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MD Research News

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Drug treatment

Ophthalmic Res. 2015 Dec 5;55(2):84-90. [Epub ahead of print]

Intravitreal Aflibercept for Treatment-Resistant Neovascular Age-Related Macular Degeneration: 12-Month Safety and Efficacy Outcomes.

Chang AA, Broadhead GK, Hong T, Joachim N, Syed A, Schlub TE, Toth L, Peto T, Zhu M.

PURPOSE: To prospectively assess the safety and efficacy of intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration (nAMD).

METHODS: This prospective, non-randomized clinical trial included 49 patients with treatment-resistant nAMD who received 2 mg intravitreal aflibercept as 3 monthly loading doses, followed by injections every 2 months over 12 months. Inclusion criteria included active nAMD on fluorescein angiography at baseline and persistent intra- or subretinal fluid on optical coherence tomography (OCT) for ≥6 months prior to baseline with a minimum of 4 injections of bevacizumab and/or ranibizumab. Patients were assessed monthly for best-corrected visual acuity (BCVA), central retinal thickness (CRT) measured with OCT and occurrence of adverse events. Retinal pigment epithelium atrophy (RPEA) was assessed at baseline and at 12 months.

RESULTS: Mean BCVA improved by 4.7 letters (95% CI: 2.1-7.3, $p < 0.001$) and CRT decreased by 97.2 μm (95% CI: 54.4-140.1, $p < 0.001$) at 12 months compared to baseline. Median RPEA area increased by 0.48 mm2 (range = -0.1 to 19.9, $p < 0.001$). There was 1 arterial thromboembolic event and 2 cases of submacular haemorrhage.

CONCLUSION: In this cohort of treatment-resistant nAMD patients, intravitreal aflibercept was effective in improving vision and reducing exudation. Early visual and anatomic outcomes may predict longer-term response to treatment, but further assessment is required.

PMID: 26637166 [PubMed - as supplied by publisher]

Exp Ther Med. 2015 Sep;10(3):1121-1126. Epub 2015 Jul 7.

Therapeutic effect of intravitreal injections of ranibizumab for the treatment of macular choroidal neovascularization caused by pathological myopia.

Ji L, Lv W, Xiao Y, Xu Z, Zhang X, Zhang W.

Abstract: The aim of the present study was to evaluate the clinical efficacy and safety of intravitreal ranibizumab injections for the treatment of macular choroidal neovascularization (CNV) caused by pathological myopia. Between one and four intravitreal injections of ranibizumab were administered to 61 eyes from 61 patients who were diagnosed with macular CNV caused by pathological myopia. Following injection, the best-corrected visual acuity (BCVA), central macular thickness (CMT) and fundus fluorescein angiography (FFA) findings were evaluated monthly for a period of 6 months. Among the 61 eyes, 10 eyes

received one injection, 44 received two injections, six received three injections and one received four injections (average, 1.97 injections). The BCVA was 0.02±0.01 prior to treatment and 0.30±0.03 subsequent to treatment, and this difference was statistically significant (P<0.01). The CMT was reduced by an average of 45.1 µm. Regarding the FFA results, 56 eyes had no CNV fluorescence leakage and five eyes had CNV fluorescence leakage following treatment; however, the intensity of CNV fluorescence leakage in the five eyes following treatment was lower than that prior to treatment. As a treatment for pathological myopia-induced macular CNV, intravitreal injections of ranibizumab may improve eyesight as well as the macular retinal tissue structure; thus, this is a safe and effective treatment method.

PMID: 26622450 [PubMed] PMCID: PMC4533214

Korean J Ophthalmol. 2015 Dec;29(6):424-32. Epub 2015 Nov 25.

Effects of Bevacizumab on Bcl-2 Expression and Apoptosis in Retinal Pigment Epithelial Cells under Oxidative Stress.

Kim S, Kim YJ, Kim NR, Chin HS.

PURPOSE: To evaluate the effects of bevacizumab on expression of B-cell leukemia/lymphoma (Bcl)-2 and apoptosis in retinal pigment epithelial (RPE) cells under oxidative stress conditions.

METHODS: RPE cells were treated with H2O2 (0, 100, 200, 300, and 400 µM) and bevacizumab at or above the doses normally used in clinical practice (0, 0.33, 0.67, 1.33, and 2.67 mg/mL). Cell apoptosis was measured using flow cytometry with annexin V-fluorescein isothiocyanate. The expression of Bcl-2 mRNA was determined using reverse transcription polymerase chain reaction.

RESULTS: Under low oxidative stress conditions (H2O2 100 µM), cell apoptosis was not significantly different at any concentration of bevacizumab, but Bcl-2 mRNA expression decreased with increasing concentration of bevacizumab (0.33, 0.67, 1.33, and 2.67 mg/mL). Under moderate oxidative stress conditions (H2O2 200 µM), Bcl-2 mRNA expression decreased with increasing concentration of bevacizumab (0.33, 0.67, 1.33, and 2.67 mg/mL), but cell apoptosis increased only at 2.67 mg/mL of bevacizumab. Under high oxidative stress (300 µM) conditions, cell apoptosis increased at high concentrations of bevacizumab (1.33 and 2.67 mg/mL), but it did not correlate with Bcl-2 expression.

CONCLUSIONS: Withdrawal of vascular endothelial growth factor can lead to RPE cell apoptosis and influences the expression of anti-apoptotic genes such as Bcl-2 under oxidative stress conditions. Since oxidative stress levels of each patient are unknown, repeated injections of intravitreal bevacizumab, as in eyes with age-related macular degeneration, might influence RPE cell survival.

PMID: 26635460 [PubMed - in process]

Korean J Ophthalmol. 2015 Dec;29(6):404-10. doi: 10.3341/kjo.2015.29.6.404. Epub 2015 Nov 25.

Intravitreal Anti-vascular Endothelial Growth Factor for Newly Diagnosed Symptomatic Polypoidal Choroidal Vasculopathy with Extrafoveal Polyps.

Kim JH, Lee DW, Choi SC, Kim JW, Lee TG, Kim CG, Cho HJ.

PURPOSE: To evaluate the 12-month outcome of anti-vascular endothelial growth factor (VEGF) treatment for extrafoveal polypoidal choroidal vasculopathy (PCV).

METHODS: This retrospective observational study included 32 eyes of 32 patients newly diagnosed with extrafoveal PCV (polyps located more than 500 µm from the center of the fovea). Patients were treated with intravitreal ranibizumab, bevacizumab, or both. The best-corrected visual acuity (BCVA) and central foveal thickness (CFT) at diagnosis and at 12 months were compared. Eyes were divided into two groups according to the presence of submacular hemorrhage. The BCVA in each group was compared at baseline

and at 12 months.

RESULTS: During the 12-month study period, patients received an average of 4.0 ± 1.1 anti-VEGF injections. The BCVA at baseline, three-month post-diagnosis, and 12-month post-diagnosis was 0.59 ± 0.40, 0.34 ± 0.38, and 0.38 ± 0.38, respectively. The BCVA at 12 months was significantly better than the baseline value ($p = 0.002$). The CFT at baseline, three-month, and 12-month post-diagnosis was 477.1 ± 194.2 µm, 214.5 ± 108.8 µm, and 229.8 ± 106.1 µm, respectively. The CFT at 12 months was significantly lower than the baseline value ($p < 0.001$). A significant improvement in BCVA was noted in eyes with and without submacular hemorrhage ($n = 13$, $p = 0.032$ and $n = 19$, $p = 0.007$, respectively).

CONCLUSIONS: Anti-VEGF therapy was beneficial in extrafoveal PCV, regardless of the presence of submacular hemorrhage.

PMID: 26635457 [PubMed - in process]

Korean J Ophthalmol. 2015 Dec;29(6):396-403. Epub 2015 Nov 25.

Effects of Vitreomacular Traction on Ranibizumab Treatment Response in Eyes with Neovascular Age-related Macular Degeneration.

Lee KH, Chin HS, Kim NR, Moon YS.

PURPOSE: To investigate the effects of vitreomacular traction (VMT) on ranibizumab treatment response for neovascular age-related macular degeneration (AMD).

METHODS: A retrospective review of 85 eyes of 85 patients newly diagnosed with neovascular AMD was conducted. Patients were eligible if they had received more than three consecutive monthly ranibizumab (0.50 mg) treatments and ophthalmic evaluations. Patients were classified into a VMT (+) group or VMT (-) group according to optical coherence tomography imaging. Best corrected visual acuity and central retinal thickness (CRT) measurements were obtained at three and six months after initial injection.

RESULTS: One month after the third injection, mean visual acuity (VA) increases of 6.36 and 9.87 letters were observed in the VMT (+) and VMT (-) groups, respectively. The corresponding mean CRT values decreased by 70.29 µm and 121.68 µm, respectively. A total 41 eyes were identified as eligible for a subsequent fourth injection; 71.1% of patients (27 eyes) in the VMT (+) group but only 29.8% of patients in the VMT (-) group needed a subsequent fourth injection. Follow-up was extended to six months for 42 of the 85 enrolled patients (49.4%). The trends in VA and optical coherence tomography were found to be maintained at six-month follow-up.

CONCLUSIONS: VA and CRT appeared to be more improved after ranibizumab treatment in the VMT (-) group compared to the VMT (+) group. VMT might antagonize the effect of ranibizumab treatment in a subpopulation of AMD patients.

PMID: 26635456 [PubMed - in process]

Retina. 2015 Dec 1. [Epub ahead of print]

TREATMENT OUTCOMES FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION PATIENTS WITH INITIAL VISION BETTER THAN 20/40 USING A TREAT-AND-EXTEND REGIMEN.

Rahimy E, Rayess N, Ho AC, Regillo CD.

PURPOSE: To determine treatment outcomes in eyes with neovascular age-related macular degeneration having visual acuity better than 20/40 after 1 years to 2 years of ranibizumab or bevacizumab therapy using a treat-and-extend regimen.

METHODS: Retrospective observational case series. Clinical records were reviewed from patients with

treatment-naive neovascular age-related macular degeneration and baseline best-corrected Snellen visual acuity >20/40 treated with intravitreal ranibizumab or bevacizumab for a minimum of 1 year using a treat-and-extend regimen. The primary outcome measures were change from initial visual acuity, proportion of eyes losing <3 best-corrected visual acuity lines, proportion of eyes maintaining visual acuity ≥20/40, change from baseline central retinal thickness, and mean number of injections after 1 years and 2 years of follow-up.

RESULTS: A total of 42 eyes from 40 patients were included. The mean follow-up period was 1.44 years. The mean initial logMAR visual acuity was 0.226, and remained stable at 0.257 and 0.267 after 1 years and 2 years of follow-up, respectively. At baseline, mean central retinal thickness was 305.8 μm, improved to 272.6 μm after 1 year of treatment (P < 0.001), and remained stable at 266.2 μm (P = 0.015) after 2 years. At 1-year follow-up period, 94.4% of eyes had lost less than 3 Snellen lines, and 94.1% of eyes lost less than 3 Snellen lines after 2 years. The percentage of eyes maintaining visual acuity ≥20/40 was 81% and 75% after each year. Eyes received on average 7.8 injections during the first year of treatment and 6.1 injections over the second year.

CONCLUSION: Eyes with neovascular age-related macular degeneration presenting with initial visual acuity better than 20/40 on average maintained vision, lost less than 3 lines of acuity, and achieved anatomical improvements using a treat-and-extend regimen over a 2-year period.

PMID: 26630316 [PubMed - as supplied by publisher]

Eye (Lond). 2015 Dec 4. [Epub ahead of print]

Ranibizumab for the treatment of wet AMD: a summary of real-world studies.

Chong V.

Abstract: Data from real-world studies of ranibizumab in neovascular (wet) age-related macular degeneration suggest that outcomes in clinical practice fail to match those seen in clinical trials. These real-world studies follow treatment regimens that differ from the fixed dosing used in the pivotal clinical trial programme. To better understand the effectiveness of ranibizumab in clinical practice, we conducted a comprehensive evaluation of 12-month outcomes reported in peer-reviewed 'real-world' publications. Key measures included in our analysis were mean change in visual acuity (VA) and the proportion of patients gaining ≥15 letters or losing ≤15 letters. Twenty studies were eligible for inclusion in our study, with 18 358 eyes having sufficient data for analysis of 12-month outcomes. Mean baseline VA ranged from 48.8 to 61.6 Early Treatment Diabetic Retinopathy Study letters. Mean change in VA was between -2.0 and +5.5 letters, with a grand mean of +2.9±3.2, and a weighted mean (adjusted for the number of eyes in the study) of +1.95. Eleven studies reported that 19±7.5 (mean value) of patients gained ≥15 letters, while in 12 studies the mean percentage of patient losing ≤15 letters was 89±6.5%. Our comprehensive analysis of real-world ranibizumab study data confirm that patient outcomes are considerably poorer than those reported in randomised control trials of both fixed and pro re nata regimens.

PMID: 26634711 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2015 Dec 1. [Epub ahead of print]

Subfoveal choroidal thickness as a predictor of treatment response to anti-vascular endothelial growth factor therapy for polypoidal choroidal vasculopathy.

Kim H, Lee SC, Kwon KY, Lee JH, Koh HJ, Byeon SH, Kim SS, Kim M, Lee CS.

PURPOSE: To investigate whether subfoveal choroidal thickness predicted treatment response to anti-vascular endothelial growth factor (VEGF) in polypoidal choroidal vasculopathy (PCV).

METHODS: This retrospective observational case series included 66 eyes of 60 patients who were

diagnosed with new-onset PCV and who were followed for a minimum of 6 months. Patients received three monthly intravitreal injections of 0.5 mg ranibizumab or 1.25 mg bevacizumab, at baseline, month 1, and month 2. "Good responders" were defined as those who showed complete resolution of subretinal and/or intraretinal fluid at month 3 after the loading injections, whereas "poor responders" were defined as those who showed persistent retinal fluid on optical coherence tomography (OCT) at month 3 after treatment. Differences in best-corrected visual acuity, indocyanine green angiography, and spectral domain-OCT findings at baseline were analyzed between the two groups.

RESULTS: The mean patient age was 68.2 ± 9.7 years, and the mean follow-up period was 27 ± 21 months. The mean subfoveal choroidal thickness was 273 ± 117 μm, and choroidal vascular hyperpermeability was observed in 35 eyes (53.0 %). Thirty-three eyes (50 %) showed good response to treatment, and a thinner subfoveal choroid at baseline significantly correlated with favorable treatment response (P = 0.024). However, there was no significant relationship between treatment response and choroidal vascular hyperpermeability (P = 0.999).

CONCLUSIONS: The subfoveal choroid was found to be significantly thinner among patients who achieved complete resolution of macular exudation after three loading injections of anti-VEGF agents.

PMID: 26626772 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2015 Sep;63(9):751.

Comment on: Intravitreal ziv-aflibercept for recurrent macular edema secondary to central retinal venous occlusion.

Sen A, Mitra A, Malhotra PP, Gupta S.

PMID: 26632138 [PubMed - in process]

Other treatment & diagnosis

Arch Soc Esp Oftalmol. 2015 Nov 25. [Epub ahead of print]

Evaluation of a follow-up protocol for patients on chloroquine and hydroxychloroquine treatment. [Article in English, Spanish]

Sanabria MR, Toledo-Lucho SC.

OBJECTIVE: To review the problems found after a new follow-up protocol for patients on chloroquine and hydroxychloroquine treatment.

METHOD: Retrospective study was conducted between May 2012 and January 2013 on the clinical files, retinographies, fundus auto-fluorescence (FAF) images, and central-10 degree visual fields (VF) of patients who were referred to the Ophthalmology Department as they had started treatment with hydroxychloroquine.

RESULTS: One hundred twenty-six patients were included; 94.4% were referred from the Rheumatology Department and 5.6% from Dermatology. Mean age was 59.7 years, and 73.8% were women. All of them were on hydroxychloroquine treatment, and 300mg was the most frequent daily dose. Rheumatoid arthritis was the most common diagnosis (40.5%), followed by systemic lupus erythematosus (15.9%). The mean Snellen visual acuity was 0.76, and 26 patients had lens opacities. The VF were normal in 97 patients, 8 had mild to moderate defects with no definite pattern, and in 9 the results were unreliable. Of the 51 patients older than 65years, 16 (31.4%) had altered or unreliable VF. The FAF was normal in 104 patients (82.5%), and abnormal, but consistent with ophthalmoscopic features, in 12 patients (pathological myopia, age related changes, early, middle or late age-related macular degeneration).

CONCLUSIONS: Visual fields as a reference test for the diagnosis of AP toxicity are not quite reliable for patients over 65. Therefore, the FAF is recommended as primary test, perhaps combined with another objective test, such as SD-OCT instead of VF.

PMID: 26627497 [PubMed - as supplied by publisher]

Pathogenesis

Sci Rep. 2015 Dec 1;5:17645.

Fisetin and luteolin protect human retinal pigment epithelial cells from oxidative stress-induced cell death and regulate inflammation.

Hytti M, Piippo N, Korhonen E, Honkakoski P, Kaarniranta K, Kauppinen A.

Abstract: Degeneration of retinal pigment epithelial (RPE) cells is a clinical hallmark of age-related macular degeneration (AMD), the leading cause of blindness among aged people in the Western world. Both inflammation and oxidative stress are known to play vital roles in the development of this disease. Here, we assess the ability of fisetin and luteolin, to protect ARPE-19 cells from oxidative stress-induced cell death and to decrease intracellular inflammation. We also compare the growth and reactivity of human ARPE-19 cells in serum-free and serum-containing conditions. The absence of serum in the culture medium did not prevent ARPE-19 cells from reaching full confluency but caused an increased sensitivity to oxidative stress-induced cell death. Both fisetin and luteolin protected ARPE-19 cells from oxidative stress-induced cell death. They also significantly decreased the release of pro-inflammatory cytokines into the culture medium. The decrease in inflammation was associated with reduced activation of MAPKs and CREB, but was not linked to NF- κB or SIRT1. The ability of fisetin and luteolin to protect and repair stressed RPE cells even after the oxidative insult make them attractive in the search for treatments for AMD.

PMID: 26619957 [PubMed - in process] PMCID: PMC4664957

Front Cell Neurosci. 2015 Nov 20;9:449.

A Method for the Isolation and Culture of Adult Rat Retinal Pigment Epithelial (RPE) Cells to Study Retinal Diseases.

Heller JP, Kwok JC, Vecino E, Martin KR, Fawcett JW.

Abstract: Diseases such as age-related macular degeneration (AMD) affect the retinal pigment epithelium (RPE) and lead to the death of the epithelial cells and ultimately blindness. RPE transplantation is currently a major focus of eye research and clinical trials using human stem cell-derived RPE cells are ongoing. However, it remains to be established to which extent the source of RPE cells for transplantation affects their therapeutic efficacy and this needs to be explored in animal models. Autotransplantation of RPE cells has attractions as a therapy, but existing protocols to isolate adult RPE cells from rodents are technically difficult, time-consuming, have a low yield and are not optimized for long-term cell culturing. Here, we report a newly devised protocol which facilitates reliable and simple isolation and culture of RPE cells from adult rats. Incubation of a whole rat eyeball in 20 U/ml papain solution for 50 min yielded 4 × 104 viable RPE cells. These cells were hexagonal and pigmented upon culture. Using immunostaining, we demonstrated that the cells expressed RPE cell-specific marker proteins including cytokeratin 18 and RPE65, similar to RPE cells in vivo. Additionally, the cells were able to produce and secrete Bruch's membrane matrix components similar to in vivo situation. Similarly, the cultured RPE cells adhered to isolated Bruch's membrane as has previously been reported. Therefore, the protocol described in this article provides an efficient method for the rapid and easy isolation of high quantities of adult rat RPE cells. This provides a reliable platform for studying the therapeutic targets, testing the effects of drugs in a preclinical setup and to perform in vitro and in vivo transplantation experiments to study retinal diseases.

PMID: 26635529 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 Nov 26. [Epub ahead of print]

Aberrant protein trafficking in retinal degenerations: The initial phase of retinal remodeling.

Gross AK, Bales KL.

Abstract: Retinal trafficking proteins are involved in molecular assemblies that govern protein transport, orchestrate cellular events involved in cilia formation, regulate signal transduction, autophagy and endocytic trafficking, all of which if not properly controlled initiate retinal degeneration. Improper function and or trafficking of these proteins and molecular networks they are involved in cause a detrimental cascade of neural retinal remodeling due to cell death, resulting as devastating blinding diseases. A universal finding in retinal degenerative diseases is the profound detection of retinal remodeling, occurring as a phased modification of neural retinal function and structure, which begins at the molecular level. Retinal remodeling instigated by aberrant trafficking of proteins encompasses many forms of retinal degenerations, such as the diverse forms of retinitis pigmentosa (RP) and disorders that resemble RP through mutations in the rhodopsin gene, retinal ciliopathies, and some forms of glaucoma and age-related macular degeneration (AMD). As a large majority of genes associated with these different retinopathies are overlapping, it is imperative to understand their underlying molecular mechanisms. This review will discuss some of the most recent discoveries in vertebrate retinal remodeling and retinal degenerations caused by protein mistrafficking.

PMID: 26632497 [PubMed - as supplied by publisher]

PLoS One. 2015 Dec 2;10(12):e0143952. eCollection 2015.

Spatiotemporal Cadence of Macrophage Polarisation in a Model of Light-Induced Retinal Degeneration.

Jiao H, Natoli R, Valter K, Provis JM, Rutar M.

BACKGROUND: The recruitment of macrophages accompanies almost every pathogenic state of the retina, and their excessive activation in the subretinal space is thought to contribute to the progression of diseases including age-related macular degeneration. Previously, we have shown that macrophages aggregate in the outer retina following damage elicited by photo-oxidative stress, and that inhibition of their recruitment reduces photoreceptor death. Here, we look for functional insight into macrophage activity in this model through the spatiotemporal interplay of macrophage polarisation over the course of degeneration.

METHODS: Rats were exposed to 1000 lux light damage (LD) for 24hrs, with some left to recover for 3 and 7 days post-exposure. Expression and localisation of M1- and M2- macrophage markers was investigated in light-damaged retinas using qPCR, ELISA, flow cytometry, and immunohistochemistry.

RESULTS: Expression of M1- (Ccl3, Il-6, Il-12, Il-1β, TNFα) and M2- (CD206, Arg1, Igf1, Lyve1, Clec7a) related markers followed discrete profiles following light damage; up-regulation of M1 genes peaked at the early phase of cell death, while M2 genes generally exhibited more prolonged increases during the chronic phase. Moreover, Il-1β and CD206 labelled accumulations of microglia/macrophages which differed in their morphological, temporal, and spatial characteristics following light damage.

CONCLUSIONS: The data illustrate a dynamic shift in macrophage polarisation following light damage through a broad swathe of M1 and M2 markers. Pro-inflammatory M1 activation appears to dominate the early phase of degeneration while M2 responses appear to more heavily mark the chronic post-exposure period. While M1/M2 polarisation represents two extremes amongst a spectrum of macrophage activity, knowledge of their predominance offers insight into functional consequences of macrophage activity over the course of damage, which may inform the spatiotemporal employment of therapeutics in retinal disease.

PMID: 26630454 [PubMed - in process]

Aging Dis. 2015 Nov 17;6(6):444-455. eCollection 2015.

Inflammatory Cytokines Induce Expression of Chemokines by Human Retinal Cells: Role in Chemokine Receptor Mediated Age-related Macular Degeneration.

Nagineni CN, Kommineni VK, Ganjbaksh N, Nagineni KK, Hooks JJ, Detrick B.

Abstract: Chemokine reeptor-3 (CCR-3) was shown to be associated with choroidal neovascularization (CNV) in age-related macular degeneration (AMD). AMD is a vision threatening retinal disease that affects the aging population world-wide. Retinal pigment epithelium and choroid in the posterior part of the retina are the key tissues targeted in the pathogenesis of CNV in AMD. We used human retinal pigment epithelial (HRPE) and choroidal fibroblast (HCHF) cells, prepared from aged adult human donor eyes, to evaluate the expression of major CCR-3 ligands, CCL-5, CCL -7, CCL-11,CCL-24 and CCL-26. Microarray analysis of gene expression in HRPE cells treated with inflammatory cytokine mix (ICM= IFN-γ+TNF-α+IL-1β) revealed 75 and 23-fold increase in CCL-5 and CCL-7 respectively, but not CCL-11, CCL-24 and CCL-26. Chemokine secretion studies of the production of CCL5 and CCL7 by HRPE corroborated with the gene expression analysis data. When the HRPE cells were treated with either individual cytokines or the ICM, both CCL-5 and CCL-7 were produced in a dose dependent manner. Similar to the gene expression data, the ICM did not enhance HRPE production of CCL-11, CCL-24 and CCL-26. CCL-11 and CCL-26 were increased with IL-4 treatment and this HRPE production was augmented in the presence of TNF-α and IL1β. When HCHF cells were treated with either individual cytokines or the ICM, both CCL-5 and CCL-7 were produced in a dose dependent fashion. IL-4 induced low levels of CCL-11 and CCL-26 in HCHF and this production was significantly enhanced by TNF-α. Under these conditions, neither HRPE nor HCHF were demonstrated to produce CCL-24. These data demonstrate that chronic inflammation triggers CCL-5 and CCL-7 release by HRPE and HCHF and the subsequent interactions with CCR3 may participate in pathologic processes in AMD.

PMID: 26618046 [PubMed - as supplied by publisher] PMCID: PMC4657816

Epidemiology

Korean J Ophthalmol. 2015 Dec;29(6):359-67. Epub 2015 Nov 25.

An Overview of Ophthalmologic Survey Methodology in the 2008-2015 Korean National Health and Nutrition Examination Surveys.

Yoon KC, Choi W, Lee HS, Kim SD, Kim SH, Kim CY, Park KH, Park YJ, Baek SH, Song SJ, Shin JP, Yang SW, Yu SY, Lee JS, Lim KH, Oh KW, Kang SW.

Abstract: The Korea National Health and Nutrition Examination Survey (KNHANES) is a national program designed to assess the health and nutritional status of the noninstitutionalized population of South Korea. The KNHANES was initiated in 1998 and has been conducted annually since 2007. Starting in the latter half of 2008, ophthalmologic examinations were included in the survey in order to investigate the prevalence and risk factors of common eye diseases such as visual impairment, refractive errors, strabismus, blepharoptosis, cataract, pterygium, diabetic retinopathy, age-related macular degeneration, glaucoma, dry eye disease, and color vision deficiency. The measurements included in the ophthalmic questionnaire and examination methods were modified in the KNHANES IV, V, and VI. In this article, we provide detailed information about the methodology of the ophthalmic examinations in KNHANES in order to aid in further investigations related to major eye diseases in South Korea.

PMID: 26635451 [PubMed - in process]

PLoS One. 2015 Dec 1;10(12):e0143924. eCollection 2015.

Effect of High-Density Lipoprotein Metabolic Pathway Gene Variations and Risk Factors on

Neovascular Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy in China.

Meng Q, Huang L, Sun Y, Bai Y, Wang B, Yu W, Zhao M, Li X.

PURPOSE: To investigate the effect of genetic variants in the high-density lipoprotein (HDL) metabolic pathway and risk factors on neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) in China.

METHODS: A total of 742 Chinese subjects, including 221 controls, 230 cases with nAMD, and 291 cases with PCV, were included in the present study. Five single nucleotide polymorphisms (SNPs) from three genes in the HDL metabolic pathway (HDLMP) including cholesteryl ester transfer protein (CETP), hepatic lipase (LIPC) and lipoprotein lipase (LPL) were genotyped in all study subjects with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS). Risk factors including gender, hypertension, hyperlipidemia, diabetes mellitus, and coronary artery disease were identified. Chi-square tests or Fisher's exact tests were applied to discover associations between SNPs and risk factors for PCV and nAMD. Gene-gene interactions and gene-environment interactions were evaluated by the multifactor-dimensionality reduction (MDR) method.

RESULTS: CETP rs3764261 were significantly associated with an increased risk for PCV (odds ratio (OR) = 1.444, P = 0.0247). LIPC rs1532085 conferred an increased risk for PCV (OR = 1.393, P = 0.0094). We found no association between PCV and LPL rs12678919, LIPC rs10468017 or CETP rs173539. No association was found between five SNPs with nAMD. Regarding risk factors, females were found to have significantly decreased risks for both PCV and nAMD (P = 0.006 and 0.001, respectively). Coronary artery disease (CAD) was a risk factor in PCV patients but played a protective role in nAMD patients. Hyperlipidemia was associated with PCV but not with nAMD. Neither hypertension nor diabetes mellitus was associated with PCV or nAMD. The MDR analysis revealed that a three-locus model with rs12678919, rs1532085, and gender was the best model for nAMD, while a five-locus model consisting of rs10468017, rs3764261, rs1532085, gender, and hyperlipidemia was best for PCV.

CONCLUSION: Our large-sample study suggested that CETP rs3764261 conferred an increased risk for PCV. We also first found the association between rs1532085 and PCV. The result of present study also showed that gender and CAD are associated with PCV and nAMD. Significant association was found between hyperlipidemia and PCV but not nAMD.

PMID: 26624898 [PubMed - in process] Free full text

Genetics

Int J Clin Exp Pathol. 2015 Sep 1;8(9):11635-40. eCollection 2015.

COL8A1 rs13095226 polymorphism shows no association with neovascular age-related macular degeneration or polypoidal choroidal vasculopathy in Chinese subjects.

Yu Y, Huang L, Wang B, Zhang C, Bai Y, Li X.

PURPOSE: Age-related macular degeneration (AMD) is the main cause of visual impairment and legal blindness in older individuals. COL8A1 rs13095226 variants have recently been implicated associated with neovascular age-related macular degeneration (nAMD) and Polypoidal Choroidal Vasculopathy (PCV) in American studies. The aim of this study was to investigate the association between the COL8A1 rs13095226 Polymorphism and neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) in Chinese people.

METHODS: 900 Chinese subjects-300 cases with nAMD, 300 cases with PCV and 300 controls, were enrolled in a cross-sectional observational study. The diagnoses of nAMD and PCV were confirmed by Fundus photography, Fluorescence Fundus Angiography (FFA) and Indocyanine Green Angiography (ICGA). Genomic DNA was extracted from venous blood leukocytes and genotypes of rs13095226 were determined by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Differences in

allele distribution between cases and controls were tested by chi-square tests, with age and gender adjusted by logistic regression analysis.

RESULT: The COL8A1 rs13095226 polymorphism was not statistically significantly different from the nAMD or PCV to the normal controls (P>0.05) in Chinese Population. The association remained insignificant after adjustmentfor age and gender differences (P>0.05).

CONCLUSIONS: This case-control study indicated that the COL8A1 rs13095226 polymorphism is not associated with nAMD or PCV, which suggesting this gene maybe not a susceptibility gene locus for nAMD or PCV in Chinese subjects.

PMID: 26617902 [PubMed - in process] PMCID: PMC4637718

Diet, lifestyle & low vision

J Ophthalmol. 2015;2015:523027. Epub 2015 Nov 5.

Management of Ocular Diseases Using Lutein and Zeaxanthin: What Have We Learned from Experimental Animal Studies?

Xue C, Rosen R, Jordan A, Hu DN.

Abstract: Zeaxanthin and lutein are two carotenoid pigments that concentrated in the retina, especially in the macula. The effects of lutein and zeaxanthin on the prevention and treatment of various eye diseases, including age-related macular degeneration, diabetic retinopathy and cataract, ischemic/hypoxia induced retinopathy, light damage of the retina, retinitis pigmentosa, retinal detachment, and uveitis, have been studied in different experimental animal models. In these animal models, lutein and zeaxanthin have been reported to have beneficial effects in protecting ocular tissues and cells (especially the retinal neurons) against damage caused by different etiological factors. The mechanisms responsible for these effects of lutein and zeaxanthin include prevention of phototoxic damage by absorption of blue light, reduction of oxidative stress through antioxidant activity and free radical scavenging, and their anti-inflammatory and antiangiogenic properties. The results of these experimental animal studies may provide new preventive and therapeutic procedures for clinical management of various vision-threatening diseases.

PMID: 26617995 [PubMed - as supplied by publisher] PMCID: PMC4651639

Methodist Debakey Cardiovasc J. 2015 Jul-Sep;11(3):156-9.

New Insights Into Tobacco-Induced Vascular Disease: Clinical Ramifications.

Cooke JP.

Abstract: Tobacco smoke contains more than 4,000 compounds. These include phenols, carbonyls, and nitrosamines that may be irritants and carcinogens; particulate matter such as tars; volatiles and gases such as carbon monoxide; and nicotine. Many of these compounds may contribute to the adverse health effects of tobacco. For example, recent findings have shown that the angiogenic and proliferative effects of nicotine are mediated by activation of nicotinic receptors on the vascular cells. Nicotine-induced activation of vascular cells may contribute to pathological neovascularization in cancer, age-related macular degeneration, and atherosclerosis. This review focuses on how nicotine adversely affects cardiovascular health and highlights intriguing new data about nicotine's potent angiogenic and proliferative properties.

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Cholesterol in mouse retina originates primarily from in situ de novo biosynthesis.

Lin JB, Mast N, Bederman IR, Li Y, Brunengraber H, Björkhem I, Pikuleva IA.

Abstract: The retina, a thin tissue in the back of the eye, has two apparent sources of cholesterol: in situ biosynthesis and cholesterol available from the systemic circulation. The quantitative contributions of these two cholesterol sources to the retinal cholesterol pool is unknown and have been determined in the present work. A new methodology was used. Mice were given separately deuterium-labeled drinking water and chow containing 0.3% deuterium-labeled cholesterol. In the retina, the rate of total cholesterol input was 21 μg of cholesterol/g retina · day, of which 15 μg of cholesterol/g retina · day were provided by local biosynthesis and 6 μg of cholesterol/g retina · day were uptaken from the systemic circulation. Thus, local cholesterol biosynthesis accounts for the majority (72%) of retinal cholesterol input. We also quantified cholesterol input to mouse brain, the organ sharing important similarities with the retina. The rate of total cerebral cholesterol input was 121 μg of cholesterol/g brain · day with local biosynthesis providing 97% of total cholesterol input. Our work addresses a long-standing question in eye research and adds new knowledge to the potential use of statins (drugs that inhibit cholesterol biosynthesis) as therapeutics for age -related macular degeneration, a common blinding disease.

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Invest Ophthalmol Vis Sci. 2015 Nov 1;56(12):7444-50.

Interactions of Prosthetic and Natural Vision in Animals With Local Retinal Degeneration.

Lorach H, Lei X, Galambos L, Kamins T, Mathieson K, Dalal R, Huie P, Harris J, Palanker D.

PURPOSE: Prosthetic restoration of partial sensory loss leads to interactions between artificial and natural inputs. Ideally, the rehabilitation should allow perceptual fusion of the two modalities. Here we studied the interactions between normal and prosthetic vision in a rodent model of local retinal degeneration.

METHODS: Implantation of a photovoltaic array in the subretinal space of normally sighted rats induced local degeneration of the photoreceptors above the chip, and the inner retinal neurons in this area were electrically stimulated by the photovoltaic implant powered by near-infrared (NIR) light. We studied prosthetic and natural visually evoked potentials (VEP) in response to simultaneous stimulation by NIR and visible light patterns.

RESULTS: We demonstrate that electrical and natural VEPs summed linearly in the visual cortex, and both responses decreased under brighter ambient light. Responses to visible light flashes increased over 3 orders of magnitude of contrast (flash/background), while for electrical stimulation the contrast range was limited to 1 order of magnitude. The maximum amplitude of the prosthetic VEP was three times lower than the maximum response to a visible flash over the same area on the retina.

CONCLUSIONS: Ambient light affects prosthetic responses, albeit much less than responses to visible stimuli. Prosthetic representation of contrast in the visual scene can be encoded, to a limited extent, by the appropriately calibrated stimulus intensity, which also depends on the ambient light conditions. Such calibration will be important for patients combining central prosthetic vision with natural peripheral sight, such as in age-related macular degeneration.

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