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MD Research News

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Drug treatment

Am J Ophthalmol. 2016 Jan 20. [Epub ahead of print]

Five Year Outcomes of Ranibizumab with Prompt or Deferred Laser versus Laser or Triamcinolone Plus Deferred Ranibizumab for Diabetic Macular Edema.

Diabetic Retinopathy Clinical Research Network (DRCR.net), Bressler SB, Glassman A, Almukhtar T, Bressler N, Ferris FL, Googe JM Jr, Gupta SK, Jampol LM, Melia M, Wells JA 3rd.

PURPOSE: To compare long-term vision and anatomic effects of ranibizumab with prompt or deferred laser versus laser or triamcinolone+laser with very deferred ranibizumab in diabetic macular edema (DME).

DESIGN: Randomized clinical trial METHODS: Eight hundred and twenty eight study eyes (588 [67%] completed the 5-year visit), at 52 sites, with visual acuity 20/32 to 20/320 and DME involving the central macula were randomly assigned to intravitreous ranibizumab (0.5mg) with either 1) prompt or 2) deferred laser; 3) sham injection+prompt laser; or 4) intravitreous triamcinolone (4mg)+prompt laser. The latter two groups could initiate ranibizumab as early as 74 weeks from baseline, for persistent DME with vision impairment. The main outcome measures were visual acuity, optical coherence central subfield thickness, and number of injections through five years.

RESULTS: At five years mean (± standard deviation) change in Early Treatment Diabetic Retinopathy Study visual acuity letter scores from baseline in the ranibizumab+deferred laser (N=111), ranibizumab+prompt laser (N=124), laser/very deferred ranibizumab (N=198), and triamcinolone+laser/very deferred ranibizumab (N=125) groups were 10±13, 8±13, 5±14, and 7±14 respectively. The difference (95% confidence interval) in mean change between ranibizumab+deferred laser and laser/very deferred ranibizumab and triamcinolone+laser/very deferred ranibizumab was 4.4 (1.2 to 7.6, P=0.001) and 2.8 (-0.9 to 6.5, P=0.067) respectively at 5 years.

CONCLUSIONS: Recognizing limitations of follow-up available at 5 years, eyes receiving initial ranibizumab therapy for center-involving DME, likely have better long-term vision improvements than eyes managed with laser or triamcinolone+laser followed by very deferred ranibizumab for persistent thickening and vision impairment.

PMID: 26802783 [PubMed - as supplied by publisher]

Int Ophthalmol. 2016 Jan 16. [Epub ahead of print]

The early effects of intravitreal anti vascular endothelial growth factor agents on intraocular pressure and central corneal thickness.

Omay E, Elgin U, Sen E, Yilmazbas P.

Abstract: To investigate the early effects of two intravitreal (IV) anti vascular endothelial growth factor

agents (anti-VEGF), bevacizumab and ranibizumab, on intraocular pressure (IOP) and central corneal thickness (CCT) within the first post-injection month. This prospective study comprised 109 eyes of 109 adult cases who had IV bevacizumab or ranibizumab injections because of age-related macular degeneration (ARMD), retinal venous occlusion (RVO), diabetic retinopathy, and macular edema or central serous chorioretinopathy (CSCR). None of the cases had medical histories of any kinds of glaucoma or increased IOP and IV injection before and all of them underwent a detailed ocular examination including measurements of IOP by non-contact tonometer and CCT by ultrasonic pachymeter pre-injection. IOP measurements were repeated at 30 min and 1st, 7th, and 30th day after the injection. CCT measurements were repeated at the 7th and 30th post-injection day. Paired sample t tests were used for the statistical analysis in order to evaluate the significance of changes in IOP and CCT. The mean age of 56 male and 53 female cases was 63.58 ± 11.04 years. Fifty-six cases (51.4 %) had diabetic retinopathy, 33 cases (30.3 %) had ARMD, 11 cases (10.1 %) had RVO, and 9 cases (8.3 %) had CSCR. Bevacizumab was used in 97 (89 %) cases and ranibizumab was used in 12 (11 %) cases. The IOP increased significantly 30 min after the injection ($p < 0.001$) but significant decreases were observed at the 1st, 7th, and 30th day post-injection ($p < 0.001$). No significant differences were observed in CCT between pre-injection and 7th and 30th post-injection day values ($p = 0.924$ and $p = 0.589$, respectively). Intravitreal bevacizumab and ranibizumab injections can cause hyper acute increase in IOP because of vitreal expansion but this effect is generally reversible in non-glaucomatous cases.

PMID: 26780098 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Jan 14. [Epub ahead of print]

Patient Preferences in the Treatment of Neovascular Age-Related Macular Degeneration: A Discrete Choice Experiment.

Mueller S, Agostini H, Ehlken C, Bauer-Steinhusen U, Hasanbasic Z, Wilke T.

PURPOSE: The objective of our study was to investigate preferences of patients with neovascular age-related macular degeneration (nAMD) for different anti-vascular endothelial growth factor (VEGF) treatment schemes.

DESIGN: We used a discrete choice experiment (DCE) design as part of a telephone interview.

PARTICIPANTS: Patients with nAMD aged at least 50 years were included in the study.

METHODS: Telephone interviews were done between November 2012 and October 2013.

MAIN OUTCOME MEASURES: In our DCE survey, we measured patient preferences toward specific levels of attributes that describe different options in the everyday intravitreal injection treatment setting: (1) treatment scheme; (2) change of visual acuity (VA); and (3) time the patient needs for each visit to the eye specialist.

RESULTS: A total of 284 patients with nAMD with a mean age of 77.4±7.1 years (women: 59.9%) completed the DCE interviews. Of them, 22.9% had poor VA at study inclusion, 54.9% had moderate VA, and 14.1% had good VA; VA was not available for 8.1% of the patients. Generally, patients preferred the attribute levels "improvement in VA" and "short time per specialist visit." The results for the attribute "treatment scheme" were inconclusive because none of the attribute levels (injections every 4 weeks, every 8 weeks, and pro re nata) were associated with statistically significant utility differences. This also mirrors the relative importance of the different attributes in patient decisions: "Change of VA" influenced decision making for a treatment option in 73.6% of cases; "waiting, treatment, and travel time" influenced decision making in 21.0% of cases; and "treatment scheme" influenced decision making for a treatment option in 5.4% of cases. To obtain improved VA instead of a worsening VA, patients in our study stated to be willing to accept a very long time needed per physician visit of 21.2 hours (8.5 hours for improved rather than stable VA and 12.7 hours for stable VA rather than worsening VA).

CONCLUSIONS: To prevent deterioration of VA, patients with nAMD seem to be willing to accept a high

treatment burden with regular intravitreal injections at short intervals and long periods of waiting, treatment, and traveling for their consultations.

PMID: 26778346 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Jan 8. [Epub ahead of print]

Angiographic Cystoid Macular Edema and Outcomes in the Comparison of Age-Related Macular Degeneration Treatments Trials.

Shah N, Maguire MG, Martin DF, Shaffer J, Ying GS, Grunwald JE, Toth CA, Jaffe GJ, Daniel E; Comparison of Age-related Macular Degeneration Treatments Trials Research Group.

PURPOSE: To describe morphologic and visual outcomes in eyes with angiographic cystoid macular edema (CME) treated with ranibizumab or bevacizumab for neovascular age-related macular degeneration (nAMD).

DESIGN: Prospective cohort study within a randomized clinical trial.

PARTICIPANTS: A total of 1185 CATT study subjects.

METHODS: Baseline fluorescein angiography (FA) images of all CATT study eyes were evaluated for CME. Grading of other characteristics on optical coherence tomography (OCT) and photographic images at baseline and during 2-year follow-up was completed by readers at the CATT Reading Centers. Three groups were created on the basis of baseline CME and intraretinal fluid (IRF) status: (1) CME, (2) IRF without CME, (3) neither CME nor IRF.

MAIN OUTCOME MEASURES: Visual acuity (VA) and total central retinal thickness (CRT) on OCT at baseline, year 1, and year 2.

RESULTS: Among 1131 participants with images of sufficient quality for determining CME and IRF at baseline, 92 (8.1%) had CME, 766 (67.7%) had IRF without CME, and 273 (24.1%) had neither. At baseline, eyes with CME had worse mean VA (letters) than eyes with IRF without CME and eyes with neither CME nor IRF (52 vs. 60 vs. 66 letters, $P < 0.001$); higher mean total CRT (μm) on OCT (514 vs. 472 vs. 404, $P < 0.001$); and greater hemorrhage, retinal angiomatous proliferation (RAP) lesions, and classic choroidal neovascularization (CNV). All groups showed improvement in VA at follow-up; however, the CME group started and ended with the worst VA among the 3 groups. Central retinal thickness, although higher at baseline for the CME group, was similar at 1 and 2 years follow-up for all groups. More eyes with CME (65.3%) developed scarring during 2 years of follow-up compared with eyes with IRF without CME (43.8%) and eyes with neither CME nor IRF (32.5%; $P < 0.001$).

CONCLUSIONS: In CATT, eyes with CME had worse baseline and follow-up VA, although all groups showed similar rates of improvement in VA during 2 years of follow-up. Cystoid macular edema seems to be a marker for poorer visual outcomes in nAMD because of underlying baseline retinal dysfunction and subsequent scarring.

PMID: 26778329 [PubMed - as supplied by publisher]

Jpn J Ophthalmol. 2016 Jan 22. [Epub ahead of print]

Effect of leaking capillaries and microaneurysms in the perifoveal capillary network on resolution of macular edema by anti-vascular endothelial growth factor treatment.

Iesato Y, Imai A, Hirano T, Toriyama Y, Murata T.

PURPOSE: To investigate the effect of leaking capillaries and microaneurysms (MAs) in the perifoveal capillary network (PCN) on the treatment of fovea-involving macular edema (ME) secondary to branch

retinal vein occlusion (BRVO) by intravitreal ranibizumab (IVR) injections combined with focal, grid, and scatter laser photocoagulation.

METHODS: Retrospective comparative case series. The MA (+) group consisted of 12 patients with leaking MAs in the PCN and the MA (-) group contained 11 patients without. At 6 months following the initial IVR injection, best corrected visual acuity (BCVA) was evaluated as the primary outcome. Secondary outcomes included central macular thickness (CMT) and the number of IVR injections performed in a pro re nata (PRN) regimen when CMT was ≥300 μm and vision deteriorated by 0.1 logMAR or greater.

RESULTS: Mean BCVA improved by 0.30 ± 0.25 logMAR in the MA (-) group and 0.28 ± 0.20 logMAR in the MA (+) group (both $P < 0.0001$). Mean CMT was reduced by 237.6 ± 221.4 μm ($P < 0.0001$) in the MA (-) and 158.2 ± 152.1 μm ($P < 0.01$) in the MA (+) group. The degrees of improvement in BCVA ($P = 0.74$) and CMT ($P = 0.33$) did not vary significantly between the groups. The mean number of additional IVR injections was significantly less in the MA (-) group than in the MA (+) group (2.2 ± 1.0 vs 3.0 ± 0.8; $P = 0.04$).

CONCLUSIONS: Although leaking MAs and capillaries in the PCN did not adversely affect improvements in BCVA and CMT, these manifestations led to an increased number of IVR injections needed to sustain resolution of ME involving the fovea.

PMID: 26801502 [PubMed - as supplied by publisher]

Biochem Pharmacol. 2016 Jan 12. [Epub ahead of print]

Single- and repeated-dose toxicity study of bevacizumab, ranibizumab, and aflibercept in ARPE-19 cells under normal and oxidative stress conditions.

Manuel-Saenz-de-Viteri, Fernández-Robredo P, Hernández M, Bezunartea J, Reiter N, Recalde S, García-Layana A.

Abstract: We assessed the effect of single and repeated doses of bevacizumab, ranibizumab, and aflibercept on cell viability, proliferation, permeability, and apoptosis of ARPE-19 cells. MTT and BrdU assays were used to determine viability and proliferation after single or repeated doses of anti-VEGF drugs under normal and oxidative stress conditions. Caspase-3 expression after single and repeated doses of the 3 drugs was assessed using immunofluorescence. Transepithelial-electrical-resistance (TER) was measured to study the effect of anti-VEGFs on retinal pigment epithelium (RPE) permeability under normal and oxidative stress conditions. Flow cytometry was used to detect intracellular accumulation of the drugs. Finally, a wound healing assay was performed to investigate the effect of the drugs on RPE cell migration. Single and multiple doses of anti-VEGF drugs had no effect on cell viability and proliferation. The oxidative effect of H2O2 decreased cell viability and proliferation; however, no difference was observed between anti-VEGF treatments. Immunofluorescence performed after single and repeated doses of the drugs revealed some caspase-3 expression. Interestingly, anti-VEGFs restored the increased permeability induced by H2O2. The 3 drugs accumulated inside the cells and were detectable 5 days after treatment. Finally, none of the drugs affected migration. In conclusion, no measureable toxic effect was observed after single or repeated doses of VEGF antagonists under normal and oxidative stress. Intracellular accumulation of the drugs does not seem to be toxic or affect cell functions. Our study suggests that anti-VEGFs could have a preventive effect in maintenance of the RPE barrier under oxidative stress.

PMID: 26793998 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2016 Jan 20. [Epub ahead of print]

Comparison of photodynamic therapy, ranibizumab/bevacizumab or combination in the treatment of myopic choroidal neovascularisation: a 9-year-study from a single centre.

Rishi P, Rishi E, Bhende M, Agarwal V, Vyas CH, Valiveti M, Bhende P, Rao C, Susvar P, Sen P, Raman R, Khetan V, Murali V, Ratra D, Sharma T.

AIM: To compare treatment outcomes for myopic choroidal neovascularisation (CNV) managed with verteporfin photodynamic therapy (vPDT), intravitreal antivascular endothelial growth factor (anti-VEGF, bevacizumab/ranibizumab) agents or combination thereof.

METHODS: Clinical data of 79 eyes with myopic CNV examined from March 2004 to July 2013 was retrospectively reviewed. Patients were managed with vPDT, intravitreal bevacizumab (1.25 mg/0.05 mL)/ ranibizumab (0.5 mg/0.05 mL) or a combination of vPDT and anti-VEGF. Outcome measures included complete regression (scarring) of CNV and best-corrected visual acuity (BCVA).

RESULTS: Treatments provided were vPDT (n=23), anti-VEGF (n=25) (ranibizumab, n=12; bevacizumab, n=13), vPDT+anti-VEGF (n=31). Mean logMAR BCVA changed from 0.59±0.44 to 0.49±0.40 at mean follow-up of 54.63±39.46 months. Mean logMAR vision changed from 0.68±0.57, 0.54±0.48 and 0.59±0.39 at presentation to 0.59±0.53, 0.38±0.44 and 0.37±0.37 at last follow-up in PDT (p=0.4), anti-VEGF (p=0.1) and vPDT+anti-VEGF groups (p=0.0002), respectively. CNV was scarred in 64 eyes (81%) at mean 11.03±13.56 months. Most common complication was macular scar (n=64), associated with reduced (n=17) or preserved (n=47) vision. Chorioretinal atrophy attributable to vPDT was seen in five eyes (vPDT, n=3; vPDT+anti-VEGF, n=2).

CONCLUSION: Combination of vPDT and intravitreal anti-VEGF (ranibizumab/bevacizumab) was associated with better visual outcomes and higher rates of regression in eyes with myopic CNV as compared with monotherapy with PDT or anti-VEGF. Larger size of CNV, and high refractive error were independent risk factors for poor visual outcomes.

PMID: 26792945 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 Jan 19. [Epub ahead of print]

Comparison of intravitreal aflibercept and ranibizumab injections on subfoveal and peripapillary choroidal thickness in eyes with neovascular age-related macular degeneration.

Yun C, Oh J, Ahn J, Hwang SY, Lee B, Kim SW, Huh K.

PURPOSE: We aimed to compare changes in subfoveal and peripapillary choroidal thickness (CT) after intravitreal aflibercept or ranibizumab injections for neovascular age-related macular degeneration (AMD).

METHODS: Medical records of 54 treatment-naïve, consecutive patients (54 eyes) who were diagnosed with neovascular AMD and received three monthly injections of aflibercept (21 eyes) or ranibizumab (33 eyes) were reviewed. Subfoveal and peripapillary CT were measured with images obtained using spectral domain optical coherence tomography at baseline and at three months.

RESULTS: Subfoveal CT decreased from 232.2 ± 94.4 μm at baseline to 207.1 ± 89.3 μm at three months in the aflibercept group ($p < 0.001$) and from 231.5 ± 102.9 μm to 220.0 ± 98.0 μm in the ranibizumab group ($p = 0.006$). The reduction was greater in the aflibercept group than in the ranibizumab group ($p = 0.024$). Peripapillary CT decreased from 157.2 ± 62.2 μm at baseline to 147.4 ± 62.2 μm at three months in the aflibercept group ($p < 0.001$). However, the change in peripapillary CT from 154.9 ± 46.5 μm at baseline to 152.3 ± 50.0 μm at three months was not significant in the ranibizumab group ($p = 0.123$).

CONCLUSIONS: Intravitreally injected aflibercept significantly decreased subfoveal CT more than ranibizumab. Choroidal thinning after aflibercept injection was not limited to the subfoveal area, but extended beyond the macula as well.

PMID: 26781585 [PubMed - as supplied by publisher]

Ophthalmologe. 2016 Jan 22. [Epub ahead of print]

[Analysis of cardiovascular diseases after the upload phase with intravitreal ranibizumab and bevacizumab in patients with exudative age-related macular degeneration]. [Article in German]

Fischer C, Schäfer K, Dschietzig T, Hoerauf H.

BACKGROUND: The intravitreal administration of vascular endothelial growth factor (VEGF) inhibitors is the gold standard in the treatment of exudative age-related macular degeneration (AMD) but the possible risks of systemic, particularly cardiovascular side effects are still discussed.

PATIENTS AND METHODS: We prospectively followed 111 patients at the University Hospital in Göttingen with exudative AMD and intravitreal ocular treatment with bevacizumab and ranibizumab during the upload phase of 3 months using a questionnaire for documentation of possible cardiovascular events.

RESULTS: In 5 out of 111 patients angina pectoris was observed and in 6 patients the antihypertensive medication had to be increased. No differences were found between bevacizumab and ranibizumab. A patient with pre-existing cardiovascular diseases suffered a stroke in the upload phase but no thromboembolic events were observed in the other patients.

CONCLUSION: In this small but prospective clinical study no increased risk for cardiovascular events during the upload phase of the VEGF inhibitors ranibizumab and bevacizumab could be detected when taking the age and pre-existing cardiovascular diseases into consideration.

PMID: 26801323 [PubMed - as supplied by publisher]

Cesk Slov Oftalmol. 2015 Fall;71(5):243-6.

[Aflibercept in the Diabetic Macular Edema Treatment]. [Article in Czech]

Studnička J.

Abstract: Diabetic retinopathy is together with the diabetic macular edema the most common cause of vision loss in the working population. It is also the most common diabetic microvascular abnormality. Aflibercept is approved for the diabetic macular edema treatment, it is a recombinant fusion protein, binding VEGF A, B, and P1GF. The efficacy and safety of the treatment comparing with the laser treatment were set by VIVID-DME and VISTA-DME studies. The T DRCR.net study protocol confirmed the efficacy of aflibercept, ranibizumab, and bevacizumab in the treatment of diabetic macular edema. The best results in the whole group were obtained if using aflibercept, especially in the group of patients with worse initial visual acuity. In all three studies, the safety of intraviteraly applied aflibercept was proven.

PMID: 26782727 [PubMed - in process]

Acta Ophthalmol. 2016 Jan 18. [Epub ahead of print]

Preservation of macular structure and function after intravitreal aflibercept for choroidal neovascularization associated with serpiginous choroiditis.

Schatz P, Skarin A, Lavaque AJ, Lima LH, Arevalo JF.

PMID: 26780597 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Feb;123(2):e14-6.

Re: Berg et al.: Comparison of ranibizumab and bevacizumab for neovascular age-related macular degeneration according to LUCAS treat-and-extend protocol (Ophthalmology 2015;122:146-52).

Avery RL.

PMID: 26802717 [PubMed - in process]

Ophthalmology. 2016 Feb;123(2):e11-2.

Re: Sophie et al.: Predictors of functional and anatomic outcomes in patients with diabetic macular edema treated with ranibizumab (Ophthalmology 2015;122:1395-401).

Shukla D.

PMID: 26802713 [PubMed - in process]

Other treatment & diagnosis

Photodiagnosis Photodyn Ther. 2016 Jan 15. [Epub ahead of print]

Photodynamic therapy in VEGF inhibition non-responders-pharmacogenetic study in age-related macular degeneration assessed with swept-source optical coherence tomography.

Teper SJ, Nowinska A, Pilat J, Wylegala E.

BACKGROUND: Treatment of neovascular age-related macular degeneration (nAMD) remains a major challenge in ophthalmology. It is essential to determine which of VEGF inhibition non-responders can benefit from photodynamic therapy (PDT). As AMD is strongly related to gene polymorphisms, genetic factors can modify efficacy of treatment. Swept-source optical coherence tomography (SS-OCT) gives exceptional insight into the retina and choroid. SS-OCT usefulness needs to be evaluated in nAMD patients.

METHODS: Prospective 6-month study included consecutive 110 patients (110 eyes) with predominantly classic neovascular AMD treated with photodynamic therapy. Only non-responders to anti-VEGF were included in the study. Greatest linear dimension (GLD) of the lesion, best corrected visual acuity (BCVA), central subfield macular thickness (CSMT) and central choroidal thickness were assessed and compared between CFH and ARMS2 genotype groups. Success rate was the main endpoint. It was defined as not active CNV in the center of the fovea and no worsening in BCVA. Multiple regression was used to assess gene polymorphisms influence on PDT results. Wilcoxon tests were performed to determine significance of changes from baseline values.

RESULTS: Following genotype frequencies were obtained - CFH CC 35 patients (31.8%), CT 52 (47.3%), TT 23 (20.9%); ARMS2 TT 28 patients (25.4%), GT 43 (39.1%), GG 39 (35.4%) Success rate in CC/CT/TT CFH and TT/GT/GG ARMS2 groups were as follows respectively: 22.9%, 28.8%, 30.4% and 28.6%, 25.6%, 28.2%. The differences were not significant with highest odds ratio TT vs. CC CFH 1.57 (95% CI 0.48-5.2, p=0.4). Significant increase in GLD was observed only in CC CFH group. Overall mean following measured parameters were obtained at baseline/day 7/Month 3/Month 6 (significant changes from baseline are marked with asterisk): GLD - 3825±1301μm/3901±1579μm/3861±1463μm/3925±1523μm; CSMT - 405±203μm/434±257μm*/321±163μm*/295±157* μm; CCT 235±103μm/278±157* μm/211±113μm*/201±107* μm; BCVA 49.3±12.5/43.2±14.2*/49.6±11.6/48.7±12.2 letters on ETDRS charts. In all patients classic component of the lesion was assessed with SS-OCT with no need to be reaffirmed in FA. Thus FA was used mainly for lesion size calculation.

CONCLUSIONS: Common genetic factors seem not to influence PDT effectiveness in VEGF inhibitors non-responders. SS-OCT is a valuable tool of nAMD monitoring, especially for choroid assessment. Deterioration of retinal structure and function is observed one week after PDT. It is related to increase in both retinal and choroidal thickness and is accompanied by mild temporary BCVA decrease.

PMID: 26780119 [PubMed - as supplied by publisher]

IEEE Trans Med Imaging. 2016 Jan 19. [Epub ahead of print]

Statistical Modeling of Retinal Optical Coherent Tomography.

Amini Z, Rabbani H.

Abstract: In this paper, a new model for retinal Optical Coherent Tomography (OCT) images is proposed. This statistical model is based on introducing a nonlinear transform, namely Gaussianization, to convert the probability distribution function (pdf) of each OCT intra-retinal layer to a Gaussian distribution. According to retina anatomy, the retina is a layered structure and in OCT images each of these layers has a specific pdf which is corrupted by speckle noise, therefore a mixture model for statistical modeling of OCT images is proposed. A Normal-Laplace distribution, which is a convolution of a Laplace pdf and Gaussian noise, is proposed as the distribution of each component of this mixture model in logarithmic domain. The reason for choosing Laplace pdf is the monotonically decaying behavior of OCT intensities in each layer for healthy cases. After fitting a Normal-Laplace mixture model to the data, each component is gaussianized and all of the gaussianized components are combined by the Averaged Maximum A Posterior (AMAP) method. To demonstrate the ability of this method for OCT image processing, a new contrast enhancement method based on this statistical model is proposed and tested on 130 randomly selected slices from thirteen healthy 3D OCTs taken by the Topcon 3D OCT and 60 randomly selected slices of five 3D OCTs from Age-related Macular Degeneration (AMD) patients, some of them presenting with pigment epithelium detachment, taken by Zeiss Cirrus HD-OCT. Comparing the results with two contending contrast enhancement techniques, the prominence of the proposed method is demonstrated both visually and numerically. Furthermore, to prove the efficacy of the proposed method for a more direct and specific purpose, an improvement in the segmentation of intra-retinal layers using the proposed contrast enhancement method as a preprocessing step, is demonstrated.

PMID: 26800532 [PubMed - as supplied by publisher]

Ophthalmologica. 2016 Jan 23. [Epub ahead of print]

Cotton Wool Spots after Anti-Vascular Endothelial Growth Factor Therapy for Macular Edema Associated with Central Retinal Vein Occlusion.

Kida T, Tsujikawa A, Muraoka Y, Harino S, Osaka R, Murakami T, Ooto S, Suzuma K, Morishita S, Fukumoto M, Suzuki H, Ikeda T.

PURPOSE: To report a case series, whereby we encountered a transient increase in retinal cotton wool spots (CWS) following anti-vascular endothelial growth factor (anti-VEGF) therapy for the treatment of macular edema secondary to central retinal vein occlusion (CRVO).

METHODS: Eighteen eyes were treated with intravitreal aflibercept (IVA), and 5 were treated with intravitreal ranibizumab (IVR). Fundus photographs obtained 1 month after initial IVA or IVR injections were retrospectively evaluated for the presence of CWS.

RESULTS: Twenty-one (91.3%) patients had the following systemic diseases: hypertension, diabetes mellitus without retinopathy, dyslipidemia, or chronic renal failure requiring dialysis. One month after treatment, reduced macular edema was observed in 21 (91.3%) eyes. Initial injections facilitated complete resolution in 14 eyes, and CWS gradually became fainter with additional injections.

CONCLUSION: Some eyes with CRVO-related macular edema can show a transient increase in CWS after initial anti-VEGF therapy; however, macular edema, retinal hemorrhage, and visual acuity were improved in almost every case.

PMID: 26800210 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Jan 9. [Epub ahead of print]

Macular Morphology and Visual Acuity in the Second Year of the Comparison of Age-related Macular Degeneration Treatments Trials.

Sharma S, Toth CA, Daniel E, Grunwald JE, Maguire MG, Ying GS, Huang J, Martin DF, Jaffe GJ; Comparison of Age-related Macular Degeneration Treatments Trials Research Group.

PURPOSE: To describe the association between morphologic features on fundus photography (FP), fluorescein angiography (FA), and optical coherence tomography (OCT) and visual acuity (VA) in the second year of the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

DESIGN: Prospective cohort study within a randomized clinical trial.

PARTICIPANTS: Participants in the CATT.

METHODS: Study eye eligibility required angiographic and OCT evidence of choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) and VA between 20/25 and 20/320. Treatment was assigned randomly to ranibizumab or bevacizumab with 3 different dosing regimens over a 2-year period.

MAIN OUTCOME MEASURES: Fluid type, location, and thickness; retina and subretinal tissue complex thickness on OCT; size and lesion composition on FP and FA; and VA.

RESULTS: Among 1185 CATT participants, 993 (84%) had fluid on OCT at baseline and completed 2 years of follow-up. At 2 years, intraretinal fluid (IRF), subretinal fluid (SRF), sub-retinal pigment epithelium (RPE) fluid, and subretinal tissue complex thickness decreased in all treatment groups. Ranibizumab monthly was best able to resolve each type of fluid. Eyes with SRF in the foveal center on OCT had better mean VA than eyes with no SRF (72.8 vs. 66.6 letters; P = 0.006). Eyes with IRF in the foveal center had worse mean VA than eyes without IRF (59.9 vs. 70.9 letters; P < 0.0001). Eyes with retinal thickness <120 μm had worse VA compared with eyes with retinal thickness 120 to 212 and >212 μm (59.4 vs. 71.3 vs. 70.3 letters; P < 0.0001). At 2 years, the mean VA (letters) of eyes varied substantially by the type of subfoveal pathology on FP and FA: 70.6 for no pathology; 74.1 for fluid only; 73.3 for CNV or pigment epithelial (RPE) detachment; 68.4 for nongeographic atrophy; and 62.9 for geographic atrophy, hemorrhage, RPE tear, or scar (P < 0.0001).

CONCLUSIONS: The associations between VA and morphologic features identified through year 1 were maintained or strengthened during year 2. Eyes with foveal IRF, abnormally thin retina, greater thickness of the subretinal tissue complex on OCT, and subfoveal geographic atrophy or scar on FP/FA had the worst VA. Subretinal fluid was associated with better VA.

PMID: 26783095 [PubMed - as supplied by publisher]

Exp Eye Res. 2016 Jan 13. [Epub ahead of print]

Subretinal AAV2.COMP-Ang1 Suppresses Choroidal Neovascularization and Vascular Endothelial Growth Factor in a Murine Model of Age-Related Macular Degeneration.

Lambert NG, Zhang X, Rai RR, Uehara H, Choi S, Carroll LS, Das SK, Cahoon JM, Kirk BH, Bentley BM, Ambati BK.

Abstract: To assess whether Tie2-mediated vascular stabilization ameliorates neovascular age-related macular degeneration (AMD), we investigated the impact of adeno-associated virus-mediated gene therapy with cartilage oligomeric matrix protein angiopoietin-1 (AAV2.COMP-Ang1) on choroidal neovascularization (CNV), vascular endothelial growth factor (VEGF), and hypoxia-inducible factor (HIF) in a mouse model of the disease. We treated mice with subretinal injections of AAV2.COMP-Ang1 or control (AAV2.AcGFP, AAV2.LacZ, and phosphate-buffered saline). Subretinal AAV2 localization and plasmid protein expression was verified in the retinal pigment epithelium (RPE)/choroid of mice treated with all AAV2 constructs. Laser-

assisted simulation of neovascular AMD was performed and followed by quantification of HIF, VEGF, and CNV in each experimental group. We found that AAV2.COMP-Ang1 was associated with a significant reduction in VEGF levels (29-33%, p<0.01) and CNV volume (60-70%, p<0.01), without a concomitant decrease in HIF1-α, compared to all controls. We concluded that a) AAV2 is a viable vector for delivering COMP-Ang1 to subretinal tissues, b) subretinal COMP-Ang1 holds promise as a prospective treatment for neovascular AMD, and c) although VEGF suppression in the RPE/choroid may be one mechanism by which AAV2.COMP-Ang1 reduces CNV, this therapeutic effect may be hypoxia-independent. Taken together, these findings suggest that AAV2.COMP-Ang1 has potential to serve as an alternative or complementary option to anti-VEGF agents for the long-term amelioration of neovascular AMD.

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Pathogenesis

PLoS One. 2016 Jan 22;11(1):e0147312. eCollection 2016.

Osmotic Induction of Angiogenic Growth Factor Expression in Human Retinal Pigment Epithelial Cells.

Veltmann M, Hollborn M, Reichenbach A, Wiedemann P, Kohen L, Bringmann A.

BACKGROUND: Although systemic hypertension is a risk factor of age-related macular degeneration, antihypertensive medications do not affect the risk of the disease. One condition that induces hypertension is high intake of dietary salt resulting in increased blood osmolarity. In order to prove the assumption that, in addition to hypertension, high osmolarity may aggravate neovascular retinal diseases, we determined the effect of extracellular hyperosmolarity on the expression of angiogenic cytokines in cultured human retinal pigment epithelial (RPE) cells.

METHODOLOGY/PRINCIPAL FINDINGS: Hyperosmolarity was induced by the addition of 100 mM NaCl or sucrose to the culture medium. Hypoxia and oxidative stress were induced by the addition of the hypoxia mimetic CoCl2 and H2O2, respectively. Alterations in gene expression were determined with real-time RT-PCR. Secretion of bFGF was evaluated by ELISA. Cell viability was determined by trypan blue exclusion. Nuclear factor of activated T cell 5 (NFAT5) expression was knocked down with siRNA. Hyperosmolarity induced transcriptional activation of bFGF, HB-EGF, and VEGF genes, while the expression of other cytokines such as EGF, PDGF-A, TGF-β1, HGF, and PEDF was not or moderately altered. Hypoxia induced increased expression of the HB-EGF, EGF, PDGF-A, TGF-β1, and VEGF genes, but not of the bFGF gene. Oxidative stress induced gene expression of HB-EGF, but not of bFGF. The hyperosmotic expression of the bFGF gene was dependent on the activation of p38α/β MAPK, JNK, PI3K, and the transcriptional activity of NFAT5. The hyperosmotic expression of the HB-EGF gene was dependent on the activation of p38α/β MAPK, ERK1/2, and JNK. The hyperosmotic expression of bFGF, HB-EGF, and VEGF genes was reduced by inhibitors of TGF-β1 superfamily activin receptor-like kinase receptors and the FGF receptor kinase, respectively. Hyperosmolarity induced secretion of bFGF that was reduced by inhibition of autocrine/paracrine TGF-β1 signaling and by NFAT5 siRNA, respectively. Hyperosmolarity decreased the viability of the cells; this effect was not altered by exogenous bFGF and HB-EGF. Various vegetable polyphenols (luteolin, quercetin, apigenin) inhibited the hyperosmotic expression of bFGF, HB-EGF, and NFAT5 genes.

CONCLUSION: Hyperosmolarity induces transcription of bFGF and HB-EGF genes, and secretion of bFGF from RPE cells. This is in part mediated by autocrine/paracrine TGF-β1 and FGF signaling. It is suggested that high intake of dietary salt resulting in osmotic stress may aggravate neovascular retinal diseases via stimulation of the production of angiogenic factors in RPE cells, independent of hypertension.

PMID: 26800359 [PubMed - in process]

Klin Monbl Augenheilkd. 2016 Jan;233(1):57-65. Epub 2016 Jan 21.

[Placenta Growth Factor (PlGF) and Retinal Vascular Diseases - Current Knowledge from Experimental and Clinical Studies]. [Article in German]

Augustin AJ.

Abstract: Pathological angiogenesis is a major characteristic of many diseases, such as cancer and retinal vascular disorders. Vascular diseases of the eye, such as diabetic retinopathy (DR) and neo-vascular age-related macular degeneration (nAMD), are the main cause of severe vision loss. The specific role of the cytokine VEGF-A in these pathologies has been proven in many ways. Thus, VEGF-A is still the major target for antiangiogenic therapy. Recently, another angiogenic factor, the placental growth factor (PlGF), has become a focal point for clinical research. This interest is based on the fact that the expression of PlGF is limited to embryonic development and PlGF can hardly be found in healthy tissues. During pathological angiogenetic processes, such as retinal vascular diseases, however, PlGF is increasingly expressed. Substances which inhibit the effect of PlGF and thus pathological angiogenesis, without simultaneously affecting healthy tissues, could significantly extend the therapeutic options for the treatment of retinal vascular diseases. Convincing results have recently been published from clinical trials in oncology, as well as preclinical investigations in animal models of retinal vascular diseases. The aim of this review is to summarise the role of PlGF in retinal vascular diseases and the available experimental data on the therapeutic potential of PlGF inhibitors.

PMID: 26797889 [PubMed - in process]

J Vis Exp. 2015 Dec 27;(106).

A Mouse Model for Laser-induced Choroidal Neovascularization.

Shah RS, Soetikno BT, Lajko M, Fawzi AA.

Abstract: The mouse laser-induced choroidal neovascularization (CNV) model has been a crucial mainstay model for neovascular age-related macular degeneration (AMD) research. By administering targeted laser injury to the RPE and Bruch's membrane, the procedure induces angiogenesis, modeling the hallmark pathology observed in neovascular AMD. First developed in non-human primates, the laser-induced CNV model has come to be implemented into many other species, the most recent of which being the mouse. Mouse experiments are advantageously more cost-effective, experiments can be executed on a much faster timeline, and they allow the use of various transgenic models. The miniature size of the mouse eye, however, poses a particular challenge when performing the procedure. Manipulation of the eye to visualize the retina requires practice of fine dexterity skills as well as simultaneous hand-eye-foot coordination to operate the laser. However, once mastered, the model can be applied to study many aspects of neovascular AMD such as molecular mechanisms, the effect of genetic manipulations, and drug treatment effects. The laser-induced CNV model, though useful, is not a perfect model of the disease. The wild-type mouse eye is otherwise healthy, and the chorio-retinal environment does not mimic the pathologic changes in human AMD. Furthermore, injury-induced angiogenesis does not reflect the same pathways as angiogenesis occurring in an age-related and chronic disease state as in AMD. Despite its shortcomings, the laser-induced CNV model is one of the best methods currently available to study the debilitating pathology of neovascular AMD. Its implementation has led to a deeper understanding of the pathogenesis of AMD, as well as contributing to the development of many of the AMD therapies currently available.

PMID: 26779879 [PubMed - in process]

Sci Rep. 2016 Jan 22;6:19718.

Association of toll-like receptor 3 polymorphism rs3775291 with age-related macular degeneration: a systematic review and meta-analysis.

Ma L, Tang FY, Chu WK, Young AL, Brelen ME, Pang CP, Chen LJ.

Abstract: Association of a polymorphism rs3775291 in the toll-like receptor 3 (TLR3) gene with age-related macular degeneration (AMD) had been investigated intensively, with variable results across studies. Here we conducted a meta-analysis to verify the effect of rs3775291 on AMD. We searched for genetic association studies published in PubMed, EMBASE and Web of Science from start dates to March 10, 2015. Totally 235 reports were retrieved and 9 studies were included for meta-analysis, involving 7400 cases and 13579 controls. Summary odds ratios (ORs) with 95% confidence intervals (CIs) for alleles and genotypes were estimated. TLR3 rs3775291 was associated with both geographic atrophy (GA) and neovascular AMD (nAMD), with marginally significant pooled-P values. Stratification analysis by ethnicity indicated that rs3775291 was associated with all forms of AMD, GA and nAMD only in Caucasians (OR = 0.87, 0.78 and 0.77, respectively, for the TT genotype) but not in East Asians. However, the associations could not withstand Bonferroni correction. This meta-analysis has thus revealed suggestive evidence for TLR3 rs3775291 as an associated marker for AMD in Caucasians but not in Asians. This SNP may have only a small effect on AMD susceptibility. Further studies in larger samples are warranted to confirm its role.

PMID: 26796995 [PubMed - in process]

Front Cell Neurosci. 2016 Jan 12;9:512. eCollection 2015.

Spontaneous Oscillatory Rhythms in the Degenerating Mouse Retina Modulate Retinal Ganglion Cell Responses to Electrical Stimulation.

Goo YS, Park DJ, Ahn JR, Senok SS.

Abstract: Characterization of the electrical activity of the retina in the animal models of retinal degeneration has been carried out in part to understand the progression of retinal degenerative diseases like age-related macular degeneration (AMD) and retinitis pigmentosa (RP), but also to determine optimum stimulus paradigms for use with retinal prosthetic devices. The models most studied in this regard have been the two lines of mice deficient in the β-subunit of phosphodiesterase (rd1 and rd10 mice), where the degenerating retinas exhibit characteristic spontaneous hyperactivity and oscillatory local field potentials (LFPs). Additionally, there is a robust ~10 Hz rhythmic burst of retinal ganglion cell (RGC) spikes on the trough of the oscillatory LFP. In rd1 mice, the rhythmic burst of RGC spikes is always phase-locked with the oscillatory LFP and this phase-locking property is preserved regardless of postnatal ages. However, in rd10 mice, the frequency of the oscillatory rhythm changes according to postnatal age, suggesting that this rhythm might be a marker of the stage of degeneration. Furthermore when a biphasic current stimulus is applied to rd10 mice degenerate retina, distinct RGC response patterns that correlate with the stage of degeneration emerge. This review also considers the significance of these response properties.

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Mol Med Rep. 2016 Jan 18. [Epub ahead of print]

Allicin attenuates H2O2‑induced cytotoxicity in retinal pigmented epithelial cells by regulating the levels of reactive oxygen species.

Tu G, Zhang YF, Wei W, Li L, Zhang Y, Yang J, Xing Y.

Abstract: Retinal pigmented epithelial cell (RPE) oxidative stress is known to have a vital role in the etiology of age‑related macular degeneration (AMD). The present study aimed to investigate whether allicin, a natural product with antioxidant activity, was able to protect RPEs (ARPE‑19) from hydrogen peroxide (H2O2)‑induced damage, and to determine the underlying mechanisms. The 3-(4,5-dimethylthiazol-2-yl)-2,5‑diphenyl tetrazolium bromide assay was used to determine cellular viability, and reactive oxygen species (ROS) were detected using a ROS Assay kit. The results demonstrated that allicin was able to protect ARPE‑19 cells from H2O2‑induced damage in a dose‑dependent manner. In addition, allicin

attenuated oxidative stress by reducing the levels of intracellular ROS and malondialdehyde (MDA), and enhancing the glutathione/glutathione disulfide (GSSG) ratio. With regards to the underlying mechanism, allicin was able to markedly modulate the expression levels of ROS‐associated enzymes, including superoxide dismutase, NADPH oxidase 4 and NAD(P)H dehydrogenase quinone 1, and elevate the activity of nuclear factor erythroid 2‐related factor 2 in the H2O2‐stimulated ARPE‐19 cells. These results suggested that allicin may exert protective effects against H2O2‐induced cytotoxicity in RPEs via ROS regulation.

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Invest Ophthalmol Vis Sci. 2016 Jan 1;57(1):94-104.

Cone Viability Is Affected by Disruption of Melatonin Receptors Signaling.

Gianesini C, Hiragaki S, Laurent V, Hicks D, Tosini G.

PURPOSE: Previous studies have demonstrated that melatonin has an important role in the modulation of photoreceptor viability during aging and may be involved in the pathogenesis of age-related macular degeneration.This hormone exerts its influence by binding to G-protein coupled receptors named melatonin receptor 1 (MT1) and 2 (MT2). Melatonin receptors 1 and 2 activate a wide variety of signaling pathways.

METHODS: Melatonin-proficient mice (C3H/f+/+) and melatonin-proficient mice lacking MT1 or MT2 receptors (MT1-/- and MT2-/-) were used in this study. Mice were killed at the ages of 3 and 18 months, and photoreceptor viability was determined by counting nuclei number in the outer nuclear layer (ONL). Cones were identified by immunohistochemistry using peanut agglutinin (PNA) and green/red and blue opsin antibodies. Protein kinase B (AKT) and forkhead box O (FOXO1) were assessed by Western blotting and immunohistochemistry.

RESULTS: The number of nuclei in the ONL was significantly reduced in C3Hf+/+, MT1-/-, and MT2-/- mice at 18 months of age with respect to 3-month-old animals. In 18-month-old MT1-/- and MT2-/- mice, but not in C3H/f+/+, the number of cones was significantly reduced with respect to young MT1-/- and MT2-/- mice or age-matched C3H/f+/+. In C3H/f+/+, activation of the AKT-FOXO1 pathway in the photoreceptors showed a significant difference between night and day.

CONCLUSIONS: Our data indicate that disruption of MT1/MT2 heteromer signaling induces a reduction in the number of photoreceptors during aging and also suggest that the AKT-FOXO1 survival pathway may be involved in the mechanism by which melatonin protects photoreceptors.

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Epidemiology

Semin Ophthalmol. 2016 Jan 21:1-5. [Epub ahead of print]

Prevalence of Pseudoexfoliation Syndrome in Turkish Patients with Senile Cataract.

Gunes A, Yasar C, Tok L, Tok O.

PURPOSE: To investigate the prevalence of pseudoexfoliation syndrome (PEX) among Turkish patients with senile cataract.

MATERIALS AND METHODS: Records of 352 eyes of 352 patients who underwent cataract surgery were analyzed in this retrospective study. The presence of PEX, type of cataract, intraocular pressure (IOP), glaucoma, age-related macular degeneration, and systemic diseases (coronary artery disease, hypertension, diabetes mellitus) were recorded.

RESULTS: The overall prevalence of PEX syndrome was detected to be 11%. The mean age of PEX patients was significantly higher than without PEX (74.4 ± 7.2 years and 69.3 ± 11.4 years, respectively, p = 0.004). The most common cataract type in the PEX patients was mixed-type cataract determined in 51.2% of patients. IOP was significantly higher in eyes with PEX than in eyes without it (16.1 ± 4.5 mmHg and 14.7 ± 3.8 mmHg, respectively; p = 0.03). Moreover, the prevalence of age-related macular degeneration was found to be significantly higher, and prevalence of glaucoma slightly higher in PEX patients than without PEX.

CONCLUSION: Pseudoexfoliation syndrome is a common condition in Turkish people. PEX is associated with mixed type of cataract, age-related macular degeneration, and elevated IOP. Therefore, PEX patients should be checked for concomitant diseases.

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Genetics

Br J Ophthalmol. 2016 Jan 22. [Epub ahead of print]

Characterising the phenotype and progression of sporadic adult-onset foveomacular vitelliform dystrophy.

Tiosano L, Grunin M, Hagbi-Levi S, Banin E, Averbukh E, Chowers I.

BACKGROUND/AIMS: Adult-onset foveomacular vitelliform dystrophy (AFVD) is a relatively common macular degeneration which might lead to substantial visual loss. Our purpose was to describe the natural course of genetically evaluated patients with sporadic AFVD.

METHODS: A retrospective, consecutive, cohort study included 95 eyes of 51 patients. Mutations in genes previously associated with AFVD (PRPH2, BEST1, IMPG-1 and IMPG-2) were evaluated. Demographics, clinical characteristics, and spectral domain optical coherence tomography features were analysed. Main outcome measures were changes in the best corrected visual acuity (BCVA) and lesion morphology during the follow-up.

RESULTS: The mean age (±SD) at diagnosis was 73.8±10.7 years. Mean (±SD) follow-up period was 30.4±16.3 months (range 0-44 months; median 25 months). All patients were genotyped negative for the evaluated mutations. Fifty-three of the eyes were followed for at least 36 months. At baseline these eyes had a mean BCVA (±SD) of 0.27±0.35 LogMAR, and at 36-months BCVA decreased to 0.38±0.35 (p=0.02). At baseline, 23 of these 53 eyes (43.4%) had the vitelliform stage, while only 10 eyes (18.9%) remained at this stage at 36 months (p=0.01). Ellipsoid zone alterations progressed during the follow-up (n=53 eyes) and showed correlation with BCVA reduction (Pearson's correlation coefficient=0.7, p=0.03).

CONCLUSIONS: Sporadic AFVD is a slowly progressing macular degeneration of older people. It is associated with visual decline at the rate of approximately one ETDRS line during 3 years. Patients with sporadic AFVD are usually negative for the known mutations previously associated with this phenotype, and present at an age that is higher than described for monogenic AFVD.

PMID: 26802173 [PubMed - as supplied by publisher]

Genet Epidemiol. 2016 Feb;40(2):133-43. Epub 2016 Jan 18.

Gene-Based Association Analysis for Censored Traits Via Fixed Effect Functional Regressions.

Fan R, Wang Y, Yan Q, Ding Y, Weeks DE, Lu Z, Ren H, Cook RJ, Xiong M, Swaroop A, Chew EY, Chen W.

Abstract: Genetic studies of survival outcomes have been proposed and conducted recently, but statistical

methods for identifying genetic variants that affect disease progression are rarely developed. Motivated by our ongoing real studies, here we develop Cox proportional hazard models using functional regression (FR) to perform gene-based association analysis of survival traits while adjusting for covariates. The proposed Cox models are fixed effect models where the genetic effects of multiple genetic variants are assumed to be fixed. We introduce likelihood ratio test (LRT) statistics to test for associations between the survival traits and multiple genetic variants in a genetic region. Extensive simulation studies demonstrate that the proposed Cox RF LRT statistics have well-controlled type I error rates. To evaluate power, we compare the Cox FR LRT with the previously developed burden test (BT) in a Cox model and sequence kernel association test (SKAT), which is based on mixed effect Cox models. The Cox FR LRT statistics have higher power than or similar power as Cox SKAT LRT except when 50%/50% causal variants had negative/positive effects and all causal variants are rare. In addition, the Cox FR LRT statistics have higher power than Cox BT LRT. The models and related test statistics can be useful in the whole genome and whole exome association studies. An age-related macular degeneration dataset was analyzed as an example.

PMID: 26782979 [PubMed - in process] PMCID: PMC4724326 [Available on 2017-02-01]

Genet Mol Res. 2015 Dec 21;14(4):17432-8.

Genome-wide analysis of single nucleotide polymorphisms in patients with atrophic age-related macular degeneration in oldest old Han Chinese.

Zhou TQ, Guan HJ, Hu JY.

Abstract: The aim of this study was to identify disease-associated loci in oldest old Han Chinese with atrophic age-related macular degeneration (AMD). This genome-wide association study (GWAS) only included oldest old (≥95 years old) subjects in Rugao County, China. Thirty atrophic AMD patients and 47 age-matched non-AMD controls were enrolled. The study subjects underwent a complete ophthalmic examination. Genomic DNA was extracted from peripheral blood samples. Single nucleotide polymorphisms (SNPs) were scanned by Genome-Wide Human Mapping SNP 6.0 Arrays and GeneChip Scanner 3000 7G. The results were read and analyzed by the Affymetrix Genotyping Console software. We filtered out the SNPs with a no-call rate ≥10%, MAF $P < 0.05$, and HWE $P < 0.001$. The remaining 561,277 SNPs were included in the association analysis. We found that the following 2 SNPs had the highest association with atrophic AMD: rs7624556 (located on 3q24) and rs13119914 (located on 4q34.3). In conclusion, we identified two atrophic AMD-associated SNPs (rs7624556 and rs13119914) in an oldest old Han Chinese population. This finding may lead to new strategies for screening of atrophic AMD for Han Chinese.

PMID: 26782385 [PubMed - in process]

Stem cells

Trends Mol Med. 2016 Jan 11. [Epub ahead of print]

Cell-Based Therapy for Degenerative Retinal Disease.

Zarbin M.

Abstract: Stem cell-derived retinal pigment epithelium (RPE) and photoreceptors (PRs) have restored vision in preclinical models of human retinal degenerative disease. This review discusses characteristics of stem cell therapy in the eye and the challenges to clinical implementation that are being confronted today. Based on encouraging results from Phase I/II trials, the first Phase III clinical trials of stem cell-derived RPE transplantation are underway. PR transplant experiments have demonstrated restoration of visual function in preclinical models of retinitis pigmentosa and macular degeneration, but also indicate that no single approach is likely to succeed in overcoming PR loss in all cases. A greater understanding of the mechanisms controlling synapse formation as well as the immunoreactivity of transplanted retinal cells is

urgently needed.

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Diet, lifestyle & low vision

Food Funct. 2016 Jan 19. [Epub ahead of print]

A protective effect of anthocyanins and xanthophylls on UVB-induced damage in retinal pigment epithelial cells.

Silván JM, Reguero M, de Pascual-Teresa S.

Abstract: Increased exposure to solar ultraviolet B (UVB) radiation causes oxidative damage that may promote age related macular degeneration (AMD) and other ocular pathologies. This study is aimed to demonstrate the protective effects of some anthocyanins and xanthophylls against the UVB-induced oxidative damage to retinal pigment epithelial (RPE) cells. ARPE-19 cells were treated with 5 μM cyanidin-3 -O-glucoside, delphinidin-3-O-glucoside, lutein, zeaxanthin or a mixture of cyanidin-3-O-glucoside : zeaxanthin prior to UVB exposure (500 J m-2). Cell viability and mitogen-activated protein kinase (MAPK) phosphorylation were determined by MTT assay and western blot analysis, respectively. Oxidative damage was evaluated by measuring the intracellular reactive oxygen species (ROS). The data showed that UVB irradiation reduces the cell viability to 46% with increasing of intracellular ROS levels and phosphorylation of MAPKs. However, pre-treatment (60 min) with 5 μM cyanidin-3-O-glucoside, lutein or zeaxanthin significantly reduced cellular ROS levels and phosphorylation of MAPKs (JNK1/2 and p38) mediated by UVB irradiation and subsequently increased cell viability. Thus, results show that UVB irradiation is able to induce apoptosis in ARPE-19 cells through oxidative stress; however anthocyanins and xanthophylls pre-treatment can attenuate this damage. This suggests that cyanidin-3-O-glucoside, lutein and zeaxanthin are effective in preventing UVB-induced damage in RPE cells and may be suitable as chemoprotective factors for the prevention of ocular damage. The use of natural dietary antioxidants might reduce ocular oxidative damage caused by UVB radiation.

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J Nutr Sci. 2016 Jan 8;5:e1. doi: 10.1017/jns.2015.35. eCollection 2016.

Lutein, zeaxanthin and meso-zeaxanthin content of eggs laid by hens supplemented with free and esterified xanthophylls.

Nolan JM, Meagher KA, Howard AN, Moran R, Thurnham DI, Beatty S.

Abstract: The xanthophyll carotenoids lutein (L), zeaxanthin (Z) and meso-zeaxanthin (MZ) are found at the macula, the central part of the retina, where they are referred to as macular pigment (MP). MP is studied in human subjects because of its proven role in enhancing visual function and its putative role in protecting against age-related macular degeneration. These benefits are probably due to the antioxidant and short-wavelength filtering properties of MP. It is known that eggs are a dietary source of L and Z. This experiment was designed to measure the egg yolk carotenoid response to hen supplementation with L, Z and MZ. A total of forty hens were used in the trial and were divided into eight groups of five hens. Each group was supplemented (with about 140 mg active xanthophylls/kg feed) with one of the following oil-based carotenoid formulations for 6 weeks: unesterified L (group 1); L diacetate (group 2); unesterified Z (group 3); Z diacetate (group 4); unesterified MZ (group 5); MZ diacetate (group 6); L-MZ (1:1) diacetate mixture (group 7); L-MZ diacetate (1:3) mixture (group 8). Yolk carotenoid content was analysed weekly (in four randomly selected eggs) by HPLC. We found that hens supplemented with Z diacetate and MZ diacetate produced eggs with significantly greater carotenoid concentrations than their free form counterparts. This finding potentially represents the development of a novel food, suitable to increase MP and its constituent carotenoids in serum.

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Br J Ophthalmol. 2016 Jan 19. [Epub ahead of print]

Past physical activity and age-related macular degeneration: the Melbourne Collaborative Cohort Study.

McGuinness MB, Karahalios A, Simpson JA, Guymer RH, Robman LD, Hodge AM, Cerin E, Giles GG, Finger RP.

BACKGROUND/AIMS: To assess the association between past physical activity and early, intermediate and late age-related macular degeneration (AMD) in a community-based cohort study in Melbourne, Australia.

METHODS: Diet and lifestyle information was recorded at baseline (1990-1994) and total recreational activity was derived from walking, vigorous and non-vigorous exercise. At follow-up (2003-2007), digital macular photographs were graded for early, intermediate and late AMD. Data were analysed using multinomial logistic regression controlling for age, sex, smoking, region of descent, diet and alcohol. Effect modification by sex was investigated.

RESULTS: Out of 20 816 participants, early, intermediate and late AMD were detected at follow-up in 4244 (21%), 2661 (13%) and 122 (0.6%) participants, respectively. No association was detected between past total recreational physical activity and early, intermediate or late AMD. Frequent (≥3 times/week) and less frequent (1-2 times/week) vigorous exercise were associated with lower odds of intermediate and late AMD in univariable models. After controlling for confounders, there was evidence of effect modification by sex and frequent vigorous exercise was associated with a 22% decrease in the odds of intermediate AMD (95% CI 4% to 36%) in women, but no association was found for men.

CONCLUSIONS: Past frequent vigorous exercise may be inversely related to the presence of intermediate AMD in women. Further studies are needed to confirm whether physical activity and exercise have a protective effect for AMD.

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Ophthalmic Epidemiol. 2016 Jan 20:1-7. [Epub ahead of print]

Self-Reported Sleep Duration in Patients with Neovascular Age-Related Macular Degeneration.

Pérez-Canales JL, Rico-Sergado L, Pérez-Santonja JJ.

PURPOSE: To examine the relationship between self-reported sleep duration and neovascular age-related macular degeneration (nAMD).

METHODS: This case-control study comprised 165 subjects (57 patients with nAMD and 108 controls). Controls were matched to cases by age and sex. Participants completed a questionnaire that included questions about sleep duration and quality. Four categories of sleep duration were established; <6 hours, 6 -7 hours, 7-8 hours and >8 hours. Association of sleep duration and nAMD was assessed by logistic regression analysis. Multiple logistic regression models were performed to control for possible confounders.

RESULTS: We found a significant association between short sleep duration and nAMD (for <6 hours, odds ratio, OR, 3.29, 95% confidence interval, CI, 1.32-8.27; for 6-7 hours, OR 2.25, 95% CI 0.80-6.32; and for >8 hours, OR 1.39, 95% CI 0.53-3.73) compared with the reference category of 7-8 hours. This association remained significant after adjustment for confounders (<6 hours, OR 3.09, 95% CI 1.20-7.97). In addition, a borderline significant association was observed between self-reported very bad sleep quality and nAMD (OR 2.84, 95% CI 1.02-7.88). The highest rate of sleep medication use was found in the nAMD group (p < 0.001).

CONCLUSION: Our findings provide evidence to support an association between short sleep duration and nAMD. Considering strategies to improve sleep in these patients may prevent the negative effects of sleep deficiency.

PMID: 26786476 [PubMed - as supplied by publisher]

PLoS One. 2016 Jan 20;11(1):e0146684. eCollection 2016.

Surface-Based Analyses of Anatomical Properties of the Visual Cortex in Macular Degeneration.

Prins D, Plank T, Baseler HA, Gouws AD, Beer A, Morland AB, Greenlee MW, Cornelissen FW.

INTRODUCTION: Macular degeneration (MD) can cause a central visual field defect. In a previous study, we found volumetric reductions along the entire visual pathways of MD patients, possibly indicating degeneration of inactive neuronal tissue. This may have important implications. In particular, new therapeutic strategies to restore retinal function rely on intact visual pathways and cortex to reestablish visual function. Here we reanalyze the data of our previous study using surface-based morphometry (SBM) rather than voxel-based morphometry (VBM). This can help determine the robustness of the findings and will lead to a better understanding of the nature of neuroanatomical changes associated with MD.

METHODS: The metrics of interest were acquired by performing SBM analysis on T1-weighted MRI data acquired from 113 subjects: patients with juvenile MD (JMD; n = 34), patients with age-related MD (AMD; n = 24) and healthy age-matched controls (HC; n = 55).

RESULTS: Relative to age-matched controls, JMD patients showed a thinner cortex, a smaller cortical surface area and a lower grey matter volume in V1 and V2, while AMD patients showed thinning of the cortex in V2. Neither patient group showed a significant difference in mean curvature of the visual cortex.

DISCUSSION: The thinner cortex, smaller surface area and lower grey matter volume in the visual cortex of JMD patients are consistent with our previous results showing a volumetric reduction in their visual cortex. Finding comparable results using two rather different analysis techniques suggests the presence of marked cortical degeneration in the JMD patients. In the AMD patients, we found a thinner cortex in V2 but not in V1. In contrast to our previous VBM analysis, SBM revealed no volumetric reductions of the visual cortex. This suggests that the cortical changes in AMD patients are relatively subtle, as they apparently can be missed by one of the methods.

PMID: 26789126 [PubMed - in process]