degenerate host niche to become mature rods with light-sensitive outer segments, reconnecting with host neurons downstream. Visual function, assayed in the same animals before and after transplantation, was restored in animals with zero rod function at baseline. These observations suggest that a cell therapy approach may reconstitute a light-sensitive cell layer de novo and hence repair a structurally damaged visual circuit. Rather than placing discrete photoreceptors among preexisting host outer retinal cells, total photoreceptor layer reconstruction may provide a clinically relevant model to investigate cell-based strategies for retinal repair.

PMID: 23288902

[PubMed - as supplied by publisher]

Pathogenesis

Am J Ophthalmol. 2013 Jan;155(1):1-35.e13. doi: 10.1016/j.ajo.2012.10.018.

Age-Related Macular Degeneration Revisited - Piecing the Puzzle: The LXIX Edward Jackson Memorial Lecture.

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PURPOSE: To present the current understanding of age-related macular degeneration (AMD) pathogenesis, based on clinical evidence, epidemiologic data, histopathologic examination, and genetic data; to provide an update on current and emerging therapies; and to propose an integrated model of the pathogenesis of AMD.

DESIGN: Review of published clinical and experimental studies.

METHODS: Analysis and synthesis of clinical and experimental data.

RESULTS: We are closer to a complete understanding of the pathogenesis of AMD, having progressed from clinical observations to epidemiologic observations and clinical pathologic correlation. More recently, modern genetic and genomic studies have facilitated the exploration of molecular pathways. It seems that AMD is a complex disease that results from the interaction of genetic susceptibility with aging and environmental factors. Disease progression also seems to be driven by a combination of genetic and environmental factors.

CONCLUSIONS: Therapies based on pathophysiologic features have changed the paradigm for treating neovascular AMD. With improved understanding of the underlying genetic susceptibility, we can identify targets to halt early disease and to prevent progression and vision loss.

PMID: 23245386 [PubMed - in process]

Ophthalmology. 2012 Dec 20. pii: S0161-6420(12)00913-X. doi: 10.1016/j.ophtha.2012.09.032. [Epub ahead of print]

Vascular Endothelial Growth Factor Promotes Progressive Retinal Nonperfusion in Patients with Retinal Vein Occlusion.

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OBJECTIVE: Central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) causes hypoperfusion, high levels of vascular endothelial growth factor (VEGF), macular edema, and loss of vision. Many patients also show areas of complete closure of retinal vessels (retinal nonperfusion [RNP]) that increase over time. The objective was to assess the effect of blocking VEGF on progression of RNP.

DESIGN: Retrospective analysis of prospectively collected data from 2 randomized, sham injection-controlled, double-masked, multicenter clinical trials.

PARTICIPANTS: A total of 392 and 397 patients with macular edema due to CRVO or BRVO.

METHODS: An independent reading center measured the area of RNP on fluorescein angiograms (FAs) in 2 phase III trials investigating the effect of ranibizumab (RBZ; Lucentis; Genentech, Inc, South San Francisco, CA) in patients with CRVO or BRVO.

MAIN OUTCOME MEASURES: The percentage of patients with no posterior RNP at months 0, 3, 6, 9, and 12.

RESULTS: There was no difference among treatment groups at baseline, but at the month 6 primary end point the percentage of patients with CRVO and no RNP was significantly greater in the RBZ groups (0.3 mg, 82.0%, P = 0.0092; 0.5 mg, 84.0%, P = 0.0067) versus the sham group (67.0%). Reperfusion of nonperfused retina was rare (1%) in sham-treated patients with CRVO, but occurred in 6% to 8% of patients with CRVO treated with RBZ (30% of those who had RNP and could improve). Results in patients with BRVO mirrored those in patients with CRVO. Crossover to 0.5 mg RBZ from sham at month 6 halted the progression of RNP and resulted in improvement in both CRVO and BRVO.

CONCLUSIONS: Treatment with RBZ did not worsen RNP in patients with RVO, but rather reduced its occurrence compared with sham. These data provide an important new insight regarding the pathogenesis of RVO; the initial vein occlusion is a precipitating event that causes baseline ischemia and release of VEGF, which then contributes to progression of RNP and thus worsening of ischemia. Timely, aggressive blockade of VEGF prevents the worsening of RNP, promotes reperfusion, and eliminates a positive feedback loop.

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Mol Immunol. 2012 Dec 22;54(2):122-131. doi: 10.1016/j.molimm.2012.11.005. [Epub ahead of print]

Toll-like receptor 3 (TLR3) protects retinal pigmented epithelium (RPE) cells from oxidative stress through a STAT3-dependent mechanism.

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Abstract: Toll-like receptors (TLRs) are essential receptors of the innate immune system and are first responders for protection against bacterial and viral pathogens. Recently, several TLRs have also been implicated in regulating cell death and survival in non-pathogen injuries such as stroke and oxidative stress. Investigating the role of TLRs during central nervous system damage is an important focus of research that may reveal new mechanisms underlying the cellular response to injury and survival. Retinal pigmented epithelium (RPE) cells form an epithelial layer underneath the neural retina that maintains the function of photoreceptors and are the primary cell type affected in the retinal disease age-related macular degeneration (AMD). Predicted loss of function polymorphisms in the TLR3 gene are associated with protection from AMD but the role of TLR3 in regulating RPE survival during AMD-like injury, such as high oxidative stress, is not known. Therefore the purpose of this study is to evaluate the effect of TLR3 signaling on RPE viability during oxidative stress. We demonstrated that TLR3 activation in the presence of oxidative stress injury

significantly increased RPE cell viability, in contrast to TLR3 reducing cell viability in the absence of cellular injury. Furthermore, we show signal transducer and activator of transcription 3 (STAT3) signaling as an essential mediator of TLR3-regulated protection of RPE cells. STAT3 signaling was increased by TLR3 activation and knockdown of STAT3 transcripts using siRNA abolished the protective effect of TLR3 during oxidative stress. Together, these results demonstrate a novel pro-survival role for TLR3 signaling within the RPE during injury. These findings support the concept that dysregulation of TLR3 activity may contribute to the development of AMD, suggesting that precise regulation of the TLR3 pathway during AMD-associated injury could be of therapeutic interest.

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Front Biosci (Schol Ed). 2013 Jan 1;5:412-25.

Potential of epigenetic mechanisms in AMD pathology .

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Abstract: Age-related macular degeneration (AMD) is an ocular disease and the main reason for sight loss in the elderly in the developed countries. The pathogenesis of the disease is complex and not fully understood, but involves several environmental and genetic risk factors. However, little is known about the role of epigenetics in this disease although it is recognized that epigenetic alterations often precede genetic changes in many pathological conditions and regulate aging and the developmental processes. There is experimental evidence for the involvement of DNA methylation and histone modifications in the pathogenesis of drusen formation, a central hallmark of AMD. However, the main impact of epigenetic modifications, including persistent lysine methylation of the H3 histone, is exerted during retinal embryonic development. This interplay opens an exciting possibility to manipulate the epigenetic pattern and to develop novel AMD therapies by physical, pharmacological or genetic interventions. One of the most intriguing questions is why different individuals develop different AMD phenotypes. Epigenetic regulation might open new perspectives into these changes in AMD pathology.

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Invest Ophthalmol Vis Sci. 2012 Dec 20. pii: iovs.12-10068v1. doi: 10.1167/iovs.12-10068. [Epub ahead of print]

Three-dimensional spheroidal culture visualization of membranogenesis of Bruch's membrane and basolateral functions of the retinal pigment epithelium.

Sato R, Yasukawa T, Kacza J, Eichler W, Nishiwaki A, Iandiev I, Ohbayashi M, Kato A, Yafai Y, Bringmann A, Takase A, Ogura Y, Seeger J, Wiedemann P.

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Purpose: Aging changes in the retinal pigment epithelium (RPE) involve lipid accumulation and membranous basal deposits onto the underlying Bruch's membrane, which may be related to age-related macular degeneration. Conventional in vitro cell culture is limited in its ability to observe the epithelial functions on the basal side. The purpose of this study was to develop a three-dimensional culture system to observe basolateral functions of the RPE.

Methods: Isolated human RPE cells were cultured in a viscous medium on a rounded-bottom culture dish, resulting in spheroid formation. The appearance and size of the spheroids were assessed by light micros-

copy. Spheroids were fixed in 4% paraformaldehyde for immunohistochemistry or sampled for Western blotting. For transmission electron microscopy (TEM) and scanning electron microscopy (SEM), spheroids were post-fixed in 1% osmium tetroxide.

Results: The spheroids had a well-differentiated RPE monolayer with a thin elastic layer, a main layer of Bruch's membrane, on their surface and showed outward deposition of lipoproteins with apoB-100. TEM revealed widely spaced collagen, which was identified as condensation of collagen fibrils by SEM. SEM showed deposition of membranous debris and lipid particles, which have been observed in human Bruch's membrane. Western blotting showed expression of RPE differentiation markers and components of Bruch's membrane and RPE lipoproteins.

Conclusions: This model provides direct views of epithelialization processes involving elastogenesis and transmural functions such as lipoprotein deposition and may elucidate not only unknown epithelial behaviors but also the pathogenesis of RPE-related diseases.

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Eye (Lond). 2013 Jan 4. doi: 10.1038/eye.2012.265. [Epub ahead of print]

Bowman lecture on the role of inflammation in degenerative disease of the eye.

Forrester JV.

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Abstract: Inflammation, in the pathogenesis of many diseases previously thought to be strictly genetic, degenerative, metabolic, or endocrinologic in aetiology, has gradually entered the framework of a general mechanism of disease. This is exemplified by conditions such as Parkinson's disease, Alzheimer's disease, atherosclerosis, diabetes, and the more recently described Metabolic Syndrome. Chronic inflammatory processes have a significant, if not primary role, in ophthalmic diseases, particularly in retinal degenerative diseases. However, inflammation itself is not easy to define, and some aspects of inflammation may be beneficial, in a process described as 'para-inflammation' by Medhzitov. In contrast, the damaging effects of inflammation, mediated by pro-inflammatory macrophages through activation of the intracellular protein-signalling complexes, termed inflammasomes, are well recognised and are important therapeutic targets. In this review, the range of inflammatory processes in the eye is evaluated in the context of how these processes impact upon retinal degenerative disease, particularly diabetic retinopathy and age-related macular degeneration.Eye advance online publication, 4 January 2013; doi:10.1038/eye.2012.265.

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Br J Ophthalmol. 2012 Dec 19. [Epub ahead of print]

Intravitreal human complement factor H in a rat model of laser-induced choroidal neovascularisation.

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PURPOSE: To investigate the inhibitory effect of intravitreally administered human complement factor H (CFH) in a rat model of laser-induced choroidal neovascularisation (CNV).

METHODS: Analysis of alternative pathway inhibition by human plasma-purified CFH was conducted by

measuring C3 deposition on zymosan particles using rat serum. CNV was induced by laser photocoagulation on Day 0 in the eyes of Brown Norway rats. Human plasma-purified CFH (50 µg/2 µl) or phosphate buffered saline was injected intravitreally on Day 0 (prevention arm) or Day 7 (treatment arm). Seven days after injection, eyes were enucleated and retinal pigment epithelium-choroid-sclera flat mounts were prepared. Areas of CNV were determined in flat mounts and quantified using an image analysis programme. Flat mounts were also stained for membrane attack complex.

RESULTS: In rat serum, human CFH inhibited activity of alternative pathway in a dose-dependent manner. On Day 3, mean membrane attack complex deposition in laser-treated retina significantly decreased in CFH-treated eyes ($p<0.001$). In the prevention arm, the mean CNV area in CFH-treated eyes decreased by 27.0% compared with phosphate buffered saline-treated control eyes on Day 7 ($p=0.011$). In the treatment arm, the mean CNV area in CFH-treated eyes decreased by 38.3% compared with control eyes on Day 14 ($p=0.001$).

CONCLUSIONS: Intravitreal injection of human CFH resulted in the suppression of formation of new, and regression of preformed laser-induced CNV in the rat model. Human CFH may be a feasible treatment for CNV associated with age-related macular degeneration or other causes.

PMID: 23258212 [PubMed - as supplied by publisher]

PLoS One. 2012;7(12):e53329. doi: 10.1371/journal.pone.0053329. Epub 2012 Dec 28.

Suppression of experimental choroidal neovascularization by curcumin in mice.

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PURPOSE: To investigate the effects of curcumin on the development of experimental choroidal neovascularization (CNV) with underlying cellular and molecular mechanisms.

METHODS: C57BL/6N mice were pretreated with intraperitoneal injections of curcumin daily for 3 days prior to laser-induced CNV, and the drug treatments were continued until the end of the study. The CNV area was analyzed by fluorescein-labeled dextran angiography of retinal pigment epithelium (RPE)-choroid flat mounts on day 7 and 14, and CNV leakage was evaluated by fluorescein angiography (FA) on day 14 after laser photocoagulation. The infiltration of F4/80 positive macrophages and GR-1 positive granulocytes were evaluated by immunohistochemistry on RPE-choroid flat mounts on day 3. Their expression in RPE-choroid complex was quantified by real-time PCR (F4/80) and Western blotting (GR-1) on day 3. RPE-choroid levels of vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF)-α, monocyte chemotactic protein (MCP)-1, and intercellular adhesion molecule (ICAM)-1 were examined by ELISA on day 3. Double immunostaining of F4/80 and VEGF was performed on cryo-sections of CNV lesions on day 3. The expression of nuclear factor (NF)-κB and hypoxia-inducible factor (HIF)-1α in the RPE-choroid was determined by Western blotting.

RESULTS: Curcumin-treated mice had significantly less CNV area ($P<0.05$) and CNV leakage ($P<0.001$) than vehicle-treated mice. Curcumin treatment led to significant inhibition of F4/80 positive macrophages ($P<0.05$) and GR-1 positive granulocytes infiltration ($P<0.05$). VEGF mainly expressed in F4/80 positive macrophages in laser injury sites, which was suppressed by curcumin treatment ($P<0.01$). Curcumin inhibited the RPE-choroid levels of TNF-α ($P<0.05$), MCP-1 ($P<0.05$) and ICAM-1 ($P<0.05$), and suppressed the activation of NF-κB in nuclear extracts ($P<0.05$) and the activation of HIF-1α ($P<0.05$).

CONCLUSION: Curcumin treatment led to the suppression of CNV development together with inflammatory and angiogenic processes including NF-κB and HIF-1α activation, the up-regulation of inflammatory and angiogenic cytokines, and infiltrating macrophages and granulocytes. This provides molecular and cellular

evidence of the validity of curcumin supplementation as a therapeutic strategy for the suppression of age-related macular degeneration (AMD)-associated CNV.

PMID: 23285282 [PubMed - in process]

Genetics

Mol Vis. 2012;18:3049-56. Epub 2012 Dec 22.

TECHNICAL BRIEF: Isolation of total DNA from postmortem human eye tissues and quality comparison between iris and retina.

Wang JC, Wang A, Gao J, Cao S, Samad I, Zhang D, Ritland C, Cui JZ, Matsubara JA.

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ABSTRACT: Recent genomic technologies have propelled our understanding of the mechanisms underlying complex eye diseases such as age-related macular degeneration (AMD). Genotyping postmortem eye tissues for known single nucleotide polymorphisms (SNPs) associated with AMD may prove valuable, especially when combined with information obtained through other methods such as immunohistochemistry, western blot, enzyme-linked immunosorbent assay (ELISA), and proteomics. Initially intending to genotype postmortem eye tissues for AMD-related SNPs, our group became interested in isolating and comparing the quality of DNA from the iris and retina of postmortem donor eyes. Since there is no previously published protocol in the literature on this topic, we present a protocol suitable for isolating high-quality DNA from postmortem eye tissues for genomic studies.

METHODS: DNA from 33 retinal samples and 35 iris samples was extracted using the phenol-chloroform-isoamyl method from postmortem donor eye tissues. The quantity of DNA was measured with a spectrophotometer while the quality was checked using gel electrophoresis. The DNA samples were then amplified with PCR for the complement factor H (CFH) gene. The purified amplified products were then genotyped for the SNPs in the CFH gene.

RESULTS: Regarding concentration, the retina yielded 936 ng/μl of DNA, while the iris yielded 78 ng/μl of DNA. Retinal DNA was also purer than iris DNA (260/280=1.78 vs. 1.46, respectively), and produced superior PCR results. Retinal tissue yielded significantly more DNA than the iris tissue per mg of sample (21.7 ng/μl/mg vs. 7.42 ng/μl/mg). Retinal DNA can be readily amplified with PCR, while iris DNA can also be amplified by adding bovine serum albumin. Overall, retinal tissues yielded DNA of superior quality, quantity, and suitability for genotyping and genomic studies.

CONCLUSIONS: The protocol presented here provides a clear and reliable method for isolating total DNA from postmortem eye tissues. Retinal tissue provides DNA of excellent quantity and quality for genotyping and downstream genomic studies. However, DNA isolated from iris tissues, and treated with bovine serum albumin, may also be a valuable source of DNA for genotyping and genomic studies.

PMID: 23288996

Future Med Chem. 2013 Jan;5(1):13-5. doi: 10.4155/fmc.12.187.

Genetics of age-related macular degeneration: application to drug design.

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Associations of the C2-CFB-RDBP-SKIV2L Locus with Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy.

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PURPOSE: To investigate the associations of the C2-CFB-RDBP-SKIV2L region with neovascular age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

DESIGN: Cross-sectional, case-control association study.

PARTICIPANTS: A Chinese case-control group of 200 neovascular AMD patients, 233 PCV patients, and 275 control subjects.

METHODS: An association analysis was performed of the C2-CFB-RDBP-SKIV2L locus with both neovascular AMD and PCV in a Chinese population using 19 haplotype-tagging single nucleotide polymorphisms (SNPs) and 6 previously reported SNPs across the C2-CFB-RDBP-SKIV2L region. All SNPs were genotyped using the TaqMan genotyping technology (TaqMan; Applied Biosystems [ABI], Foster City, CA).

MAIN OUTCOME MEASURES: Allele and haplotype frequencies of the SNPs in the C2-CFB-RDBP-SKIV2L region.

RESULTS: The SKIV2L SNPs rs429608 and rs453821 were significantly associated with neovascular AMD (P = 7.39×10(-5); odds ratio [OR], 0.22; 95% confidence interval [CI], 0.10-0.50; and P = 0.001; OR, 0.38; 95% CI, 0.21-0.70, respectively), whereas borderline associations were detected for C2 rs547154 (P = 0.002) and RDBP rs760070 (P = 0.003). Conditional haplotype analysis revealed that SKIV2L rs429608 could account fully for the global haplotype association identified in this region. The association of SKIV2L rs429608 with neovascular AMD remained significant after adjusting for CFH rs800292 and HTRA1 rs11200638. No individual SNP or haplotype was associated significantly with PCV.

CONCLUSIONS: In this concurrent investigation of the associations of the entire C2-CFB-RDBP-SKIV2L region with neovascular AMD and PCV, the results suggested that SKIV2L is a likely causal gene for neovascular AMD, conferring a significant protective effect independent of CFH and HTRA1. These data do not support a significant role of this region in PCV, suggesting different molecular mechanisms between neovascular AMD and PCV.

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Association between polymorphism of the NQO1, NOS3 and NFE2L2 genes and AMD.

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Abstract: Oxidative stress may play a role in the pathogenesis of age-related macular degeneration (AMD). In this study we examined the association between AMD risk and polymorphisms of genes encoding enzymes involved in the generation and removal of iron-mediated oxidation: NQO1 (609C> T, rs1800566), NOS3 (894G>T, rs1799983) and NFE2L2 (28312647A>G, rs6726395). We found that the G/G genotype of the rs6726395 polymorphism was associated with a decreased risk of AMD wet form (OR 0.44) and on the

other hand the T allele of the rs1799983 polymorphism increased such risk (OR 1.63). We also observed that the C/C-G/T combined genotype of the rs1800566 and rs1799983 polymorphisms was positively correlated with a reduced risk of AMD as well as of its dry form (OR 0.40 and 0.35). The presence of the G/T-G/G combined genotype of the rs1799983 and rs6726395 polymorphisms decreased the risk of this disease (OR 0.35). The results obtained in our study suggest a potential role of the rs1800566, rs1799983 and rs6726395 polymorphisms in the AMD pathogenesis.

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Different impact of high-density lipoprotein-related genetic variants on polypoidal choroidal vasculopathy and neovascular age-related macular degeneration in a Chinese Han population.

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Abstract: Neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) are both major serosanguinous maculopathies among the Asian elderly. They are similar in phenotype. Genetic variants in high-density lipoprotein (HDL) pathway were discovered to be associated with AMD in two genome-wide association studies. In this study with a Chinese Han cohort, we investigated the impacts of these genetic variants on nAMD and PCV separately. The missense coding variants and previously identified variants at LIPC, ABCA1, CETP, LPL and FADS1 loci were genotyped in 157 nAMD patients, 250 PCV patients and 204 controls without any macular abnormality. The known variants in CFH, ARMS2 and near HTRA1 were also genotyped. Fasting serum cholesterol levels were determined. The variants in CFH, ARMS2 and near HTRA1 were strongly associated with both PCV ($P < 10(-6)$, 10(-7) and 10(-7) respectively) and nAMD ($P < 10(-6)$, 10(-16) and 10(-17) respectively). None of the studied HDL-related variants was significantly associated with nAMD. A missense variant in CETP, rs5882, was significantly associated with PCV ($P = 2.73\times10(-4)$). The rs5882 GG genotype had a 3.53-fold (95% CI: 1.93-6.45) increased risk for PCV, and conferred a significantly lower serum HDL-cholesterol level for PCV patients than the AA genotype ($P = 0.048$). These results suggest the need to separate PCV from nAMD in association studies especially with Asian cohorts, and that the HDL pathway may involve in the pathogenesis of PCV and nAMD differently.

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Genetic mechanisms and age-related macular degeneration: common variants, rare variants, copy number variations, epigenetics, and mitochondrial genetics.

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ABSTRACT: Age-related macular degeneration (AMD) is a complex and multifaceted disease involving contributions from both genetic and environmental influences. Previous work exploring the genetic contributions of AMD has implicated numerous genomic regions and a variety of candidate genes as modulators of AMD susceptibility. Nevertheless, much of this work has revolved around single-nucleotide polymorphisms (SNPs), and it is apparent that a significant portion of the heritability of AMD cannot be explained through

these mechanisms. In this review, we consider the role of common variants, rare variants, copy number variations, epigenetics, microRNAs, and mitochondrial genetics in AMD. Copy number variations in regulators of complement activation genes (CFHR1 and CFHR3) and glutathione S transferase genes (GSTM1 and GSTT1) have been associated with AMD, and several additional loci have been identified as regions of potential interest but require further evaluation. MicroRNA dysregulation has been linked to the retinal pigment epithelium degeneration in geographic atrophy, ocular neovascularization, and oxidative stress, all of which are hallmarks in the pathogenesis of AMD. Certain mitochondrial DNA haplogroups and SNPs in mitochondrially encoded NADH dehydrogenase genes have also been associated with AMD. The role of these additional mechanisms remains only partly understood, but the importance of their further investigation is clear to elucidate more completely the genetic basis of AMD.

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Epidemiology

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Long-term Use of Aspirin and Age-Related Macular Degeneration.

Klein BE, Howard KP, Gangnon RE, Dreyer JO, Lee KE, Klein R.

CONTEXT: Aspirin is widely used for relief of pain and for cardioprotective effects. Its use is of concern to ophthalmologists when ocular surgery is being considered and also in the presence of age-related macular degeneration (AMD).

OBJECTIVE: To examine the association of regular aspirin use with incidence of AMD.

DESIGN, SETTING, AND PARTICIPANTS: The Beaver Dam Eye Study, a longitudinal population-based study of age-related eye diseases conducted in Wisconsin. Examinations were performed every 5 years over a 20-year period (1988-1990 through 2008-2010). Study participants (N = 4926) were aged 43 to 86 years at the baseline examination. At subsequent examinations, participants were asked if they had regularly used aspirin at least twice a week for more than 3 months. MAIN OUTCOME MEASURE Incidence of early AMD, late AMD, and 2 subtypes of late AMD (neovascular AMD and pure geographic atrophy), assessed in retinal photographs according to the Wisconsin Age-Related Maculopathy Grading System.

RESULTS: The mean duration of follow-up was 14.8 years. There were 512 incident cases of early AMD (of 6243 person-visits at risk) and 117 incident cases of late AMD (of 8621 person-visits at risk) over the course of the study. Regular aspirin use 10 years prior to retinal examination was associated with late AMD (hazard ratio [HR], 1.63 [95% CI, 1.01-2.63]; P = .05), with estimated incidence of 1.76% (95% CI, 1.17%-2.64%) in regular users and 1.03% (95% CI, 0.70%-1.51%) in nonusers. For subtypes of late AMD, regular aspirin use 10 years prior to retinal examination was significantly associated with neovascular AMD (HR, 2.20 [95% CI, 1.20-4.15]; P = .01) but not pure geographic atrophy (HR, 0.66 [95% CI, 0.25-1.95]; P = .45). Aspirin use 5 years (HR, 0.86 [95% CI, 0.71-1.05]; P = .13) or 10 years (HR, 0.86 [95% CI, 0.65-1.13]; P = .28) prior to retinal examination was not associated with incident early AMD.

CONCLUSIONS: Among an adult cohort, aspirin use 5 years prior to observed incidence was not associated with incident early or late AMD. However, regular aspirin use 10 years prior was associated with a small but statistically significant increase in the risk of incident late and neovascular AMD.

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Prevalence and Risk Factors for Age-Related Macular Degeneration in Indians: A Comparative Study in Singapore and India.

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PURPOSE: To compare the prevalence and risk factors for age-related macular degeneration (AMD) in 2 Indian populations, 1 living in urban Singapore and 1 in rural central India.

DESIGN: Population-based, cross-sectional studies of Indians aged 40+ years.

METHODS: Our analysis included 3337 Singapore-residing participants and 3422 India-residing participants. All participants underwent comprehensive systemic and ocular examinations and retinal photography. AMD was graded from retinal photographs according to the Wisconsin Age-Related Maculopathy Grading System. Systemic and ocular risk factors were assessed for association with AMD.

RESULTS: Singapore-residing participants were older (mean age 57.8 years vs 53.8 years) and, after adjusting for age and sex, were more likely to have previous cataract surgery, higher body mass index, hypertension, diabetes, previous myocardial infarction, higher cholesterol, and lower creatinine levels, but less likely to be current smokers, than India-residing participants. The age-standardized prevalence of early and late AMD was 4.45% and 0.34%, respectively, in Singapore and 5.80% and 0.16%, respectively, in India. Shorter axial length was associated with early AMD in both Singapore and India, whereas previous cataract surgery, higher body mass index, hypertension, and lower cholesterol were associated with early AMD in Singapore but not in India.

CONCLUSION: The prevalence of AMD was similar among Indian adults living in urban Singapore and rural India, despite differences in cardiovascular risk factor profile and demographics.

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Eye disorders in old people.

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BACKGROUND: Visual impairment is one of a major public health problem among elderly people.

OBJECT: Aim of this study was determining the prevalence of visual impairment in median and old peoples in Qazvin (Iran).

METHOD: In this cross sectional study, with a simple random sampling, 446 patients older than 5o years who were referred to outpatient ophthalmology clinics at Avecina hospital of Qazvin (a province of Iran) in 2010 were enrolled. Participants first complete a questionnaire with 25 questions toward demographic and past medical history and then were examined by ophthalmologist. These examinations includes direct and indirect ophthalmoscopy, slit lamp examination, measurement of uncorrected visual acuity and visual acuity with current glasses, lensometery of the previous glasses, refraction with and without the use of cycloplegic and determining the best corrected visual acuity. All slit lamp examinations were performed by the same ophthalmologist. Data were analyzed with SPSS16 with use of Chi - Square test with P value <0.05.

RESULTS: In this study 446 patients were examined that 54.7% were male. Mean age of study population was 62+-9.3 years old. 96.4% of participants had refractory disorder. Prevalence of myopia, hyperopia and astigmatism were 33.6%, 45.9% and 16.8% respectively. Of patients 17.4% had diabetes. Of participants 28.9% had temporal headache, 37% red eye, 41.2% flashing, 27.3% and 28% had dryness and discharge of eye respectively. 31.1% of participants had eyelide problem, 4.7% Color Vision Deficiency (CVD) and 3.8% had family history of CVD. Of total 4.5% had glaucoma, 3.3% macular degeneration and 21.7% had hypertension. 0.6% of population had macular degeneration, 0.4% of population had glaucoma Of 892 eyes (446 individuals), 36.2% had visual acuity less than 7/10, 1.7% light perception (LP) and 0.22% no light perception (NLP) and 2.7% finger count.

CONCLUSION: Refractory errors, cataract and amblyopia were most important eye disorders in older people in Qazvin.

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