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MD Research News

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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

Ophthalmology. 2013 Apr 9. pii: S0161-6420(13)00016-X. doi: 10.1016/j.ophtha.2013.01.014. [Epub ahead of print]

Genetic Influences on the Outcome of Anti-Vascular Endothelial Growth Factor Treatment in Neovascular Age-related Macular Degeneration.

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PURPOSE: To determine the association of genetic variants in known age-related macular degeneration (AMD) risk-associated genes with outcome of anti-vascular endothelial growth factor (VEGF) treatment in neovascular AMD.

DESIGN: Prospective cohort study.

PARTICIPANTS: We enrolled 224 consecutive patients with neovascular AMD at the Royal Victorian Eye and Ear Hospital, Australia.

METHODS: Patients were treated with 3 initial monthly ranibizumab or bevacizumab injections followed by 9 months of "as required" injections based on clinician's decision at each follow-up visit according to retreatment criteria. Seventeen single nucleotide polymorphisms (SNPs) in known AMD risk-associated genes including CFH (rs800292, rs3766404, rs1061170, rs2274700 and rs393955), HTRA1 (rs11200638), CFHR1-5 (rs10922153, rs16840639, rs6667243, and rs1853883), LOC387715/ARMS2 (rs3793917 and rs10490924), C3 (rs2230199 and rs1047286), C2 (rs547154), CFB (rs641153) and F13B (rs6003) were examined. Multivariate analysis was used to determine the role of each SNP in treatment outcome.

MAIN OUTCOME MEASURES: The influence of selected SNPs on mean change in visual acuity (VA) at 12 months.

RESULTS: Mean baseline VA was 51±16.8 Early Treatment Diabetic Retinopathy Study letters. Overall, the mean change in VA from baseline was +3.2±14.9 letters at 12 months. The AA (homozygote risk) genotype at rs11200638 - HTRA1 promoter SNP (P = 0.001) and GG (homozygote risk) genotype at rs10490924 (A69S) in LOC387715/ARMS2 (P = 0.002) were each significantly associated with poorer VA outcome at 12 months after multiple correction. Mean ± standard deviation change in VA from baseline in patients with AA genotype at rs11200638 was -2.9±15.2 letters after 12 months compared with +5.1±14.1 letters in patients with AG or GG genotypes at this SNP. Patients with either of these genotypes were also significantly more likely to lose >15 letters after 12 months. SNPs rs11200638 and rs10490924 were in high

linkage disequilibrium (r2 = 0.92). None of the other examined SNPs was associated with outcome.

CONCLUSIONS: The HTRA1 promoter SNP (rs11200638) and A69S at LOC387715/ARMS2 were associated with a poorer visual outcome for ranibizumab or bevacizumab treatment in neovascular AMD, suggesting strong pharmacogenetic associations with anti-VEGF treatment. This finding could aid in applying more individualized treatment regimens based on patients' genotype to achieve optimal treatment response in AMD.

PMID: 23582991 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Apr 17. [Epub ahead of print]

Optimising assessment intervals improves visual outcomes in ranibizumab-treated age-related neovascular degeneration: using the stability phase as a benchmark.

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BACKGROUND: To observe visual acuity change in the stability phase when follow-up intervals are decreased in ranibizumab-treated neovascular age-related macular degeneration (nvAMD).

METHODS: Selection of patients was based on a review of a cohort of 189 eyes of 154 patients with nvAMD treated with intravitreal ranibizumab in routine clinical practice. Patients were transferred from a base hospital with a 8-week follow-up interval to a community eye clinic, enabling a new follow-up interval of 4 weeks. Staff, assessment, and treatment protocols were equivalent in the two centres. Patients were included when they were in the stability phase of treatment defined 1 month after having completed their three initiation treatments with ranibizumab. Each patient was required to have attended at least a further 12 visits; this means a follow-up time for a year or longer, consisting of six visits at the base hospital followed by six visits at the new eye clinic. The best-corrected visual acuity (BCVA), follow-up intervals and injection numbers were collected.

RESULTS: Seventy-two eyes of 62 patients were included. The mean follow-up interval for the six visits in the base hospital was 56.81 days, and in the new eye centre 31.81 days. The BCVA loss in the base hospital was -1.13 letters, compared to a gain of +4.61 letters in the community eye clinic over the six visits. The number of ranibizumab injections was 3.67 in the base hospital, compared with 3.91 in the other centre over the respective periods.

CONCLUSION: Visual acuity improves and severe visual loss decreases when follow-up intervals reduce from approximately 8 weeks to 4 weeks. Furthermore, using the stability phase to evaluate the outcome and effectiveness of our treatments for age-related macular degeneration appeared to be an efficient tool.

PMID: 23591940 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2013 Apr 12. [Epub ahead of print]

Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Choroidal Neovascularization due to Sorsby Macular Dystrophy.

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Abstract Purpose: To report the first case of intravitreal bevacizumab and ranibizumab to treat choroidal neovascularization secondary to Sorsby macular dystrophy.

Case: A 57-year-old male with metamorphopsia, color vision deficits, and ocular family history of Sorsby macular dystrophy was found to have a choroidal neovascular membrane (CNVM) in his left eye. He was initially treated with intravitreal bevacizumab and had visual acuity improvement and resolution of the subretinal fluid on OCT. After 8 injections, he developed presumed mild inflammation secondary to intravitreal bevacizumab and was switched to combination intravitreal bevacizumab/dexamethasone in his left eye, which consistently demonstrated efficacy in stabilizing his vision and the CNVM without producing intraocular inflammation. The right eye later developed the CNVM and he was started on intravitreal bevacizumab in this eye as well. After 8 injections in the right eye, he experienced a similar inflammatory reaction following intravitreal bevacizumab injections and was switched to combination intravitreal bevacizumab/dexamethasone in the right eye as well. Subsequently, he was switched to intravitreal ranibizumab in the left eye alone, which continued to stabilize his vision and OCT and did not cause an inflammatory reaction as he previously experienced with bevacizumab. After 5 ranibizumab injections, he experienced no inflammatory response that he appeared to have with bevacizumab, but chose to switch back to combination intravitreal bevacizumab and dexamethasone due to financial reasons. Initially, in his clinical course, he experienced consistent visual acuity improvements with intravitreal antivascular endothelial growth factor therapy and continues to enjoy functional vision nearly 7 years after his initial symptoms.

Conclusions: Intravitreal bevacizumab and ranibizumab demonstrated efficacy in this case in the treatment of CNVM associated with Sorsby macular dystrophy.

PMID: 23581613 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2013 May;91(3):e184-90. doi: 10.1111/aos.12008.

Long-term results of the effect of intravitreal ranibizumab on the retinal arteriolar diameter in patients with neovascular age-related macular degeneration.

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Purpose: To study the effect of intravitreal (IVT) ranibizumab on the retinal arteriolar diameter in patients with neovascular age-related macular degeneration (AMD).

Methods: Ten eyes of 10 patients with previously untreated neovascular AMD were included. All eyes had three monthly IVT injections of ranibizumab and then were retreated as needed, based on visual acuity and optical coherence tomography (OCT) criteria. The diameter of the retinal arterioles was measured in vivo with a retinal vessel analyser (RVA) before the first IVT injection, 7 and 30 days after the first, the second and the third injection, and at month 12 of follow-up.

Results: A significant vasoconstriction of the retinal arterioles was observed following each one of the first three IVT injections of ranibizumab. Thirty days following the first, second and third injection, there was a mean decrease of 8.4 ± 3.2%, 11.9 ± 4.5% and 18.5 ± 7.2%, respectively, of the retinal arteriolar diameter compared with baseline ($p < 0.01$). At month 12, the vasoconstriction was still present with a mean decrease of 19.1 ± 8.3% of the retinal arteriolar diameter compared with baseline ($p < 0.01$). Median number of ranibizumab injections was 4 (range 3-10). There was no correlation between the number of injections and percentage diameter decrease at month 12 ($r = -0.54$, $p > 0.1$). There was no significant change in mean arterial pressure (MAP) during the period of follow-up ($p > 0.05$).

Conclusions: These results suggest that IVT ranibizumab induces sustained retinal arteriolar vasoconstriction in eyes with neovascular AMD.

PMID: 23590391 [PubMed - in process]

World J Diabetes. 2013 Apr 15;4(2):19-26. doi: 10.4239/wjd.v4.i2.19.

Bevacizumab for the management of diabetic macular edema.

Stefanini FR, Arevalo JF, Maia M.

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Abstract: Diabetic retinopathy (DR) is a leading cause of vision loss in the working-age population and is relatedto 1%-5% of cases of blindness worldwide. Diabetic macular edema (DME) is the most frequent cause of DR vision loss and is an important public health problem. Recent studies have implicated vascular endothelial growth factor (VEGF) in DR and DME pathogenesis, as well as provided evidence of the benefits of anti-VEGF agents for the management of such conditions. Despite the benefits of intravitreal ranibizumab injection for the management of DME, the cost-effectiveness of intravitreal bevacizumab therapy has gained increasing interest in the scientific community. This review summarizes the studies examining bevacizumab for the management of DME, focusing on the efficacy and duration of the clinical benefits of decreasing DME and the improvement of best-corrected visual acuity (BCVA). There is strong evidence that intravitreal bevacizumab injection therapy has a good cost-effective profile in the management of DME and may be associated with laser photocoagulation; however, its clinical superiority in terms of the duration of DME regression and the improvement of BCVA compared with intravitreal ranibizumab and other intravitreal anti-VEGF therapies remains unclear and deserves further investigation.

PMID: 23593532 [PubMed] PMCID: PMC3627413

Clin Ophthalmol. 2013;7:703-6. doi: 10.2147/OPTH.S42208. Epub 2013 Apr 9.

Intravitreal ranibizumab in treating extensive traumatic submacular hemorrhage.

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Abstract: Herein, we report our experience in treating extensive traumatic submacular hemorrhage with a single dose of intravitreal ranibizumab. A 23-year-old healthy Malay man presented with a progressive reduction of central vision in the left eye of 2 days' duration following a history of blunt trauma. Visual acuity was reduced to counting fingers. Examination revealed infero-temporal subconjunctival hemorrhage, traumatic anterior uveitis, and an extensive sub-macular hemorrhage with suspicion of a choroidal rupture in the affected eye. He was initially treated conservatively with topical prednisolone acetate 1%. The subconjunctival hemorrhage and anterior uveitis resolved but his vision remained poor with minimal resolution of the submacular hemorrhage at 1 week follow-up (day 12 post-trauma). In view of the poor resolution of submacular hemorrhage, he was treated with a single dose of 0.5 mg intravitreal ranibizumab at day 20 post-trauma. At 4 weeks post-intravitreal ranibizumab, there was an improvement in visual acuity (from counting fingers to 6/45) and complete resolution of the submacular hemorrhage with presence of a choroidal rupture scar temporal to the fovea, which was not seen clearly at presentation due to obscuration by blood. His visual acuity further improved to 6/18 at 3 months post-trauma. Although this single case had a favorable outcome, a large population cohort study is needed to establish the effectiveness of intravitreal ranibizumab in treating extensive traumatic submacular hemorrhage.

PMID: 23589678 [PubMed] PMCID: PMC3625028

Retina. 2013 Apr 11. [Epub ahead of print]

INTERLEUKIN 8 PROMOTER POLYMORPHISM PREDICTS THE INITIAL RESPONSE TO

BEVACIZUMAB TREATMENT FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To study the association of single-nucleotide polymorphisms of interleukin 8, vascular endothelial growth factor, erythropoietin, complement factor H, complement component C3, and LOC387715 genes with the response to bevacizumab treatment in exudative age-related macular degeneration.

METHODS: Clinical records, smoking history, optical coherence tomography, and angiographies of 96 bevacizumab-treated exudative age-related macular degeneration patients were analyzed retrospectively. Blood DNA was collected. Based on the disappearance of intra- or subretinal fluid in optical coherence tomography, patients were graded as responders, partial responders, or nonresponders after 3 initial treatment visits and a median time of 3.5 months.

RESULTS: Interleukin 8 promoter polymorphism -251A/T was significantly associated with persisting fluid in optical coherence tomography. The A allele was more frequent in nonresponders than in responders (P = 0.033). In multivariate modeling, the AA genotype of -251A/T (P = 0.043) and occult (P = 0.042) or predominantly classic (P = 0.040) lesions predicted poorer outcome. Visual acuity change was better in responders than in nonresponders (P = 0.006). Baseline lesion size (P = 0.006) and retinal cysts after the treatment (P < 0.001) correlated with less visual acuity gain.

CONCLUSION: The A allele and the homozygous AA genotype of interleukin 8 -251A/T were associated with anatomical nonresponse to bevacizumab treatment.

PMID: 23584701 [PubMed - as supplied by publisher]

Retina. 2013 Apr 17. [Epub ahead of print]

ALTERATIONS OF VASCULAR PIGMENT EPITHELIUM DETACHMENTS ASSOCIATED WITH AGE-RELATED MACULAR DEGENERATION DURING UPLOAD WITH INTRAVITREAL RANIBIZUMAB.

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PURPOSE: To describe morphologic alterations of pigment epithelial detachments (PEDs) associated with neovascular age-related macular degeneration during anti-vascular endothelial growth factor upload therapy with ranibizumab.

METHODS: Prospective, single-arm interventional study. Primary outcome was the reduction of height of PED during monthly treatment using ranibizumab. Secondary outcomes were factors influencing the regression of PED. Inclusion criteria were presence of PED associated with naive neovascular age-related macular degeneration, visual acuity of >20/200, and height of PED >150 μm on optical coherence tomography. All eyes (n = 54) received 3 injections of ranibizumab in monthly intervals ("upload therapy"). Last review examination was performed 14 weeks after the initial treatment.

RESULTS: The mean PED height decreased from 515 µm (SD, 268.3) to 294 µm (SD, 201.9) at Week 14 with the highest degree of regression after the first treatment. A complete resolution of PED was noted in 8 eyes (15%). Using conventional regression model, none of the factors investigated, including height of PED, presence of intraretinal or subretinal fluid, intraretinal cysts, macular volume, retinal thickness, presence of foveal depression, presence of hemorrhage, and visual acuity, had a significant impact on the morphologic response. Using a modified binary logistic regression model ("bootstrapping"), presence of foveal depression ($P > 0.033$), and retinal thickness ($P > 0.004$) showed statistical significance.

CONCLUSION: This study on the responses and potential predictive factors associated with vascularized PED during the uploading phase of intravitreal ranibizumab shows a complete resolution of the PED in 15% of the cases.

PMID: 23598795 [PubMed - as supplied by publisher]

Retina. 2013 Apr 11. [Epub ahead of print]

RESPONSE OF RETINAL SENSITIVITY TO RANIBIZUMAB TREATMENT OF MACULAR EDEMA AFTER ACUTE BRANCH RETINAL VEIN OCCLUSION.

Mylonas G, Sacu S, Dunavoelgyi R, Matt G, Blum R, Buehl W, Pruente C, Schmidt-Erfurth U; on behalf of the Macula Study Group.

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

PURPOSE: To evaluate microperimetry changes in patients with acute macular edema secondary to branch retinal vein occlusion during a follow-up period of 12 months with intravitreal ranibizumab treatment (Lucentis; Novartis).

METHODS: Patients with macular edema secondary to branch retinal vein occlusion received an intravitreous injection of 0.5 mg of ranibizumab (0.05 mL). Best-corrected visual acuity, Spectralis OCT (Heidelberg Engineering), and color fundus photography were performed at monthly intervals over a follow-up period of 1 year. Macular function was documented by microperimetry (Nidek, MP-1) at baseline, 3, and 12 months.

RESULTS: Data of 20 patients without lack of microperimetry results were included to the statistical analyses. The size of the area of absolute scotoma was reduced from 16% at baseline to 11.7% at Month 3 and remained stable in the entire study duration ($P > 0.05$). Mean differential light threshold improved significantly under therapy from 9.47 dB at baseline to 12.53 dB at 12 months ($P < 0.001$). Best-corrected visual acuity correlated significantly with central millimeter thickness and mean retinal sensitivity at baseline and at 12-month follow-up visits.

CONCLUSION: In addition to anatomical restoration and increased visual acuity, intravitreal ranibizumab also improved the central macular function in patients with acute macular edema after branch retinal vein occlusion.

PMID: 23584689 [PubMed - as supplied by publisher]

Am J Pathol. 2013 Apr 3. pii: S0002-9440(13)00140-5. doi: 10.1016/j.ajpath.2013.01.052. [Epub ahead of print]

Ranibizumab Is a Potential Prophylaxis for Proliferative Vitreoretinopathy, a Nonangiogenic Blinding Disease.

Pennock S, Kim D, Mukai S, Kuhnle M, Chun DW, Matsubara J, Cui J, Ma P, Maberley D, Samad A, Van Geest RJ, Oberstein SL, Schlingemann RO, Kazlauskas A.

The Schepens Eye Research Institute, Massachusetts Eye and Ear Infirmary, and the Department of Ophthalmology, Harvard Medical School, Boston, Massachusetts.

Abstract: Proliferative vitreoretinopathy (PVR) exemplifies a disease that is difficult to predict, lacks effective treatment options, and substantially reduces the quality of life of an individual. Surgery to correct a rhegmatogenous retinal detachment fails primarily because of PVR. Likely mediators of PVR are growth factors in vitreous, which stimulate cells within and behind the retina as an inevitable consequence of a breached retina. Three classes of growth factors [vascular endothelial growth factor A (VEGF-A), platelet-derived growth factors (PDGFs), and non-PDGFs (growth factors outside of the PDGF family)] are relevant to PVR pathogenesis because they act on PDGF receptor α, which is required for experimental PVR and is associated with this disease in humans. We discovered that ranibizumab (a clinically approved agent that neutralizes VEGF-A) reduced the bioactivity of vitreous from patients and experimental animals with PVR, and protected rabbits from developing disease. The apparent mechanism of ranibizumab action involved derepressing PDGFs, which, at the concentrations present in PVR vitreous, inhibited non-PDGF-mediated activation of PDGF receptor α. These preclinical findings suggest that available approaches to neutralize VEGF-A are prophylactic for PVR, and that anti-VEGF-based therapies may be effective for managing more than angiogenesis- and edema-driven pathological conditions.

PMID: 23582767 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2013 Apr;36(4):297-8. doi: 10.1016/j.jfo.2013.03.003.

[New French guidelines: Diagnosis and management of age-related macular degeneration. A work, a story…].[Article in French]

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PMID: 23582523 [PubMed - in process]

Other treatment & diagnosis

Eye (Lond). 2013 Apr 19. doi: 10.1038/eye.2013.78. [Epub ahead of print]

Variability of subfoveal choroidal thickness measurements in patients with age-related macular degeneration and central serous chorioretinopathy.

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Purpose: To evaluate the variability in subfoveal choroidal thickness measurements in patients with age-related macular degeneration (AMD) and central serous chorioretinopathy using enhanced depth imaging optical coherence tomography (EDI-OCT).

Methods: One hundred and sixty eyes of 160 patients who were diagnosed with early AMD (N=40), exudative AMD (N=40), polypoidal choroidal vasculopathy (PCV, N=40), or central serous chorioretinopathy (CSC, N=40) were included in this retrospective observational study. In addition, we included 40 normal eyes of 40 subjects. Subfoveal choroidal thickness was measured manually by two masked observers based on EDI-OCT images. The correlation of choroidal thickness with the absolute value of the difference in the choroidal thickness measurement was estimated for all 200 eyes. Intraobserver and interobserver coefficients of repeatability (CRs) were calculated.

Results: There was a significant positive correlation between subfoveal choroidal thickness and both intraobserver (P<0.001) and interobserver (P<0.001) difference in choroidal thickness measurements. The mean intraobserver CRs in nonexudative AMD, exudative AMD, PCV, CSC, and normal eyes were ~15-21, 23-29, 24-35, 32-38, and 19-25 µm, respectively. The mean interobserver CRs were ~24-28, 30-36, 39-45, 46-57, and 26-35 µm, respectively.

Conclusions: Relatively great measurement variability should be considered when investigating eyes with pathologic conditions related to a thick choroid, including PCV or CSC.Eye advance online publication, 19 April 2013; doi:10.1038/eye.2013.78.

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Retina. 2013 Apr 15. [Epub ahead of print]

VITREOUS ATTACHMENT IN AGE-RELATED MACULAR DEGENERATION, DIABETIC MACULAR EDEMA, AND RETINAL VEIN OCCLUSION: A Systematic Review and Metaanalysis.

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PURPOSE: To determine if there is an association of vitreous attachment and wet age-related macular degeneration (AMD), diabetic macular edema, and retinal vein occlusion.

METHODS: Systematic review and metaanalysis.

RESULTS: Sixteen of 1,025 articles were eligible. In wet AMD, the prevalence of vitreomacular adhesion and posterior vitreous detachment was 23% (654 eyes) and 41% (251), respectively. Vitreomacular adhesion prevalence was 2.15 times that of controls (95% confidence interval, 1.34-3.48; p = 0.002) and 2.54 times that of dry AMD (confidence interval, 0.88-7.36; p 0.09); posterior vitreous detachment prevalence was lower than controls (relative risk 0.77; confidence interval, 0.64-0.93; p = 0.007) and dry AMD (0.56; confidence interval, 0.27-1.14; p = 0.11). It was not possible to determine the prevalence of vitreous attachment in diabetic macular edema, but vitreomacular traction was present in 29% of 188 surgical cases. The prevalence of posterior vitreous detachment in eyes with central and branch retinal vein occlusion was 30% (56 eyes) and 31% (71 eyes), respectively, versus 25% (64 eyes) in controls.

CONCLUSION: Observational studies of sufficient quality indicate that eyes with wet AMD have double the expected prevalence of vitreomacular adhesion and are less likely to have a posterior vitreous detachment. More controlled studies of diabetic macular edema and retinal vein occlusion are needed.

PMID: 23591535 [PubMed - as supplied by publisher]

Mol Biol Rep. 2013 Apr 16. [Epub ahead of print]

High yield of cells committed to the photoreceptor-like cells from conjunctiva mesenchymal stem cells on nanofibrous scaffolds.

Nadri S, Kazemi B, Eeslaminejad MB, Yazdani S, Soleimani M.

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Abstract: Transplantation of stem cells using biodegradable and biocompatible nanofibrous scaffolds is a promising therapeutic approach for treating inherited retinal degenerative diseases such as retinitis pigmentosa and age-related macular degeneration. In this study, conjunctiva mesenchymal stem cells (CJMSCs) were seeded onto poly-L-lactic acid (PLLA) nanofibrous scaffolds and were induced to differentiate toward photoreceptor cell lineages. Furthermore, the effects of orientation of scaffold on photoreceptor differentiation were examined. Scanning electron microscopy (SEM) imaging, quantitative real time RT-PCR (qPCR) and immunocytochemistry were used to analyze differentiated cells and their expression of photoreceptor-specific genes. Our observations demonstrated the differentiation of CJMSCs to photoreceptor cells on nanofibrous scaffolds and suggested their potential application in retinal regeneration. SEM imaging showed that CJMSCs were spindle shaped and well oriented on the aligned nanofiber scaffolds. The expression of rod photoreceptor-specific genes was significantly higher in CJMSCs differentiated on randomly-oriented nanofibers compared to those on aligned nanofibers. According to our results we may conclude that the nanofibrous PLLA scaffold reported herein could be used as a potential cell carrier for retinal tissue engineering and a combination of electrospun nanofiber scaffolds and MSC-derived conjunctiva stromal cells may have potential application in retinal regenerative therapy.

PMID: 23588957 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2013 Apr 15;13(1):13. [Epub ahead of print]

M-charts as a tool for quantifying metamorhopsia in age-related macular degeneration treated with the bevacizumab injections.

Nowomiejska K, Oleszczuk A, Brzozowska A, Grzybowski A, Ksiazek K, Maciejewski R, Ksi Ek P, Rejdak R.

BACKGROUND: This article is aimed to assess quantitatively metamorphopsia using M-charts in patients suffering from wet age-related macular degeneration (AMD) treated with the intravitreal bevacizumab injections and to compare the results with traditional Amsler grid and ocular coherence tomography (OCT).

METHODS: Thirty-six patients diagnosed with wet AMD were examined one day before and one month after the intraocular injection of bevacizumab. Horizontal and vertical metamorphopsia scores using M-charts, distance visual acuity, Amsler test and OCT were performed at each visit. Additionally, 23 healthy subjects were examined as a control group.

RESULTS: The horizontal metamorphopsia score improved in 22 patients, the vertical metamorphopsia score improved in 16 patients, the Amsler grid results improved in 6 patients, visual acuity improved in 17 patients. There was no correlation between the degree of metamorphopsia and the visual acuity or the central retinal thickness (CRT). The specificity of both the M-charts and Amsler grid was 100%.

CONCLUSIONS: The rate of metamorphopsia detection in wet AMD patients was better with M-charts than with Amsler grid. M-charts may be used in the assessment of efficacy of treatment with intravitreal bevacizumab injections as another outcome measure, moreover they can be used even at home for the self -assessment. M-charts provide additional information concerning the visual function, independent of the visual acuity, CRT and morphological changes in OCT.

PMID: 23587218 [PubMed - as supplied by publisher]

Retina. 2013 Apr 11. [Epub ahead of print]

SAFETY AND EFFICACY OF ORAL FLUORESCEIN ANGIOGRAPHY IN DETECTING MACULAR EDEMA IN COMPARISON WITH SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY.

Barteselli G, Chhablani J, Lee SN, Wang H, El Emam S, Kozak I, Cheng L, Bartsch DU, Azen S, Freeman

WR.

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PURPOSE: To evaluate the safety of oral fluorescein angiography (FA) and to compare its efficacy in detection of macular edema (ME) with spectral-domain optical coherence tomography (SD-OCT).

METHODS: Results of imaging studies for 1,928 eyes of 1,019 patients who had simultaneously undergone both oral FA and SD-OCT by a confocal laser ophthalmoscope were reviewed. Sensitivity in detecting ME, discrepancy rate, and "kappa" agreement were determined for both the techniques and with eyes stratified by disease diagnosis.

RESULTS: No allergic reactions occurred after oral FA. Mild gastric discomfort was noted in <1% of the patients; 1,840 eyes (95.4%) showed concordance between the two techniques, and kappa agreement was 90.3%. For ME, oral FA showed an overall sensitivity of 0.97 and SD-OCT of 0.91. Equivalent sensitivity was found in cases of wet age-related macular degeneration (0.99). Oral FA was more sensitive than SD-OCT in cases of retinovascular diseases. The SD-OCT showed higher sensitivity in cases of macular holes. Detection of ME by SD-OCT was significantly higher in cases of intense leakage on oral FA ($P < 0.001$).

CONCLUSION: Oral FA proved to be a safe and an adequate technique to evaluate ME. It is more sensitive than SD-OCT in detection of ME in cases of retinovascular diseases but can fail to detect ME in cases of macular holes. A noninvasive examination with simultaneous oral FA and SD-OCT may be considered to obtain a comprehensive evaluation of the presence of ME from different pathologies.

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THERAPEUTIC INTERVENTIONS FOR MACULAR DISEASES SHOW CHARACTERISTIC EFFECTS ON NEAR AND DISTANCE VISUAL FUNCTION.

Munk M, Kiss C, Huf W, Sulzbacher F, Bolz M, Sayegh R, Eisenkölbl S, Simader C, Schmidt-Erfurth U.

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PURPOSE: To compare therapy-induced reading and distance visual acuity (dVA) increases in neovascular age-related macular degeneration (nAMD) and uveitis-associated cystoid macular edema.

METHODS: This longitudinal study included 68 treatment-naive eyes: 39 subfoveal nAMD eyes with disrupted photoreceptor layers treated with monthly ranibizumab and 29 uveitis-associated cystoid macular edema eyes with intact photoreceptor layer treated with 1 triamcinolone injection. Patients were examined with high-definition optical coherence tomography, Early Treatment Diabetic Retinopathy Study dVA (logarithm of the minimum angle of resolution), reading acuity (logRADscore), and maximum reading speed (words per minute) over 3 months of therapy.

RESULTS: In uveitis-associated cystoid macular edema, logarithm of the minimum angle of resolution and logRADscore improved 1 day post treatment, from 0.49 ± 0.28 to 0.39 ± 0.3 ($P = 0.018$) and 0.71 ± 0.53 to 0.56 ± 0.49 ($P = 0.012$), respectively. In nAMD, logarithm of the minimum angle of resolution improved 1 week after anti-vascular endothelial growth factor therapy from 0.59 ± 0.29 to 0.49 ± 0.24 ($P = 0.002$), with no change in logRADscore. One month after treatment, logRADscore improved from 1.09 ± 0.65 to 0.90 ± 0.60 ($P = 0.002$). In uveitis-associated cystoid macular edema, the recovery course of reading and dVA was comparable, and in nAMD, reading acuity recovery was delayed. Irrespective of disease, a small reduction

in dVA resulted in a larger reading acuity decrease.

CONCLUSION: Cystoid macular edema resolution was associated with rapid synchronous reading and dVA improvement, whereas nAMD was followed by faster recovery of distance than reading acuity. In both conditions, reading acuity expressed by critical angular resolution was more suppressed by active disease and recovered relatively more than distance acuity. These discrepancies indicate that reading acuity might be a more sensitive measure for vision decrease in macular diseases than dVA. Reading acuity seems to be an important adjunct assessing intravitreal therapy efficacy.

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Retina. 2013 Apr 11. [Epub ahead of print]

SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY IMAGING OF DRUSENOID PIGMENT EPITHELIAL DETACHMENTS.

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PURPOSE: To evaluate drusenoid retinal pigment epithelial detachments (DPED) secondary to age-related macular degeneration (AMD) using spectral-domain optical coherence tomography imaging.

METHODS: In this prospective natural history study, eyes from patients with the diagnosis of nonexudative AMD and DPEDs were followed for at least 6 months. Eyes were scanned using the Cirrus spectral-domain optical coherence tomography instrument and the 200 × 200 A-scan raster pattern. A custom software was used to quantify volumetric changes in DPEDs and to detect the evolution and formation of geographic atrophy and choroidal neovascularization. Changes in DPED area and volume and development of the advanced forms of AMD were the main outcome.

RESULTS: Of the 130 patients (186 eyes) with nonadvanced AMD, 11 patients (16 eyes) presented with DPEDs during the study. Mean follow-up was 18.5 months. Most DPEDs had an area exceeding 1 disk area (14 of 16 eyes) based on color fundus images with a mean area of 4.19 mm (SD = 1.35) measured by spectral-domain optical coherence tomography. The mean volume at the time the DPED was diagnosed was 0.48 mm (SD = 0.28). Four different patterns of progression were observed: DPEDs remained unchanged in 8 of 16 eyes (50%), DPEDs tended to increase in volume before progressing to geographic atrophy in 5 eyes (31.25%) and choroidal neovascularization in 2 eyes (12.5%), and a DPED decreased by more than 50% without progressing to geographic atrophy or choroidal neovascularization in 1 eye (6.25%).

CONCLUSION: Spectral-domain optical coherence tomography imaging is able to detect subtle changes in the area and volume of DPEDs. Quantitative spectral-domain optical coherence tomography imaging of DPEDs is useful for identifying the natural history of disease progression and as a clinical tool for monitoring eyes with AMD in clinical trials.

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Stem Cells Transl Med. 2013 Apr 12. [Epub ahead of print]

A Simple and Scalable Process for the Differentiation of Retinal Pigment Epithelium From Human Pluripotent Stem Cells.

Maruotti J, Wahlin K, Gorrell D, Bhutto I, Lutty G, Zack DJ.

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Abstract: Age-related macular degeneration (AMD), the leading cause of irreversible vision loss and blindness among the elderly in industrialized countries, is associated with the dysfunction and death of the retinal pigment epithelial (RPE) cells. As a result, there has been significant interest in developing RPE culture systems both to study AMD disease mechanisms and to provide substrate for possible cell-based therapies. Because of their indefinite self-renewal, human pluripotent stem cells (hPSCs) have the potential to provide an unlimited supply of RPE-like cells. However, most protocols developed to date for deriving RPE cells from hPSCs involve time- and labor-consuming manual steps, which hinder their use in biomedical applications requiring large amounts of differentiated cells. Here, we describe a simple and scalable protocol for the generation of RPE cells from hPSCs that is less labor-intensive. After amplification by clonal propagation using a myosin inhibitor, differentiation was induced in monolayers of hPSCs, and the resulting RPE cells were purified by two rounds of whole-dish single-cell passage. This approach yields highly pure populations of functional hPSC-derived RPE cells that display many characteristics of native RPE cells, including proper pigmentation and morphology, cell type-specific marker expression, polarized membrane and vascular endothelial growth factor secretion, and phagocytic activity. This work represents a step toward mass production of RPE cells from hPSCs.

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Stem Cells Transl Med. 2013 Apr 18. [Epub ahead of print]

Rapid and Efficient Directed Differentiation of Human Pluripotent Stem Cells Into Retinal Pigmented Epithelium.

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Abstract: Controlling the differentiation of human pluripotent stem cells is the goal of many laboratories, both to study normal human development and to generate cells for transplantation. One important cell type under investigation is the retinal pigmented epithelium (RPE). Age-related macular degeneration (AMD), the leading cause of blindness in the Western world, is caused by dysfunction and death of the RPE. Currently, RPE derived from human embryonic stem cells are in clinical trials for the treatment of AMD. Although protocols to generate RPE from human pluripotent stem cells have become more efficient since the first report in 2004, they are still time-consuming and relatively inefficient. We have found that the addition of defined factors at specific times leads to conversion of approximately 80% of the cells to an RPE phenotype in only 14 days. This protocol should be useful for rapidly generating RPE for transplantation as well as for studying RPE development in vitro.

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Age-Related Macular Degeneration, ed. 2. Book Review

[No authors listed]

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Pathogenesis

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Differential regulation of microRNA-146a and microRNA-146b-5p in human retinal pigment epithelial cells by interleukin-1β, tumor necrosis factor-α, and interferon-γ.

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PURPOSE: The inflammatory response of the retinal pigment epithelium (RPE) is implicated in the pathogenesis of age-related macular degeneration. The microRNAs miR-146a and miR-146b-5p can regulate the inflammatory process by attenuating cytokine signaling via the nuclear factor-κB pathway. The aim of the present study is to investigate the expression of miR-146a and miR-146b-5p in human RPE cells and their response to proinflammatory cytokines.

METHODS: Confluent cultures of RPE cells established from adult human donor eyes were treated with the proinflammatory cytokines interferon (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-1β. The expression of microRNAs was analyzed by real-time PCR using total RNA fraction. The retinal pigment epithelial cell line ARPE-19 was employed to analyze the promoter activity of the genes encoding miR-146a and miR-146b-5p. STAT1-binding activity of oligonucleotides was analyzed by electrophoretic mobility shift assay. ARPE-19 cells were transiently transfected with miR-146a and miR-146b-5p mimics for the analysis of IRAK1 expression by western immunoblotting.

RESULTS: Real-time PCR analysis showed that miR-146a and 146b-5p are expressed in RPE cells. The cells responded to proinflammatory cytokines (IFN-γ + TNF-α + IL-1β) by highly increasing the expression of both miR-146a and miR-146b-5p. This was associated with an increase in the expression of transcripts for CCL2, CCL5, CXCL9, CXCL10, and IL-6, and a decrease in that for HMOX1. The miR-146a induction was more dependent on IL-1β, since its omission from the cytokine mix resulted in a greatly reduced response. Similarly, the induction of miR-146b-5p was more dependent on IFN-γ, since its omission from the cytokine mix minimized the effect. In addition, the increase in MIR146B promoter activity by the cytokine mix was effectively blocked by JAK inhibitor 1, a known inhibitor of the JAK/STAT signaling pathway. The expression of IRAK1 protein was decreased when ARPE-19 cells were transiently transfected with either miR-146a mimic or miR-146b-5p mimic.

CONCLUSIONS: Our results clearly show that both miR-146a and miR-146b-5p are expressed in human RPE cells in culture and their expression is highly induced by proinflammatory cytokines (IFN-γ + TNF-α + IL-1β). The induction of miR-146a showed a dependency on IL-1β, while that of miR-146b-5p on IFN-γ. Our results show for the first time that miR-146b-5p expression is regulated by IFN-γ, potentially via the JAK/STAT pathway. These two microRNAs could play a role in inflammatory processes underlying age-related macular degeneration or other retinal degenerative diseases through their ability to negatively regulate the nuclear factor-κB pathway by targeting the expression of IRAK1.

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Early degeneration of photoreceptor synapse in Ccl2/Cx3cr1deficient mice on Crb1rd8 background.

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Abstract: Photoreceptor ribbon synapse releases glutamate to postsynaptic targets. The synaptic ribbon may play multiple roles in ribbon synapse development, synaptic vesicle recycling, and synaptic transmission. Age-related macular degeneration (AMD) patients appear to have fewer or no detectable synaptic ribbons as well as abnormal swelling in the photoreceptor terminals in the macula. However, reports on changes of photoreceptor synapses in AMD are scarce and photoreceptor type and quantity affected in early AMD is still unclear. Here, we employed multiple anatomical techniques to investigate these questions in Ccl2-/- /Cx3cr1-/- mouse on Crb1rd8 background (DKO rd8) at one month of age. We found that approximately 17% of photoreceptors over the focal lesion were lost. Immunostaining for synapse-associated proteins (CtBP2, synaptophysin and vesicular glutamate transporter 1) showed significantly reduced expression pattern and ectopic localization. Cone opsins demonstrated dramatic reduction in expression (S-opsins) and extensive mislocalization (M-opsins). Quantitative ultrastructural analysis confirmed a significant decrease in the number of cone terminals and nuclei, numerous vacuoles in remaining cone terminals, reduction in the number of synaptic ribbons in photoreceptor terminals and ectopic rod ribbon synapses. In addition, glutamate receptor immunoreactivity on aberrant sprouting of rod bipolar cells and horizontal cells were identified at the ectopic synapses. These results indicate that synaptic alterations occur at the early stages of disease and cones are likely more susceptible to damage caused by DKO rd8 mutation. They provide a new insight into potential mechanism of vision function lost due to synaptic degeneration prior to cell death in the early stages of AMD. Synapse, 2013. © 2013 Wiley Periodicals, Inc.

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Autophagy. 2013 Apr 9;9(7). [Epub ahead of print]

Autophagy and heterophagy dysregulation leads to retinal pigment epithelium dysfunction and development of age-related macular degeneration.

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Abstract: Age-related macular degeneration (AMD) is a complex, degenerative and progressive eye disease that usually does not lead to complete blindness, but can result in severe loss of central vision. Risk factors for AMD include age, genetics, diet, smoking, oxidative stress and many cardiovascular-associated risk factors. Autophagy is a cellular housekeeping process that removes damaged organelles and protein aggregates, whereas heterophagy, in the case of the retinal pigment epithelium (RPE), is the phagocytosis of exogenous photoreceptor outer segments. Numerous studies have demonstrated that both autophagy and heterophagy are highly active in the RPE. To date, there is increasing evidence that constant oxidative stress impairs autophagy and heterophagy, as well as increases protein aggregation and causes inflammasome activation leading to the pathological phenotype of AMD. This review ties together these crucial pathological topics and reflects upon autophagy as a potential therapeutic target in AMD.

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Prevalence of Neutralizing Factors Against Adeno-Associated Virus Types 2 in Age related macular degeneration and Polypoidal Choroidal Vasculopathy.

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Abstract: Adeno-associated virus type 2 (AAV2) mediated gene therapy providing a potential treatment in the eye. However, immune responses can limit virally mediated gene transfer and therapy. To assess preexisting AAV2 neutralizing factors (NF) titers in peripheral blood and the vitreous in patients with age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV). 130 subjects were enrolled: 50 with neovascular AMD, 30 with PCV, and 50 controls. The serum and the vitreous were obtained for AAV2 NF assay. We found AAV2 NF are present in all of AMD, PCV patients and controls we tested. There were no significant differences in prevalence of NAb in serum between AMD, PCV and controls (P =0.999). There was no correlation between NF in serum and in vitreous (P>0.05), and NF in vitreous was significantly less than in serum. Our results for the first time showed in Chinese population, NF against AAV2 was present in serum of all the patients with AMD or PCV and controls, and there were no significant differences among these groups. Therefore, it demonstrated there were no correlations between AAV2 NF titer and these diseases. We found NF in vitreous was considerably less than in serum in all groups. We also found no direct correlation between NF in vitreous and in serum suggesting serum antibody levels may not be used to predict their counterparts in the vitreous. Our results will provide crucial information for future clinical studies in the development of new therapies based on AAV2 mediated gene delivery in the eye.

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Ocul Immunol Inflamm. 2013 Feb;21(1):36-43. doi: 10.3109/09273948.2012.726393.

Detection of Chlamydia and Complement Factors in Neovascular Membranes of Patients with Age-related Macular Degeneration.

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Purpose: To investigate whether Chlamydia pneumoniae and complement factors were present in surgically removed choroidal neovascular membranes (CNV) of patients with age-related macular degeneration (AMD).

Methods: Paraffin sections of 26 CNV were stained for C. pneumoniae or the complement factors H (CFH) and C5, whereas macrophages were identified by positive CD68 staining. Clinical characteristics have been correlated to the immunohistochemical findings.

Results: C. pneumoniae was found in 68% of the investigated membranes, and 88% of these membranes were also positive for CD68. Staining for CFH and C5 gave a positive reaction in 68 and 41% of the membranes, respectively. Patients with C5-positive membranes had significantly larger CNV mean area and were younger than patients with CFH-positive membranes at the operation time point.

Conclusions: Correlations between clinical symptoms and complement factor C5 could be shown. The results strengthen the hypothesis of an involvement of the complement system in AMD.

PMID: 23590149 [PubMed - in process]

Curr Pharm Biotechnol. 2013 Apr 11. [Epub ahead of print]

The Potential Roles of Metallothionein as a Therapeutic Target for Cerebral Ischemia and Retinal Diseases.

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Abstract: Methallothionein (MT) is a low molecular weight cysteine rich metalloprotein. In mammals, there are four isoforms (MT-1, -2, -3, and -4) and they have multiple roles, such as the detoxification of heavy metals, regulating essential metal homeostasis, and protecting against oxidative stress. Recently, accumulating studies have suggested that MTs (especially MT-1, -2, and -3) are an important neuroprotective substance for cerebral ischemia and retinal diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP), that are characterized by a progressive retinal degeneration. Oxidative stress and/or zinc toxicity has been implicated as part of the common pathway in these diseases. Studying the expression patterns and functions of MTs may broaden our understanding of the endogenous molecular responses that these diseases trigger, and may help us to develop new therapeutic strategies to treat them. However, the precise roles of MTs within the brain and retina are not fully understood in terms of neuropathological conditions. In this review, we discuss the recent findings focusing on MTs' functions following cerebral ischemia, AMD, and RP.

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Association of age and macular pigment optical density using dual-wavelength autofluorescence imaging.

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BACKGROUND: Several lines of evidence suggest that macular pigment may play a protective role against age-related macular degeneration, but the influence of age on macular pigment density levels remains unclear. This study was designed to investigate the relationship between age and the normal distribution of macular pigment optical density (MPOD) values surrounding the fovea.

METHODS: Consecutive healthy subjects with no evidence of ocular disease were enrolled in this study. After inclusion, MPOD values were measured at specific eccentricities (0.5, 1, and 2 degrees) from the foveal center using a dual-wavelength autofluorescence method employing a modified confocal scanning laser ophthalmoscope. Whenever both eyes were eligible, one was randomly selected for analysis. The correlation between age and MPOD values was investigated using regression analysis.

RESULTS: Thirty subjects (30 eyes) were included (mean age 48.6 ± 16.4 [range 23-77] years). Significant differences were found between MPOD values measured at 0.5, 1, and 2 degrees from the center of the fovea (0.49 ± 0.12 density units, 0.37 ± 0.11 density units, and 0.13 ± 0.05 density units, respectively, $P < 0.05$). Significant correlations between age and MPOD values at 0.5 and 1 degree were found ($P \leq 0.02$). Values measured at 2 degrees did not correlate significantly with age ($P = 0.06$).

CONCLUSION: In healthy subjects, MPOD values were highest near the foveal center. These values appeared to increase during adulthood (peak at 45-50 years), followed by a gradual reduction after 60 years of age.

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670nm LED ameliorates inflammation in the CFH-/- mouse neural retina.

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Abstract: Para-inflammation in the neural retina is thought to contribute to the onset of some age-related retinal diseases. Continuous innate immune system activation, manifests in progressive chronic inflammation, macrophage invasion and cell loss, resulting in visual loss. We have previously shown that mitochondrial function is augmented following 670nm LED exposure, leading to reduced retinal inflammation. Here, it was asked whether 670nm LED regulates para-inflammation in an aged-related macular degeneration mouse model. Mutant CFH-/- mice were exposed to four 90s exposures over 2days for 1week and 8weeks. These regimes significantly reduced activated macrophage number, TNF-alpha and MIF protein expression levels. Immuno-reactivity to C3, C3b and calcitonin, all markers of inflammatory status were also altered. Finally, innate immune proteins, TLR 2 and 4, showed a marked decrease in protein expression. These findings support the notion that 670nm LED regulates innate immunity, alleviating inflammation in the neural retina of an age-related macular degeneration mouse model.

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Epidemiology

Nepal J Ophthalmol. 2013 Jan;5(9):57-62. doi: http://dx.doi.org/10.3126/nepjoph.v5i1.7823.

Vitreo-retinal disorders at high altitude in Nepal.

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Introduction: Nepal has many mountains including the highest one in the world. People living in high altitude are often involved in climbing mountains. Objective: To explore the pattern of vitreo-retinal disorders at high altitude in Nepal.

Materials and methods: Consecutive patients aged 40 years and older who presented at the micro-surgical eye camp at Lukla of Solukhumbu district (2,860 metres) were included. Detailed ocular and systemic histories and ocular examination including dilated fundus evaluation were done.

Results: There were a total 81 patients with the mean age of 56.7 years (S.D 11.15). Females (51.9 %) outnumbered males. Sherpa comprised of 76.5 % followed by Rai (9.8 %). The main occupation was agriculture (51.9 %) followed by mountain trekking (28.4 %). Smokers comprised of 13.5 %. Hypertension was the predominant systemic problem (28 %). The best corrected visual acuity of 6/18 and better was found in 86.4 % of cases and less than 3/ 60 in 3.6 % of cases. Age-related macular degeneration (AMD) was found in 19.6 % of cases with a predominant mild AMD (16 %), hypertensive retinopathy in 12.2 %, with grade I hypertensive change in 8.6 %, retinal vein occlusion (RVO) in 7.1 % of cases and with a branch RVO in 4.9 %. Dilated and tortuous retinal vessels were present in 25.9 % of cases; out of this, 9.8 % of the cases had concurrent AMD and/or hypertensive retinopathy. Other retinal problems were macular hole (2.46 %), solar retinopathy (2.46 %) and choroidal tear (1.2 %).

Conclusion: AMD, hypertensive retinopathy, and RVO are the main vitreo-retinal disorders besides the dilated and tortuous retinal vessels in people living at high altitude in Nepal.

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Pattern of blindness in a community based hospital of Nepal.

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Introduction: Because of the availability of modern health facilities and moderately easy access to health services in the last 25 years, the blindness due to cataract and trachoma is expected to decline in Nepal. So it is felt that the causes of blindness need to be revised. Objective: To regroup the disease pattern leading to permanent blindness in patients attending a suburban multidisciplinary community-based hospital of Nepal.

Materials and methods: A cross-sectional, descriptive study was conducted in patients attending Dhulikhel hospital over a period of 12 months, from March 2010. Only the patients with best corrected visual acuity of less than 3/60 were enrolled in the study. A detailed ocular examination was carried out.

Results: A total of 76 eyes of 58 patients were analyzed. Of all, 32 were male (55.2 %). The mean age of the patients was 43.03 ± 22.98, with a range of 7 years to 84 years. Retinal diseases had the higher prevalence (23, 39.7 %) followed by amblyopia (10, 17.2 %) and corneal diseases (9, 15.51 %). Anisometropic amblyopia (3.94 %) was the commonest type of amblyopia. Retinitis pigmentosa (9.21 %) and age-related macular degeneration (7.89 %) were common retinal diseases whereas anterior staphyloma (5.26 %) and leucoma (3.94 %) were common corneal diseases. Other important and rare causes of blindness included ethambutol-induced optic neuropathy and vitelliform dystrophy.

Conclusion: Periodic collection of statistics on the relative frequency of the causes of blindness is important in socioeconomically developing nations like Nepal. This helps to revise the pattern of blinding diseases so that priorities can be redefined.

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Genetics

PLoS One. 2013 Apr 15;8(4):e60424. doi: 10.1371/journal.pone.0060424. Print 2013.

Alterations of choroidal blood flow regulation in young healthy subjects with complement factor h polymorphism.

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Abstract: A common polymorphism in the complement factor H gene (rs1061170, Y402H) is associated with a high risk of age-related macular degeneration (AMD). In the present study we hypothesized that healthy young subjects homozygous for the high-risk haplotype (CC) show abnormal choroidal blood flow (ChBF) regulation decades before potentially developing the disease. A total of 100 healthy young subjects were included in the present study, of which 4 subjects were excluded due to problems with genotyping or blood flow measurements. ChBF was measured continuously using laser Doppler flowmetry while the subjects performed isometric exercise (squatting) for 6 minutes. The increase in ChBF was less pronounced than the response in ocular perfusion pressure (OPP), indicating for some degree of choroidal blood flow regulation. Eighteen subjects were homozygous for C, 47 subjects were homozygous for T and 31 subjects were heterozygous (CT). The increase in OPP during isometric exercise was not different between groups. By contrast the increase in ChBF was more pronounced in subjects homozygous for the

high risk C allele (p=0.041). This was also evident from the pressure/flow relationship, where the increase in ChBF in homozygous C carriers started at lower OPPs as compared to the other groups. Our data indicate that the regulation of ChBF is abnormal in rs1061170 CC carriers. So far this polymorphism has been linked to age related macular degeneration (AMD) mainly via inflammatory pathways associated with the complement system dysfunction. Our results indicate that it could also be related to vascular factors that have been implicated in AMD pathogenesis.

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Mol Vis. 2013 Apr 5;19:822-8. Print 2013.

Association of the del443ins54 at the ARMS2 locus in Indian and Australian cohorts with age-related macular degeneration.

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PURPOSE: The ARMS2/HTRA1 genes at the 10q26 locus have been associated with risk of age-related macular degeneration (AMD), with the most significantly associated variants being A69S (rs10490924), del443ins54 (EU427539) and rs11200638. We wished to explore the association of the del443ins54 in two ethnically different populations from India and Australia.

METHODS: The del443ins54 was screened in a large cohort of ~1500 subjects from these two populations by a combination of PCR-based agarose gel electrophoresis and validated by resequencing. Statistical analysis comprised the calculations of allele, genotype and haplotype frequencies along with their p values and corresponding odds ratios (OR), and 95% confidence intervals (95% CI) and measures of linkage disequilibrium (LD).

RESULTS: The del443ins54 was significantly associated with AMD in both the Indian (p=1.74×10(-13); OR=2.80, 95%CI, 2.12-3.70) and Australian cohorts (p=2.78×10(-30); OR=3.15, 95%CI, 2.58-3.86). These associations were similar to those previously identified for the A69S and the rs11200638 variant in these populations that also exhibited high degrees of LD (D' of 0.87-0.99). A major risk haplotype of "T-indel-A" (p=5.7×10(-16); OR=3.16, 95%CI, 2.34-4.19 and p=6.33×10(-30); OR=3.15, 95%CI, 2.57-3.85) and a protective haplotype of "G-wild type-G" (p=2.35×10(-11); OR=0.39, 95%CI, 0.29-0.52 and p=1.02×10(-30); OR=0.31, 95%CI, 0.25-0.38) were identified in the Indian and Australian cohorts, respectively.

CONCLUSIONS: These data provide an independent replication of the association of del443ins54 variant in two different ethnicities, despite differences in allele and haplotype frequencies between them. High levels of LD in both populations limit further genetic dissection of this region in AMD.

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Diet

Ophthalmology. 2013 Apr 10. pii: S0161-6420(13)00036-5. doi: 10.1016/j.ophtha.2013.01.021. [Epub ahead of print]

Long-Term Effects of Vitamins C and E, β-Carotene, and Zinc on Age-Related Macular Degeneration: AREDS Report No. 35.

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OBJECTIVE: To describe the long-term effects (10 years) of the Age-Related Eye Disease Study (AREDS) formulation of high-dose antioxidants and zinc supplement on progression of age-related macular degeneration (AMD).

DESIGN: Multicenter, randomized, controlled, clinical trial followed by an epidemiologic follow-up study.

PARTICIPANTS: We enrolled 4757 participants with varying severity of AMD in the clinical trial; 3549 surviving participants consented to the follow-up study.

METHODS: Participants were randomly assigned to antioxidants C, E, and β-carotene and/or zinc versus placebo during the clinical trial. For participants with intermediate or advanced AMD in 1 eye, the AREDS formulation delayed the progression to advanced AMD. Participants were then enrolled in a follow-up study. Eye examinations were conducted with annual fundus photographs and best-corrected visual acuity assessments. Medical histories and mortality were obtained for safety monitoring. Repeated measures logistic regression was used in the primary analyses.

MAIN OUTCOME MEASURES: Photographic assessment of progression to, or history of treatment for, advanced AMD (neovascular [NV] or central geographic atrophy [CGA]), and moderate visual acuity loss from baseline (≥15 letters).

RESULTS: Comparison of the participants originally assigned to placebo in AREDS categories 3 and 4 at baseline with those originally assigned to AREDS formulation at 10 years demonstrated a significant ($P<0.001$) odds reduction in the risk of developing advanced AMD or the development of NV AMD (odds ratio [OR], 0.66, 99% confidence interval [CI], 0.53-0.83 and OR, 0.60; 99% CI, 0.47-0. 78, respectively). No significant reduction ($P = 0.93$) was seen for the CGA (OR, 1.02; 99% CI, 0.71-1.45). A significant reduction ($P = 0.002$) for the development of moderate vision loss was seen (OR 0.71; 99% CI, 0.57-0.88). No adverse effects were associated with the AREDS formulation. Mortality was reduced in participants assigned to zinc, especially death from circulatory diseases.

CONCLUSIONS: Five years after the clinical trial ended, the beneficial effects of the AREDS formulation persisted for development of NV AMD but not for CGA. These results are consistent with the original recommendations that persons with intermediate or advanced AMD in 1 eye should consider taking the AREDS formulation.

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Calorie restriction (CR) and CR mimetics for the prevention and treatment of age-related eye disorders.

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Abstract: The morbidity of ocular diseases, including macular degeneration, diabetic retinopathy, and dry eye disease, has been gradually increasing worldwide. Because these diseases develop from age-associated ocular dysfunctions, interventions against the aging process itself may be a promising strategy for their management. Among the several approaches to interrupt aging processes, calorie restriction (CR)

has been shown to recover and/or slow age-related functional declines in various organs, including the eye. Here, we review interventions against the aging process as potential therapeutic approaches to age-related ocular diseases. The effects of CR and CR mimetics in animal models of age-related eye diseases are explored. Furthermore, we discuss the possibilities of expanding this research to prospective studies to elucidate the molecular mechanisms by which CR and/or CR mimetics preserve ocular functions.

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