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MD Research News

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Drug treatment

Clin Ophthalmol. 2013;7:395-401. doi: 10.2147/OPTH.S41585. Epub 2013 Feb 27.

Three-year follow-up of visual outcome and quality of life in patients with age-related macular degeneration.

Rung L, Lövestam-Adrian M.

Department of Ophthalmology, Helsingborg Hospital, Helsingborg, Sweden.

BACKGROUND: The purpose of this study was to evaluate the visual outcome and self-reported vision-targeted health status in patients treated with intravitreal ranibizumab for wet age-related macular degeneration (AMD).

METHODS: A total of 51 eyes from 50 patients aged 76 ± 7 years, with wet AMD not previously treated, were included in this prospective study. Best corrected visual acuity was examined using Early Treatment Diabetic Research Study charts and near vision reading. All patients underwent an ophthalmological examination, including fluorescein and indocyanine green angiography (occult cases) and optical coherence tomography. The Visual Function Questionnaire test was completed before and 37 ± 7 months after the start of intravitreal injections.

RESULTS: The patients received a mean number of 7.8 ± 5.0 (range 2-22) injections. One month after the third intravitreal injection, significant improvement was seen in both visual acuity (53 ± 14 to 61 ± 14 letter, = 0.001) and near vision (17 ± 9 to 11 ± 8 points, = 0.001). During follow-up, mean visual acuity decreased from 53 ± 14 to 44 ± 24 letters (= 0.011), and near vision decreased from 17 ± 9 to 20 ± 11 points (= 0.048). Despite visual impairment, the quality of life test revealed no significant decrease in mental health (= 0.529) or ability to read a newspaper (= 0.21), but a decrease in distance activities (reading street signs, steps, going to the theater) from 57 ± 27 to 46 ± 31 points (= 0.007) was documented.

CONCLUSION: Decreased visual acuity was related to a decrease in self-reported visual function for distance activities, while mental health items, such as worrying, were not influenced.

PMID: 23467557 [PubMed]

Am J Ophthalmol. 2013 Feb 25. pii: S0002-9394(13)00068-8. doi: 10.1016/j.ajo.2013.01.012. [Epub ahead of print]

Management of Submacular Hemorrhage Secondary to Neovascular Age-Related Macular

Degeneration With Anti-Vascular Endothelial Growth Factor Monotherapy.

Shienbaum G, Garcia Filho CA, Flynn HW Jr, Nunes RP, Smiddy WE, Rosenfeld PJ.

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PURPOSE: To report the visual and anatomic outcomes of anti-vascular endothelial growth factor (VEGF) monotherapy in the management of marked submacular hemorrhage secondary to neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective, interventional, consecutive case series.

METHODS: Nineteen eyes of 18 patients with neovascular AMD and fovea involving submacular hemorrhage comprising greater than 50% of the lesion area were treated with anti-VEGF monotherapy. Main outcome measures included mean visual acuity change from baseline, mean central lesion thickness change from baseline, mean number of injections at 6 months, and adverse events. Snellen visual acuity was converted to approximate ETDRS letter score for the purpose of statistical analysis.

RESULTS: The mean change in approximate ETDRS letter score from baseline was +12 letters at 3 months (P = .003), +18 letters at 6 months (P = .001), and +17 letters at 12 months follow-up (P = .02). Seven eyes received ranibizumab, 6 eyes received bevacizumab, and 6 eyes received both at various time points. The mean number of injections at 6 months was 4.7. The mean OCT central lesion thickness decreased from 755 μm to 349 μm at 6 months follow-up (P = .0008).

CONCLUSIONS: Management with anti-VEGF monotherapy may yield visual and anatomic improvements in eyes with marked submacular hemorrhage secondary to neovascular AMD.

PMID: 23465269 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2013;7:437-42. doi: 10.2147/OPTH.S40427. Epub 2013 Feb 27.

Changes in neurophysiologic markers of visual processing following beneficial anti-VEGF treatment in macular degeneration.

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PURPOSE: Antivascular endothelial growth factor (VEGF) agents have been shown to improve visual acuity and prevent vision loss in exudative age-related macular degeneration. As the vision improves relatively quickly in response to intravitreal injections, we wanted to know whether this improvement is reflected in electrophysiological markers of visual cortical processing.

PATIENTS AND METHODS: Our interventional case series included six elderly patients who underwent injection treatment to the affected eye. Their visual acuity, tomographic images of retinal thickness, and visual evoked potentials (VEP) were assessed before treatment and six weeks after the last injection.

RESULTS: All patients showed improved visual acuity and reduced retinal fluid after the treatment. All but one patient showed increased VEP P100 component amplitudes and/or shortened latencies in the treated eye. These VEP changes were consistent with improved vision while the untreated eyes showed no changes.

CONCLUSIONS: Our results indicate that antivascular endothelial growth factor injections improved visual function of the treated eyes both in the level of the retina and in the level of visual cortical processing.

PMID: 23467427 [PubMed]

Ophthalmology. 2013 Feb 28. pii: S0161-6420(12)01162-1. doi: 10.1016/j.ophtha.2012.11.042. [Epub ahead of print]

Ranibizumab Treatment Outcomes in Phakic versus Pseudophakic Eyes: An Individual Patient Data Analysis of 2 Phase 3 Trials.

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OBJECTIVE: To compare visual outcomes in phakic and pseudophakic eyes treated with monthly intravitreal ranibizumab for exudative age-related macular degeneration (AMD).

DESIGN: Meta-analysis of individual patient data from 2 phase 3 clinical trials of intravitreal ranibizumab in neovascular AMD (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration [ANCHOR], ClinicalTrials.gov number, NCT00061594; and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration [MARINA], ClinicalTrials.gov number NCT00056836).

PARTICIPANTS AND CONTROLS: A total of 1137 patients from 2 phase 3 clinical trials.

METHODS: Phakic and pseudophakic eyes were treated with monthly intravitreal ranibizumab (0.3 mg or 0.5 mg), sham injections plus verteporfin photodynamic therapy (ANCHOR), or sham injections alone (MARINA).

MAIN OUTCOME MEASURES: Mean change from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity (VA) and the proportion of patients gaining or losing 15 or more ETDRS letters.

RESULTS: After adjusting for baseline covariates, no differences were seen in mean change in VA for phakic versus pseudophakic eyes. Pseudophakic eyes were more likely to lose 15 or more letters of vision than phakic eyes at 12 months, but not at 24 months.

CONCLUSIONS: Overall, in this analysis, lens status did not demonstrate an independent influence on mean VA for eyes treated with monthly ranibizumab. It is possible that phakic eyes may be less prone to severe vision loss.

PMID: 23453513 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2013 Mar 4. doi: 10.1111/aos.12091. [Epub ahead of print]

A three-year follow-up of ranibizumab treatment of exudative AMD: impact on the outcome of carrying forward the last acuity observation in drop-outs.

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Department of Ophthalmology, Linköping University, Sweden.

Purpose: To analyse a 3-year clinical patient cohort of ranibizumab treatment of exudative age-related macular degeneration (AMD), to investigate the impact on visual outcome of carrying forward the last acuity observation in drop-outs and to explore possible differences between the early and the late phase of the study.

Methods: A retrospective study of 312 eyes with neovascular AMD. The patients were followed up monthly, received three initial monthly injections of 0.5 mg ranibizumab and were re-treated pro re nata (PRN). Time-domain optical coherence tomography (TD-OCT) was used until spectral-domain (SD)-OCT

was introduced during the last year of enrolment. Sixty-five patients were discontinued from the study.

Primary outcome: change in best corrected visual acuity (BCVA).

Results: Best corrected visual acuity was 58.4 (CI 56.9-59.9) ETDRS (Early Treatment Diabetic Retinopathy Study) letters. At three months, it had increased by 4.1 letters (p = 0.0004), at 12 months by 1.8 letters, at 24 months by 1.0 letter and at 36 months by 0.1 letter. However, if the last available acuity of drop-outs was carried forward one step and included, acuity had increased by 3.9 letters at 3 months (p < 0.0001) and by 1.0 letter at 12 months but had decreased by 3.8 letters at 24 months (p = 0.019) and by 4.1 letters (p = 0.003) at 36 months. At 24 months, the result was significantly (p = 0.030) less favourable when drop-outs were included. In patients enrolled during the late phase, BCVA was 59.3 (CI 56.7-62.0). It had increased by 5.7 letters (p < 0.0001) at three months and by 5.8 letters at 12 months (p = 0.0016). In patients enrolled during the early phase, BCVA was 57.9 (CI 55.0-60.8). At three months, it had increased by 3.5 letters (p = 0.0008), but at 12 months, it had decreased by 2.3 letters (ns). The result at 12 months was significantly (p = 0.0033) better for the late than for the early phase. The number of injections was also significantly (p = 0.011) higher in the late phase. Adverse events were similar to those in earlier clinical trials.

Conclusions: The results of this 3-year cohort showed that the initial average acuity could be maintained over 36 months, which was comparable to those of many other clinical cohorts. However, if the last available acuity of drop-outs was carried forward one step and included, the acuity figures would have fallen significantly. The results in patients enrolled during the late phase of the study were fairly similar to those in clinical trials.

PMID: 23452436 [PubMed - as supplied by publisher]

Cesk Slov Oftalmol. 2012 Nov;68(5):171-7.

[Ranibizumab in the ARMD Wet Form Treatment - Two Years Results Obtained from the AMADEuS Registry]. [Article in Czech]

Matušková V, Kolář P, Vysloužilová D, Vlková E, Dušek L, Kandrnal V, Jarkovský J, Uher M.

Aim: The aim of this study was the retrospective follow up of Age-Related Macular Degeneration (ARMD) wet form patients treated with ranibizumab during 24 months period. The data were recorded into the AMADEuS (Age-related MAcular DEgeneration in patientS in the Czech Republic) Registry and after their evaluation compared with treatment results obtained from other departments of ophthalmology collaborating in the AMADEuS project or results of some foreign studies as well.

Patients and methods: The group consisted of patients registered since October 1, 2008 until June 11, 2012, followed up for 24 months period. There were 90 eyes of 89 patients. All patients were completely examined in the Macular ambulance of the Department of Ophthalmology in the Faculty Hospital Brno-Bohunice, Czech Republic, E.U., and consequently the ranibizumab (Lucentis, Novartis) was applied intravitreally in three initials doses one month apart. Thereafter, ranibizumab was applied "on demand". In 43.3 % of eyes the mostly classical, in 27.8 % of eyes occult, and in 28.9 % of eyes the minimally classical choroid neovascular membrane was present. The initial visual acuity was in 3.3 % of eyes in the range 15 - 30 letters of ETDRS optotypes (20/500 - 20/200), in 61.1 % of eyes in the range 31 - 60 letters (20/200 - 20/63), and the visual acuity better than 61 letters of ETDRS optotypes (better than 20/63) was in 35.6 % of eyes.

Results: The average initial best-corrected visual acuity (BCVA) in our group of patients was 54.2 letters of EDTRS (SD ± 14.4). At the visit at three months after the start of the treatment the BCVA was 59.6 letters of EDTRS (SD ± 15.0), at the visit after 6 months 57.3 letters of EDTRS (SD ± 14.7), after one year of the study 54.8 letters of EDTRS (SD ± 16), after 18 months of the study 53.4 letters of EDTRS (SD ± 16,8), and after 24 months of the study was the BCVA 51.7 letters of EDTRS (SD ± 16.9). The average CRT (central

retinal thickness) value by means of the OCT (optic coherence tomography) examination was at the beginning of the treatment 311.4 µm (SD ± 117.9), after 3 months of treatment 233.5 µm, (SD ± 85.4), after 6 months of treatment 262.2 µm, (SD ± 102,4), after 12 months 261 µm (SD ± 88,4), after 18 months 254.9 µm (SD ± 70.0), and after 24 months 249 µm (SD ± 87.5). The average number of ranibizumab doses during the follow-up period was 5.6. After the 24 months follow-up period, the gain of 15 or more letters of EDTRS was recorded in 11.1 % of patients, the gain of 1 - 14 letters of EDTRS optotypes was recorded in 32.2 % of patients, the decrease of 14 or less letters of EDTRS optotypes was found in 21.2 % of patients, and the decrease of 15 or more letters was found in our group in 22.2 % of patients.

Conclusion: The ARMD wet form treatment using ranibizumab is up to date the most effective available therapy. The AMADEuS registry is of great importance in the reviewing of the effectiveness of the ARMD wet form treatment. Klíčová slova: VPMD, registr, Amadeus, ranibizumab, vlhká forma, léčba.

PMID: 23461368 [PubMed - in process]

BMJ Open. 2013 Mar 1;3(3). pii: e002269. doi: 10.1136/bmjopen-2012-002269. Print 2013.

Current treatments in diabetic macular oedema: systematic review and meta-analysis.

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OBJECTIVES: The aim of this systematic review is to appraise the evidence for the use of anti-VEGF drugs and steroids in diabetic macular oedema (DMO) as assessed by change in best corrected visual acuity (BCVA), central macular thickness and adverse events

DATA SOURCE: MEDLINE, EMBASE, Web of Science with Conference Proceedings and the Cochrane Library (inception to July 2012). Certain conference abstracts and drug regulatory web sites were also searched.

STUDY ELIGIBILITY CRITERIA, PARTICIPANTS AND INTERVENTIONS: Randomised controlled trials were used to assess clinical effectiveness and observational trials were used for safety. Trials which assessed triamcinolone, dexamethasone, fluocinolone, bevacizumab, ranibizumab, pegaptanib or aflibercept in patients with DMO were included.

STUDY APPRAISAL AND SYNTHESIS METHODS: Risk of bias was assessed using the Cochrane risk of bias tool. Study results are narratively described and, where appropriate, data were pooled using random effects meta-analysis.

RESULTS: Anti-VEGF drugs are effective compared to both laser and placebo and seem to be more effective than steroids in improving BCVA. They have been shown to be safe in the short term but require frequent injections. Studies assessing steroids (triamcinolone, dexamethasone and fluocinolone) have reported mixed results when compared with laser or placebo. Steroids have been associated with increased incidence of cataracts and intraocular pressure rise but require fewer injections, especially when steroid implants are used.

LIMITATIONS: The quality of included studies varied considerably. Five of 14 meta-analyses had moderate or high statistical heterogeneity. CONCLUSIONS AND IMPLICATIONS OF KEY FINDINGS: The anti-VEGFs ranibizumab and bevacizumab have consistently shown good clinical effectiveness without major unwanted side effects. Steroid results have been mixed and are usually associated with cataract formation and intraocular pressure increase. Despite the current wider spectrum of treatments for DMO, only a small proportion of patients recover good vision (≥20/40), and thus the search for new therapies needs to continue.

PMID: 23457327 [PubMed]

Retina. 2013 Feb 28. [Epub ahead of print]

POLYPOIDAL CHOROIDAL VASCULOPATHY: Evidence-Based Guidelines for Clinical Diagnosis and Treatment.

Koh AH, Chen LJ, Chen SJ, Chen Y, Giridhar A, Iida T, Kim H, Yuk Yau Lai T, Lee WK, Li X, Han Lim T, Ruamviboonsuk P, Sharma T, Tang S, Yuzawa M; ON BEHALF OF THE EXPERT PCV PANEL.

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BACKGROUND: Polypoidal choroidal vasculopathy (PCV) is an exudative maculopathy affecting vision, with clinical features distinct from neovascular age-related macular degeneration. Currently, no evidence-based guidelines exist for its diagnosis and treatment.

METHODS: A panel of experts analyzed a systematic literature search on PCV together with results of the EVEREST trial, the only published randomized controlled clinical trial in PCV. At a subsequent Roundtable meeting, recommendations for the management of PCV were agreed based on this analysis and their own expert opinion.

RESULTS: Diagnosis of PCV should be based on early-phase nodular hyperfluorescence from choroidal vasculature visualized using indocyanine green angiography. Recommended initial treatment of juxtafoveal and subfoveal PCV is either indocyanine green angiography-guided verteporfin photodynamic therapy or verteporfin photodynamic therapy plus 3 × 0.5 mg ranibizumab intravitreal injections 1 month apart. If there is incomplete regression of polyps by indocyanine green angiography, eyes should be retreated with verteporfin photodynamic therapy monotherapy or verteporfin photodynamic therapy plus ranibizumab. If there is complete regression of polyps by indocyanine green angiography, but there is leakage on fluorescein angiography and other clinical or anatomical signs of disease activity, eyes should be retreated with ranibizumab.

CONCLUSION: Practical guidance on the clinical management of PCV is proposed based on expert evaluation of current evidence.

PMID: 23455233 [PubMed - as supplied by publisher]

PLoS One. 2013;8(3):e57642. doi: 10.1371/journal.pone.0057642. Epub 2013 Mar 4.

Structural characterization of a recombinant fusion protein by instrumental analysis and molecular modeling.

Wu Z, Zhou P, Li X, Wang H, Luo D, Qiao H, Ke X, Huang J.

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Abstract: Conbercept is a genetically engineered homodimeric protein for the treatment of wet age-related macular degeneration (wet AMD) that functions by blocking VEGF-family proteins. Its huge, highly variable architecture makes characterization and development of a functional assay difficult. In this study, the primary structure, number of disulfide linkages and glycosylation state of conbercept were characterized by high-performance liquid chromatography, mass spectrometry, and capillary electrophoresis. Molecular modeling was then applied to obtain the spatial structural model of the conbercept-VEGF-A complex, and to study its inter-atomic interactions and dynamic behavior. This work was incorporated into a platform useful for studying the structure of conbercept and its ligand binding functions.

PMID: 23469213 [PubMed - in process]

Other treatment and diagnosis

Consult Pharm. 2013 Mar;28(3):184-8. doi: 10.4140/TCP.n.2013.184.

Charles bonnet syndrome: treating nonpsychiatric hallucinations.

Nguyen ND, Osterweil D, Hoffman J.

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Abstract: Charles Bonnet syndrome (CBS) is characterized by recurrent or persistent complex visual hallucinations that occur in visually impaired individuals with intact cognition and no evidence of psychiatric illness. Patients usually retain insight into the unreal nature of their hallucinations.3,4 CBS is often misdiagnosed, and predominantly affects elderly patients with vision changes (e.g., age-related macular degeneration, glaucoma, and cataract). While many require only the assurance of the benign nature of the hallucinations, nonpharmacological and pharmacological interventions have been reported to be useful in the treatment of CBS. This case involves an 83-year-old female, with a two-year history of CBS, who presented to the clinic with worsening visual hallucinations over the past few months. She was starting to lose insight into her hallucinations secondary to her new diagnosis of dementia. Several pharmacological agents were explored to determine the most appropriate choice for our patient. Ultimately, this patient was started on donepezil (reported to be successful in a CBS case report), which helped improve her cognitive function. At future follow-up visits, her hallucinations improved and her cognitive function stabilized. Pharmacists should be aware of CBS and its treatment options to properly assist physicians in the medication-selection process to alleviate distress experienced by patients with CBS. In patients who may benefit from pharmacological treatment, physicians should weigh the risks and benefits of the different treatment options. Donepezil can be a favorable option in CBS patients with Alzheimer's type dementia.

PMID: 23462028 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2013 Mar 7. pii: iovs.12-11569v1. doi: 10.1167/iovs.12-11569. [Epub ahead of print]

COMPARISON OF DRUSEN AREA DETECTED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY AND COLOR FUNDUS IMAGING.

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PURPOSE: To compare the measurements of drusen area from manual segmentation of color fundus photographs with those generated by an automated algorithm designed to detect elevations of the retinal pigment epithelium (RPE) on spectral domain optical coherence tomography (SDOCT) images.

METHODS: Fifty eyes with drusen secondary to non-exudative age-related macular degeneration (AMD) were enrolled. All eyes were imaged with the Cirrus HD-OCT instrument (Carl Zeiss Meditec, Dublin, CA) using a 200x200 A-scan raster pattern covering a 6mm X 6mm area centered on the fovea. Digital color fundus images were taken on the same day. Drusen were traced manually on the fundus photos by graders at the Doheny Image Reading Center (DIRC) while quantitative OCT measurements of drusen were obtained by using a fully automated algorithm. The color fundus images were registered to the OCT dataset and measurements within corresponding 3mm and 5mm circles centered at the fovea were compared.

RESULTS: The mean areas (± standard deviation [range]) for the 3mm circles were SDOCT= 1.57 (±1.08 [0.03-4.44]); 3mm color fundus= 1.92 (±1.08 [0.20-3.95]); 5mm SDOCT=2.12 (±1.55 [0.03-5.40]); 5mm color fundus=3.38 (1.90 [0.39-7.49]). The mean differences between color images and the SDOCT and (Color - SDOCT) were 0.36 (±0.93) (p=0.008) for the 3mm circle and 1.26 (±1.38) (p<0.001) for the 5mm circle measurements. Intraclass correlation coefficients of agreements for 3mm and 5mm measurements were 0.599 and 0.540 respectively.

CONCLUSIONS: There was only fair agreement between drusen area measurements obtained from SDOCT images and color fundus photos. Drusen area measurements on color fundus images were larger than with SDOCT scans. This difference can be attributed to the fact that the OCT algorithm defines drusen in terms of RPE deformations above a certain threshold, and will not include small, flat drusen and subretinal drusenoid deposits. The two approaches provide complementary information about drusen.

PMID: 23471895 [PubMed - as supplied by publisher]

J Transl Med. 2013 Mar 1;11(1):53. [Epub ahead of print]

Stem cells: a new paradigm for disease modeling and developing therapies for age-related macular degeneration.

Melville H, Carpiniello M, Hollis K, Staffaroni A, Golestaneh N.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in people over age 55 in the U.S. and the developed world. This condition leads to the progressive impairment of central visual acuity. There are significant limitations in the understanding of disease progression in AMD as well as a lack of effective methods of treatment. Lately, there has been considerable enthusiasm for application of stem cell biology for both disease modeling and therapeutic application. Human embryonic stem cells and induced pluripotent stem cells (iPSCs) have been used in cell culture assays and in vivo animal models. Recently a clinical trial was approved by FDA to investigate the safety and efficacy of the human embryonic stem cell-derived retinal pigment epithelium (RPE) transplantation in sub-retinal space of patients with dry AMD These studies suggest that stem cell research may provide both insight regarding disease development and progression, as well as direction for therapeutic innovation for the millions of patients afflicted with AMD.

PMID: 23452406 [PubMed - as supplied by publisher]

PLoS One. 2013;8(2):e57828. doi: 10.1371/journal.pone.0057828. Epub 2013 Feb 28.

Treatment with 670 nm Light Up Regulates Cytochrome C Oxidase Expression and Reduces Inflammation in an Age-Related Macular Degeneration Model.

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Abstract: Inflammation is an umbrella feature of ageing. It is present in the aged retina and many retinal

diseases including age-related macular degeneration (AMD). In ageing and in AMD mitochondrial function declines. In normal ageing this can be manipulated by brief exposure to 670 nm light on the retina, which increases mitochondrial membrane potential and reduces inflammation. Here we ask if 670 nm exposure has the same ability in an aged mouse model of AMD, the complement factor H knockout (CFH) where inflammation is a key feature. Further, we ask whether this occurs when 670 nm is delivered briefly in environmental lighting rather than directly focussed on the retina. Mice were exposed to 670 nm for 6 minutes twice a day for 14 days in the form of supplemented environmental light. Exposed animals had significant increase in cytochrome c oxidase (COX), which is a mitochondrial enzyme regulating oxidative phosphorylation.There was a significant reduction in complement component C3, an inflammatory marker in the outer retina. Vimetin and glial fibrillary acidic protein (GFAP) expression, which reflect retinal stress in Muller glia, were also significantly down regulated. There were also significant changes in outer retinal macrophage morphology. However, amyloid beta (Aβ) load, which also increases with age in the outer retina and is pro-inflammatory, did not change. Hence, 670 nm is effective in reducing inflammation probably via COX activation in mice with a genotype similar to that in 50% of AMD patients even when brief exposures are delivered via environmental lighting. Further, inflammation can be reduced independent of Aβ. The efficacy revealed here supports current early stage clinical trials of 670 nm in AMD patients.

PMID: 23469078 [PubMed - in process]

Pathogenesis

J Nutr Health Aging. 2013;17(3):219-22. doi: 10.1007/s12603-012-0095-z.

Biomarkers of oxidative stress in patients with wet age related macular degeneration.

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Objective: The aim of this study was to analyze biomarkers of oxidative stress in patients with wet age related macular degeneration (AMD).

Participants and Measurements: Case-control study that includes 163 patients with wet AMD (age group of 55-82 years with the mean age of 71 years and 170 age-matched healthy controls in the age group of 55-78 years with the mean age of 71 years. The following parameters were determined: reduced and oxidized Glutathione (GSH/GSSH), protein carbonyl groups, total antioxidant activity in plasma and the activity of endogenous antioxidant enzymes, such as, gluthatione peroxidase, gluthatione reductase and superoxide dismutase.

Results: We observed total antioxidant activity higher in control group (CG) compared with patients with wet AMD (7.1 ± 1.2 μM Trolox vs 5.8 ± 1.1 μM Trolox). Values of superoxide dismutase activity (SOD), gluthatione reductase (GR) and gluthatione peroxidase (GPx) are higher in control group than in patients with wet AMD. According to the GSH/GSSH results, average values were higher in the CG than in patients with wet AMD and data were not significantly different. Values of protein carbonyl groups were higher in patients with wet AMD than in CG and significant differences were found.

Conclusions: The finding of the present study suggests that the patients with wet AMD are an altered metabolic state of oxidation-reduction and that it is convenient to give therapeutic interventions with antioxidants. We have demonstrated that systematic oxidative stress, measured by different biomarkers is closely associated with the wet AMD.

PMID: 23459973 [PubMed - in process]

ACS Nano. 2013 Mar 6. [Epub ahead of print]

Targeted Intraceptor Nanoparticle Therapy reduces Angiogenesis and Fibrosis in Primate & Murine Macular Degeneration.

Luo L, Zhang X, Hirano Y, Tyagi P, Barabás P, Uehara H, Miya TR, Singh N, Archer B, Qazi Y, Jackman K, Das SK, Olsen T, Chennamaneni SR, Stagg BC, Ahmed F, Emerson L, Zygmunt K, Whitaker R, Mamalis C, Huang W, Gao G, Srinivas SP, Krizaj D, Baffi J, Ambati J, Kompella UB, Ambati BK.

Abstract: Monthly intraocular injections are widely used to deliver protein-based drugs that cannot cross the blood-retina barrier for the treatment of leading blinding diseases such as age-related macular degeneration (AMD). This invasive treatment carries significant risks, including bleeding, pain, infection, and retinal detachment. Further, current therapies are associated with a rate of retinal fibrosis and geographic atrophy significantly higher than that which occurs in the described natural history of AMD. A novel therapeutic strategy which improves outcomes in a less invasive manner, reduces risk, and provides long-term inhibition of angiogenesis and fibrosis is a felt medical need. Here we show that a single intravenous injection of targeted, biodegradable nanoparticles delivering a recombinant Flt23k intraceptor plasmid homes to neovascular lesions in the retina and regresses CNV in primate and murine AMD models. Moreover, this treatment suppressed subretinal fibrosis, which is currently not addressed by clinical therapies. Murine vision, as tested by OptoMotry©, significantly improved with nearly 40% restoration of visual loss induced by CNV. We found no evidence of ocular or systemic toxicity from nanoparticle treatment. These findings offer a nanoparticle-based platform for targeted, vitreous-sparing, extended-release, nonviral gene therapy.

PMID: 23464925 [PubMed - as supplied by publisher]

PLoS One. 2013;8(2):e56819. doi: 10.1371/journal.pone.0056819. Epub 2013 Feb 14.

Inhibitory Effects of Resveratrol on PDGF-BB-Induced Retinal Pigment Epithelial Cell Migration via PDGFRβ, PI3K/Akt and MAPK pathways.

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PURPOSE: In diseases such as proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy, and age-related macular degeneration, retinal pigment epithelial (RPE) cells proliferate and migrate. Moreover, platelet-derived growth factor (PDGF) has been shown to enhance proliferation and migration of RPE cells in PVR. Even resveratrol can suppress the migration and adhesion of many cell types, its effects on RPE cell migration and adhesion remain unknown. In this study, we investigated the inhibitory effects of resveratrol on RPE cell migration induced by PDGF-BB, an isoform of PDGF, and adhesion to fibronectin, a major ECM component of PVR tissue.

METHODS: The migration of RPE cells was assessed by an electric cell-substrate impedance sensing migration assay and a Transwell migration assay. A cell viability assay was used to determine the viability of resveratrol treated-cells. The cell adhesion to fibronectin was examined by an adhesion assay. The interactions of resveratrol with PDGF-BB were analyzed by a dot binding assay. The PDGF-BB-induced signaling pathways were determined by western blotting and scratch wound healing assay.

RESULTS: Resveratrol inhibited PDGF-BB-induced RPE cell migration in a dose-dependent manner, but showed no effects on ARPE19 cell adhesion to fibronectin. The cell viability assay showed no cytotoxicity of resveratrol on RPE cells and the dot binding assay revealed no direct interactions of resveratrol with PDGF-BB. Inhibitory effects of resveratrol on PDGF-BB-induced platelet-derived growth factor receptor β (PDGFRβ) and tyrosine phosphorylation and the underlying pathways of PI3K/Akt, ERK and p38 activation

were found; however, resveratrol and PDGF-BB showed no effects on PDGFRα and JNK activation. Scratch wound healing assay demonstrated resveratrol and the specific inhibitors of PDGFR, PI3K, MEK or p38 suppressed PDGF-BB-induced cell migration.

CONCLUSIONS: These results indicate that resveratrol is an effective inhibitor of PDGF-BB-induced RPE cell migration via PDGFRβ, PI3K/Akt and MAPK pathways, but has no effects on the RPE cell adhesion to fibronectin.

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Levels of Aqueous Humor Trace Elements in Patients with Non-Exsudative Age-related Macular Degeneration: A Case-control Study.

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Abstract: Trace elements might play a role in the complex multifactorial pathogenesis of age-related macular degeneration (AMD). The aim of this study was to measure alterations of trace elements levels in aqueous humor of patients with non-exsudative (dry) AMD.For this pilot study, aqueous humor samples were collected from patients undergoing cataract surgery. 12 patients with dry AMD (age 77.9±6.62, female 8, male 4) and 11 patients without AMD (age 66.6±16.7, female 7, male 4) were included. Aqueous levels of cadmium, cobalt, copper, iron, manganese, selenium, and zinc were measured by use of Flow-Injection-Inductively-Coupled-Plasma-Mass-Spectrometry (FI-ICP-MS), quality controlled with certified standards.PATIENTS WITH AMD HAD SIGNIFICANTLY HIGHER AQUEOUS HUMOR LEVELS OF CADMIUM (MEDIAN: 0.70 µmol/L, IQR: 0.40-0.84 vs. 0.06 µmol/L; IQR: 0.01-.018; p=0.002), cobalt (median: 3.1 µmol/L, IQR: 2.62-3.15 vs. 1.17 µmol/L; IQR: 0.95-1.27; p<0.001), iron (median: 311 µmol/L, IQR: 289-329 vs. 129 µmol/L; IQR: 111-145; p<0.001) and zinc (median: 23.1 µmol/L, IQR: 12.9-32.6 vs. 5.1 µmol/L; IQR: 4.4-9.4; p=0.020) when compared with patients without AMD. Copper levels were significantly reduced in patients with AMD (median: 16.2 µmol/L, IQR: 11.4-31.3 vs. 49.9 µmol/L; IQR: 32.0-.142.0; p=0.022) when compared to those without. No significant differences were observed in aqueous humor levels of manganese and selenium between patients with and without AMD. After an adjustment for multiple testing, cadmium, cobalt, copper and iron remained a significant factor in GLM models (adjusted for age and gender of the patients) for AMD.Alterations of trace element levels support the hypothesis that cadmium, cobalt, iron, and copper are involved in the pathogenesis of AMD.

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Inflammatory Mediators Induced by Amyloid-Beta in the Retina and RPE in vivo: Implications for Inflammasome Activation in Age-Related Macular Degeneration.

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PURPOSE: Drusen are hallmarks of age-related macular degeneration (AMD). Amyloid beta 1-40 (Aβ 1-40), a constituent of drusen, is known to stimulate inflammatory pathways in RPE, however, its effect in vivo

is not known. The purpose of this study is to examine the effect of Aβ 1-40 on cytokine expression and inflammasome activation relevant to AMD in an animal model.

METHODS: Wild-type rats received intravitreal injections of Aβ 1-40 and eyes were taken from Day 1, 4, 14 and 49 post-injection. The RPE, neuroretina and vitreous were analyzed for cytokine expression, inflammasome activation, and microglial response via RT-PCR, immunohistochemistry and suspension array assay. Retinal cell loss was assessed via apoptotic markers and retinal thickness.

RESULTS: Aβ 1-40 stimulated upregulation of IL-6, TNF-α, IL-1β, IL-18, caspase-1, NLRP3 and XAF1 genes in the RPE/choroid and the neuroretina. Increased IL-1β and IL-6 immunoreactivity was found in retinal sections and elevated levels of IL-1β and IL-18 in the vitreous of Aβ-injected eyes. Aβ 1-40 induced a moderate increase in CD11b/c-reactive cells on Day 1 post-injection only. No evidence of the pro-apoptotic XAF1 protein, p53, TUNEL, or retinal thinning was observed.

CONCLUSION: These results confirm earlier in vitro work and support the pro-inflammatory role of drusen component Aβ 1-40 in the RPE and retina. Inflammasome activation may be responsible for this effect in vivo. This model is useful to understand cellular triggers of inflammasome activation and proposed early inflammatory events in the outer retina associated with the etiology of AMD.

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TNF-α disrupts morphologic and functional barrier properties of polarized retinal pigment epithelium.

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Abstract: Retinal pigment epithelial (RPE) cells form a blood-ocular barrier, and their polarized property is crucial for maintaining the barrier functions. Tumor necrosis factor alpha (TNF-α), a major pleotropic inflammatory cytokine that disrupts the barrier function and eventual angiogenesis, is expressed in the choroidal neovascularizations of age-related macular degeneration eyes. Thus, it most likely plays an important role in the progression of the disease. The purpose of this study was to compare the effects of TNF-α on the barrier function of polarized RPE cells. Non-polarized RPE cells were used as negative controls. Isolated porcine RPE cells were seeded on Transwell™ membranes. The polarization of the RPE cells was determined by their high transepithelial electrical resistance (TER >150 Ω cm2) and by their differential secretion of vascular endothelial growth factor (lower layer/upper layer >2.5X). Polarized RPE cells were incubated with 10 ng/ml of TNF-α and the TER was measured. TNF-α significantly decreased the TER of polarized RPE cells by 17.6 ± 2.7% ($P < 0.001$) of the control at 24 h and that of non-polarized RPE cells by 5.4 ± 6.5% ($P = 0.401$). The p38 mitogen-activated protein kinase (MAPK) inhibitor, SB203580, blocked the effects of TNF-α of decreasing the TER. Cell junction-related molecules, e.g., ZO-1, located between cells in control RPE cells, were disassembled by TNF-α, and this breakdown was suppressed by SB203580 in polarized RPEs. These results indicate that the breakdown of the RPE barrier function was caused exclusively by TNF-α in polarized RPEs, and TNF-α was acting through the p38 MAPK pathways. Investigations of polarized RPE cells should be more suitable for in vitro studies of the pathophysiology of retinochoroidal diseases.

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Morphometric analyses of the visual pathways in macular degeneration.

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INTRODUCTION: Macular degeneration (MD) causes central visual field loss. When field defects occur in both eyes and overlap, parts of the visual pathways are no longer stimulated. Previous reports have shown that this affects the grey matter of the primary visual cortex, but possible effects on the preceding visual pathway structures have not been fully established.

METHODS: In this multicentre study, we used high-resolution anatomical magnetic resonance imaging and voxel-based morphometry to investigate the visual pathway structures up to the primary visual cortex of patients with age-related macular degeneration (AMD) and juvenile macular degeneration (JMD).

RESULTS: Compared to age-matched healthy controls, in patients with JMD we found volumetric reductions in the optic nerves, the chiasm, the lateral geniculate bodies, the optic radiations and the visual cortex. In patients with AMD we found volumetric reductions in the lateral geniculate bodies, the optic radiations and the visual cortex. An unexpected finding was that AMD, but not JMD, was associated with a reduction in frontal white matter volume.

CONCLUSION: MD is associated with degeneration of structures along the visual pathways. A reduction in frontal white matter volume only present in the AMD patients may constitute a neural correlate of previously reported association between AMD and mild cognitive impairment.

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Epidemiology

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Incidence of Visual Impairment Over a 20-Year Period: The Beaver Dam Eye Study.

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PURPOSE: To describe visual impairment (VI) over a 20-year period and its associations with age-related eye diseases and socioeconomic factors in the Beaver Dam Eye Study.

DESIGN: Population-based cohort study.

PARTICIPANTS: Four thousand nine hundred twenty-six persons 43 to 86 years of age participated in the baseline examination phase from 1988 through 1990, and 3721, 2962, 2375, and 1913 persons participated in follow-up examinations each spaced 5 years apart from 1993 through 1995, 1998 through 2000, 2003 through 2005, and 2008 through 2010, respectively.

METHODS: Best-corrected visual acuity after refraction, assessed by the Early Treatment Diabetic Retinopathy Study protocol.

MAIN OUTCOME MEASURES: Incidence of VI, defined as best-corrected visual acuity of poorer than 20/40 in the better eye in persons with one or both eyes 20/40 or better at the beginning of a 5-year interval, and incidence of severe VI, defined as best-corrected visual acuity of 20/200 or worse in the better eye in persons with one or both eyes better than 20/200 at the beginning of a 5-year interval.

RESULTS: Overall incidence of VI between examinations (5-year interval) was 1.4% (varying from 0.1% in persons 50-54 years of age to 14.6% in those 85 years of age and older), whereas for severe VI it was 0.4% (varying from 0.0% in persons 50-54 years of age to 6.9% in those ≥85 years of age). The incidence of VI decreased for each period after adjustment for age, from the first 5-year interval between examinations (1988-1990 to 1993-1995) to the fourth and most recent 5-year interval (2003-2005 to 2008-2010; odds ratio fourth interval vs. first interval, 0.53; 95% confidence interval, 0.32-0.87; P = 0.01). This period effect was no longer significant after adjustment for age-related macular degeneration. Age-related macular degeneration remained the leading cause of incident severe VI (54% of eyes with incident severe VI, which was as low as 40% and as high as 57% for specific visits), with no evidence of a trend across visits. The overall frequency of VI correctable with new refraction was 38% of all eyes with VI.

CONCLUSIONS: These data provide population-based estimates that show a high (15%) 5-year incidence of VI in persons 85 years of age and older. Age-related macular degeneration remained the leading cause of severe VI in this population over the 20 years of the study.

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Macular Pigment Optical Density in Young Adults of South Asian Origin.

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PURPOSE: To assess the range of macular pigment optical density (MPOD) in a healthy group of young adults of South Asian origin; to investigate whether any dietary factors or personal characteristics were related to inter-subject variations in MPOD; and to compare the mean MPOD of the South Asian group with the mean MPOD of a white group.

METHODS: Heterochromatic flicker photometry was used to measure the MP levels of 169 healthy volunteers, of which 117 were Asian and 52 were white. In addition, the Asian participants completed a questionnaire pertaining to the various physical, ocular, lifestyle, dietary and environmental factors that may be associated with MPOD or age-related macular degeneration (AMD).

RESULTS: The mean MPOD of the Asian subjects was 0.43±0.14. The male participants had a higher mean MPOD than the females (0.47±0.13 vs 0.41±0.14, $p<0.01$). Possible associations also emerged between MPOD and form of refractive correction, and iris colour. No MPOD associations were found for the other variables examined in the questionnaire. The mean MPOD of the white subject group was 0.33±0.13, which was significantly lower than the Asian group ($p<0.0005$).

CONCLUSIONS: This study adds to the currently limited information on MPOD in South Asians, and while a comparison between Asians and Whites was not the main focus here, highly significant differences between these two ethnicities were revealed. This provokes the possibility that South Asian individuals could have a lower risk for AMD, and it warrants further study.

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Prevalence and causes of blindness in an urban area of Paraguay.

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PURPOSE: To determine the prevalence and causes of blindness in Piribebuy, Paraguay.

METHODS: A population based study was conducted from September to November 2007 in Piribebuy, Paraguay. Based on the city map, seven clusters were randomly selected, containing 22 to 36 squares (423 to 578 houses) each, where all subjects > 40 years old who agreed to participate were included in the study. Presenting vision acuity (VA) was obtained for each eye, with 'E' Snellen charts 6 meters far from the patient with appropriate light. Eyes with VA<20/60 were also tested with the pinhole. Objective and subjective refraction was performed, followed by examination of anterior segment under the slit-lamp, Goldmann applanation tonometry, and pupil dilatation with 0.5% tropicamide plus 0.5% phenylephrine, followed by evaluation of the posterior pole. Best corrected visual acuity was used to classify the patients as follows: blindness was defined as visual acuity of the better eye <20/400, low vision as 20/400 <VA <20/60 and visual impairment as VA <20/60. Similar to the methodology followed by the Rapid Assessment of Avoidable Blindness studies, in patients presenting more than one eye disease equally contributing to visual loss, only the most treatable or avoidable cause was recorded.

RESULTS: 402 subjects received ophthalmological evaluation (92.2% of the original sample). Prevalence of blindness and low vision adjusted for gender and age was 1.0% (95% CI: 0.3-2.7) and 4.5% (95% CI: 2.8 -7.1), respectively. Cataract was the only cause of blindness and the main cause of low vision (77.8% of the cases), followed by age-related macular degeneration (11.1%), pterygium (5.6%) and bilateral macular scar (5.6%).

CONCLUSION: The prevalence of blindness in Piribebuy was 1% and the main cause was cataract.

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Diabetes, Diabetic Retinopathy, and Age-Related Macular Degeneration: An Unexpected Relationship. Editorial

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Genetics

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Conditional ablation of the choroideremia gene causes age-related changes in mouse retinal pigment epithelium.

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Abstract: The retinal pigment epithelium (RPE) is a pigmented monolayer of cells lying between the photoreceptors and a layer of fenestrated capillaries, the choriocapillaris. Choroideremia (CHM) is an X-linked progressive degeneration of these three layers caused by the loss of function of Rab Escort protein-1 (REP1). REP1 is involved in the prenylation of Rab proteins, key regulators of membrane trafficking. To study the pathological consequences of chronic disruption of membrane traffic in the RPE we used a cell type-specific knock-out mouse model of the disease, where the gene is deleted only in pigmented cells (). Transmission electron microscopy (TEM) was used to quantitate the melanosome distribution in the RPE and immunofluorescent staining of rhodopsin was used to quantitate phagocytosed rod outer segments in retinal sections. The ultrastructure of the RPE and Bruch's membrane at different ages was characterised by TEM to analyse age-related changes occurring as a result of defects in membrane traffic pathways. gene knockout in RPE cells resulted in reduced numbers of melanosomes in the apical processes and delayed phagosome degradation. In addition, the RPE accumulated pathological changes at 5-6 months of age similar to those observed in 2-year old controls. These included the intracellular accumulation of lipofuscin-containing deposits, disorganised basal infoldings and the extracellular accumulation of basal laminar and basal linear deposits. The phenotype of the mice suggests that loss of the gene causes premature accumulation of features of aging in the RPE. Furthermore, the striking similarities between the present observations and some of the phenotypes reported in age-related macular degeneration (AMD) suggest that membrane traffic defects may contribute to the pathogenesis of AMD.

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