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MD Research News

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Drug treatment

Retina. 2013 Mar 30. [Epub ahead of print]

VISUAL AND ANATOMICAL OUTCOMES OF INTRAVITREAL AFLIBERCEPT IN EYES WITH PERSISTENT SUBFOVEAL FLUID DESPITE PREVIOUS TREATMENTS WITH RANIBIZUMAB IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Kumar N, Marsiglia M, Mrejen S, Fung AT, Slakter J, Sorenson J, Freund KB.

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PURPOSE: To assess the efficacy of intravitreal aflibercept (2.0 mg) in patients with treatment-resistant neovascular age-related macular degeneration.

METHODS: Retrospective analysis of eyes treated with aflibercept with persistent subretinal and/or intraretinal fluid despite previous treatments with intravitreal ranibizumab (0.5 mg). All patients were switched to intravitreal aflibercept (2.0 mg) and analyzed after 3 consecutive injections and after 6 months of treatment. Main outcome measures included change in visual acuity, central foveal thickness, and the height and diameter of the pigment epithelial detachment on the subfoveal scan on optical coherence tomography.

RESULTS: Thirty-four eyes of 33 patients were analyzed. Mean duration of symptoms and average number of previous injections with anti-vascular endothelial growth factor agents was 44.7 ± 29.8 months (interquartile range [IQR] 24-76 months) and 28.6 ± 20.1 (IQR 10-47), respectively. At the 6-month follow-up, mean visual acuity and central foveal thickness improved significantly from 20/75 (logarithm of minimum angle of resolution 0.57 ± 0.36; IQR 0.30-1.0) and 416 ± 217 μm (IQR 263-487 μm) at baseline to 20/60 (logarithm of minimum angle of resolution 0.47 ± 0.32; IQR 0.30-0.60) ($P = 0.004$) and 248 ± 171 μm (IQR 235-419 μm) ($P < 0.001$), respectively. Maximum pigment epithelial detachment height improved significantly from 260 ± 162 μm (IQR 129-368 μm) to 214 ± 142 μm (IQR 111-305 μm) ($P < 0.001$) and PED diameter decreased significantly from 3,265 ± 1,622 μm (IQR 2,353-4,555 μm) to 2,949 ± 1,653 μm (IQR 1,721-4,484 μm) ($P = 0.04$).

CONCLUSION: Intravitreal injections of aflibercept resulted in a significant improvement in visual and anatomical outcomes in eyes with persistent subfoveal fluid despite previous treatment with ranibizumab.

PMID: 23549101 [PubMed - as supplied by publisher]

Eye (Lond). 2013 Apr 5. doi: 10.1038/eye.2013.31. [Epub ahead of print]

Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab.

Patel KH, Chow CC, Rathod R, Mieler WF, Lim JI, Ulanski LJ 2nd, Leiderman YI, Arun V, Chau FY.

Department of Ophthalmology and Visual Sciences, Illinois Eye and Ear Infirmary, University of Illinois at Chicago, Chicago, IL, USA.

Purpose: The aim of this study is to report the short-term efficacy of aflibercept in the treatment of neovascular age-related macular degeneration (AMD) with associated retinal pigment epithelial detachment (PED) which is refractory or develops tachyphylaxis to bevacizumab and ranibizumab.

Methods: The method comprised a retrospective review of the medical records of patients with neovascular AMD and associated PEDs recently treated with aflibercept and previously treated with bevacizumab and ranibizumab.

Results: Three eyes of three female patients of ages 49, 55, and 65 years old with large serous PEDs and subretinal fluid (SRF) associated with occult choroidal neovascularization and neovascular AMD were treated with aflibercept after intravitreal bevacizumab and/or ranibizumab failed to resolve the lesions. All had complete resolution of SRF and complete or near-complete resolution of the PEDs after aflibercept injections over a 3-month period. Visual acuity improved in all three eyes.

Conclusion: Intravitreal aflibercept may be an effective treatment option for serous PED in neovascular AMD patients after bevacizumab and ranibizumab have previously failed. Larger studies with longer follow-up are required to determine the role of aflibercept in treatment of PED in neovascular AMD.Eye advance online publication, 5 April 2013; doi:10.1038/eye.2013.31.

PMID: 23558214 [PubMed - as supplied by publisher]

Retina. 2013 Mar 30. [Epub ahead of print]

LUCEDEX: A Prospective Study Comparing Ranibizumab plus Dexamethasone Combination Therapy Versus Ranibizumab Monotherapy for Neovascular Age-Related Macular Degeneration.

Ranchod TM, Ray SK, Daniels SA, Leong CJ, Ting TD, Verne AZ.

Bay Area Retina Associates, Walnut Creek, California.

BACKGROUND: The LuceDex prospective randomized pilot trial compared the combination of intravitreal ranibizumab and dexamethasone with ranibizumab monotherapy for treatment of neovascular age-related macular degeneration.

METHODS: Thirty-seven eyes of 37 patients were randomized 1:1 between combination therapy with intravitreal ranibizumab and dexamethasone (Group 1) and intravitreal ranibizumab monotherapy (Group 2). All study eyes received 4 monthly treatments followed by monthly treatment on indication.

RESULTS: In the LuceDex study, eyes gained an average of 11.1 and 5.9 Early Treatment of Diabetic Retinopathy Study letters in Groups 1 and 2, respectively, at Month 12. No more than zero Early Treatment of Diabetic Retinopathy Study letters were lost in 88% of Group 1 eyes and 70% of Group 2 eyes. The average number of treatments per study eye by Month 12 was 7.1 in Group 1 and 6.6 in Group 2. Choroidal neovascular membrane size decreased in Group 1 significantly compared with Group 2 ($P < 0.05$).

CONCLUSION: The LuceDex pilot study suggested a possible benefit of adding intravitreal dexamethasone to treatment of neovascular age-related macular degeneration with intravitreal ranibizumab. A larger study is needed to further identify and define possible benefits of this combination therapy.

PMID: 23549100 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Mar 16. [Epub ahead of print]

Long-Term Intraocular Pressure Changes in Patients with Neovascular Age-Related Macular Degeneration Treated with Ranibizumab.

Menke MN, Salam A, Framme C, Wolf S.

Department of Ophthalmology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland.

Background/Aims: To investigate the long-term effects of multiple intravitreal injections (IVTs) of ranibizumab (Lucentis) on intraocular pressure (IOP) in patients with neovascular age-related macular degeneration.

Methods: In 320 eyes, IOP measurements were performed at baseline prior to injection and compared with IOP measurements of the last visit. Correlations between mean IOP change and total number of IVTs, visual acuity or patient age were tested.

Results: The mean IOP increase was 0.8 ± 3.1 mm Hg ($p < 0.0001$). Seven eyes showed final IOP values between 22 and 25 mm Hg. The mean follow-up was 22.7 ± 14.1 months. No further correlations between IOP change and number of IVTs, visual acuity or patient age have been found.

Conclusions: This study demonstrated a statistically significant IOP increase in patients treated with repeated injections of ranibizumab. However, IOP increase required no glaucoma treatment during the study. Therefore, repeated injections with ranibizumab can be considered safe with regard to long-term IOP changes in patients without ocular hypertension or glaucoma.

PMID: 23548723 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2013;6(1):62-6. doi: 10.3980/j.issn.2222-3959.2013.01.13. Epub 2013 Feb 18.

Predictors of visual outcome in eyes with choroidal neovascularization secondary to age related macular degeneration treated with intravitreal bevacizumab monotherapy.

Chhablani J, Kim JS, Freeman WR, Kozak I, Wang HY, Cheng L.

Jacob's Retina Center at Shiley Eye Center, University of California, San Diego, USA ; L V Prasad Eye Institute, Hyderabad, India.

AIM: To evaluate the predictors of visual improvement in eyes with naive choroidal neovascularization secondary to age-related macular degeneration (CNV -AMD) treated with intravitreal bevacizumab (IVB) monotherapy.

METHODS: Fifty eyes with naive CNV- AMD with pretreatment best-corrected visual acuity (BCVA) better than 20/200 and treated with IVB monotherapy were evaluated. Several variables including age, sex, pre-treatment BCVA, CNV type and lesion size on fluorescein angiogram as well as SD-OCT parameters including pre-treatment central macular thickness (CMT), inner-segment/outer-segment (IS/OS) junction integrity, and external limiting membrane (ELM) integrity were analyzed to predict visual outcome.

RESULTS: On univariate regression, pretreatment ELM damage was associated with less visual improvement after treatment (P=0.0145). However, ELM damage predicted only 10% of the visual outcome. On multivariate regression, pretreatment BCVA, IS/OS junction, and ELM integrity on SD-OCT were the significant predictors for the treatment effect and together predicted 37% of visual improvement.

CONCLUSION: Pretreatment BCVA, ELM and IS/OS junction integrity on SD-OCT are of significant value in predicting the visual improvement in naive wet AMD patients treated with IVB monotherapy.

PMID: 23549041 [PubMed]

BMC Ophthalmol. 2013 Apr 4;13(1):10. [Epub ahead of print]

Effectiveness of intravitreal ranibizumab in exudative age-related macular degeneration (AMD): comparison between typical neovascular AMD and polypoidal choroidal vasculopathy over a 1 year follow-up.

Matsumiya W, Honda S, Kusuhara S, Tsukahara Y, Negi A.

BACKGROUND: The effects of intravitreal ranibizumab (IVR) against exudative age-related macular degeneration (AMD) may be different associated with the lesion phenotype. This study was conducted to compare the outcomes of IVR between two different phenotypes of exudative AMD: typical neovascular AMD (tAMD) and polypoidal choroidal vasculopathy (PCV).

METHODS: This is a retrospective cohort study of 54 eyes from 54 subfoveal exudative AMD patients (tAMD 24, PCV 30 eyes). Three consecutive IVR treatments (0.5 mg) were performed every month, followed by re-injections as needed. Change in the best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were then compared between the tAMD and PCV groups over 12 months of follow-up.

RESULTS: The mean BCVA was significantly improved (-0.11 logMAR units) at month 3 after the initial IVR ($p < 0.001$, Wilcoxon signed-rank test), and was sustained up to 12 months in all AMD patients ($p = 0.02$). In the subgroup analysis, the tAMD group showed a significant improvement in their mean BCVA (-0.06, -0.17, -0.15 and -0.16 logMAR units at 1, 3, 6 and 12 months, respectively), but there was only a slight but non-significant improvement in the PCV group. The improvement in the BCVA was significantly greater in the tAMD group than in the PCV group ($p = 0.043$, repeated measures ANOVA) over 12 months. Both phenotypes showed significant improvements in the CRT during 12 months after the initial IVR.

CONCLUSIONS: IVR is an effective therapy for tAMD and PCV in the BCVA improvement in Japanese patients over 12 months of follow-up. The phenotype of tAMD showed a significantly better outcome with IVR than PCV in terms of BCVA improvement.

PMID: 23557322 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Apr 5. [Epub ahead of print]

Two-year results of combined intravitreal ranibizumab and photodynamic therapy for polypoidal choroidal vasculopathy.

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BACKGROUND: To clarify the efficacy of combined therapy with intravitreal ranibizumab injections and photodynamic therapy (PDT) in patients with symptomatic polypoidal choroidal vasculopathy (PCV).

METHODS: We retrospectively reviewed 57 treatment-naïve eyes of 57 patients. Thirty-two patients were treated with standard fluence PDT (PDT group), and 25 patients were treated with three consecutive monthly intravitreal injections of ranibizumab and standard fluence PDT (ranibizumab plus PDT group). All patients were followed for at least 24 months.

RESULTS: In the ranibizumab plus PDT group, the mean best-corrected visual acuity (BCVA) levels of decimal (logMAR equivalent) significantly improved from 0.30 (0.52) at baseline to 0.55 (0.26) at 24 months ($P < 0.001$). In the PDT group, the BCVA levels stabilized from 0.26 (0.58) at baseline to 0.25 (0.60) at 24 months. The mean changes in the BCVA in the ranibizumab plus PDT group and the PDT group were improvement of 2.63 lines and decline of 0.16 lines respectively ($P = 0.010$). The mean number of PDTs at 24 months in the ranibizumab plus PDT group and the PDT group were 1.4 and 2.6 respectively. Increased

subretinal hemorrhages were seen in eight (18.0 %) eyes, all of which were belonging to the PDT group.

CONCLUSIONS: Combined intravitreal ranibizumab and PDT was significantly more effective in maintaining and improving VA for PCV patients compared with PDT monotherapy over 24 months.

PMID: 23553286 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2013 Apr 1. doi: 10.1111/aos.12090. [Epub ahead of print]

Shifting exudative age-related macular degeneration patients to ranibizumab after insufficient response to bevacizumab.

de Geus SJ, Jager MJ, Luyten GP, Dijkman G.

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PMID: 23551594 [PubMed - as supplied by publisher]

Mol Vis. 2013;19:702-9. Epub 2013 Mar 21.

Pharmacogenetic association with early response to intravitreal ranibizumab for age-related macular degeneration in a Korean population.

Chang W, Noh DH, Sagong M, Kim IT.

Department of Ophthalmology, Yeungnam University College of Medicine, Daegu, South Korea.

PURPOSE: To determine whether genetic factors that influence age-related macular degeneration (AMD) have an early pharmacogenetic effect on treating exudative AMD with ranibizumab in a Korean population.

METHODS: A retrospective study of 102 patients (70 with typical neovascular AMD and 32 with polypoidal choroidal vasculopathy) with exudative AMD treated with intravitreal ranibizumab monotherapy was conducted. Optical coherence tomography, fluorescein, and indocyanine green angiography were taken at the baseline. The best-corrected visual acuity (BCVA) and the central subfield macular thickness (CSMT) were recorded at the baseline and at each monthly visit. The genotypes of the polymorphisms in the known AMD susceptibility loci (CFH, AMRS2, HTRA1, VEGFA, and KDR) were determined, and association between their frequencies and the changes in the BCVA and the CSMT were evaluated.

RESULTS: The mean baseline visual acuity was 0.96±0.59 logMAR (approximately 20/200 in the Snellen equivalent), and the mean number of injections was 3.87 before the month 6 visit. No association was observed between the change in BCVA and each genotype. For the changes in the CSMT, a significant difference was observed only with the VEGF-A (rs833069) gene. The decrease in the CSMT at month 3 for the major allele homozygote AA genotype, the heterozygote AG genotype, and the risk allele homozygote GG genotype was 25.66±85.40, 86.93±92.31, and 85.30±105.30 μm, respectively (p=0.012, p=0.044, and p=0.002 for AG, GG, and combined AG or GG genotype, respectively, compared to the AA genotype). This trend was maintained until month 6.

CONCLUSIONS: The VEGF-A (rs833069) polymorphism showed a significant association with the anatomic response to intravitreal ranibizumab. No significant difference was found between the genotype of the potential risk polymorphism for development of AMD and the early visual improvement after intravitreal ranibizumab.

PMID: 23559864 [PubMed - in process]

JAMA Ophthalmol. 2013 Feb;131(2):139-45.

Ranibizumab for edema of the macula in diabetes study: 3-year outcomes and the need for prolonged frequent treatment.

Do DV, Nguyen QD, Khwaja AA, Channa R, Sepah YJ, Sophie R, Hafiz G, Campochiaro PA; READ-2 Study Group.

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OBJECTIVE: To assess the benefit of increased follow-up and treatment with ranibizumab between months 24 and 36 in the Ranibizumab for Edema of the Macula in Diabetes (READ-2) Study.

DESIGN: Prospective, interventional, multicenter follow-up of a randomized clinical trial.

METHODS: Patients who agreed to participate between months 24 and 36 (ranibizumab, 28 patients; laser, 22; and ranibizumab + laser, 24) returned monthly and received ranibizumab, 0.5 mg, if foveal thickness (FTH, center subfield thickness) was 250 µm or greater. Main outcome measures were improvement in best-corrected visual acuity (BCVA) and reduction in FTH between months 24 and 36.

RESULTS: Mean improvement from the baseline BCVA in the ranibizumab group was 10.3 letters at month 36 vs 7.2 letters at month 24 (ΔBCVA letters = 3.1, P = .009), and FTH at month 36 was 282 µm vs 352 µm at month 24 (ΔFTH = 70 µm, P = .006). Changes in BCVA and FTH in the laser group (-1.6 letters and -36 µm, respectively) and the ranibizumab + laser group (+2.0 letters and -24 µm) were not statistically significant. The mean number of ranibizumab injections was significantly greater in the ranibizumab group compared with the laser group (5.4 vs 2.3 injections, P = .008) but not compared with the ranibizumab + laser group (3.3, P = .11).

CONCLUSIONS: More aggressive treatment with ranibizumab during year 3 resulted in a reduction in mean FTH and improvement in BCVA in the ranibizumab group. More extensive focal/grid laser therapy in the other 2 groups may have reduced the need for more frequent ranibizumab injections to control edema.

APPLICATION TO CLINICAL PRACTICE: Long-term visual outcomes for treatment of diabetic macular edema with ranibizumab are excellent, but many patients require frequent injections to optimally control edema and maximize vision.

PMID: 23544200 [PubMed - in process]

Other treatment & diagnosis

Ophthalmologe. 2013 Apr 6. [Epub ahead of print]

[Adjuvant stereotactic low energy radiation therapy of exudative age-dependent macular degeneration (Oraya system).] [Article in German]

Pollithy S, Celik N, Höh H, Dithmar S.

Schwerpunkt Retinologie, Universitäts-Augenklinik Heidelberg, Im Neuenheimer Feld 400, 69120, Heidelberg, Deutschland.

Abstract: With respect to the increasing number of patients and the risk and burden for patients caused by injections, a reduction in the number and frequency of injections with vascular endothelial growth factor (VEGF) inhibitors in exudative age-related macular degeneration (ARMD) is desirable. Stereotactic low-voltage x-ray irradiation seems to be a promising approach. For this purpose the Oraya system is available and has shown positive results in initial studies. Pending presentation of phase II and III study data this adjuvant irradiation should only be used in clinical trials.

PMID: 23559322 [PubMed - as supplied by publisher]

J Biomed Mater Res A. 2013 Mar 29. doi: 10.1002/jbm.a.34726. [Epub ahead of print]

Bioactive substrates for human retinal pigment epithelial cell growth from elastin-like recombinamers.

Singh AK, Srivastava GK, Martín L, Alonso M, Pastor JC.

IOBA-Eye Institute, University of Valladolid, Valladolid, Spain.

Abstract: The aim of this study was to investigate the use of bioactive RGD-containing elastin-like recombinamers (ELR-RGDs) as a substrate that can maintain hRPE cell phenotype and growth pattern. Results obtained are compared with previously published behaviour of ARPE19 cells. The extension of these results to hRPE is required since ARPE19 cells cannot be used clinically to treat age-related macular degeneration.

METHODS: hRPE cells were isolated, cultured, seeded and grown on surface of glass, TCP and solvent-cast ELR-RGD and ELR-IK film with no specific sequence. Cells were analyzed to study cell adhesion, proliferation, morphology and RPE65 protein expression by staining with DAPI, RP and antiRPE65 antibody at 12, 24, 72, 120, 168 and 360 hours.

RESULTS: hRPE cells always grew better on ELR-RGD than on glass and ELR-IK but not as well as on TCP. The kinetic hRPE growth curves confirmed that growth differences started to appear at 24 hours for these surfaces in ascending order of cell growths, namely glass, ELR-IK, ELR-RGD and TCP. There was a very clear difference at 360 hours. ELR-RGD maintained hRPE cells stable morphology and RPE65 protein expression.

CONCLUSIONS: ELR-RGD seems to be a good substrate for growing hRPE cells with stable morphology and RPE65 protein expression. As such, this work confirms our hypothesis regarding ELR-RGD substrates viability, which can be used as a Bruch's membrane prosthesis for further studies in animals. However, these results must subsequently be extrapolated to use of hRPE cells in animals in order to evaluate them as a transplantation vehicle in human.

PMID: 23554132 [PubMed - as supplied by publisher]

Pathogenesis

Mol Vis. 2013;19:729-36. Epub 2013 Mar 21.

Serum levels of matrix metalloproteinase 2 and matrix metalloproteinase 9 elevated in polypoidal choroidal vasculopathy but not in age-related macular degeneration.

Zeng R, Wen F, Zhang X, Su Y.

State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China.

PURPOSE: Age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) are the leading causes of vision loss in the elderly Asian population. Previous studies have confirmed that abnormal extracellular matrix (ECM) metabolism plays an important role in the pathogenesis of AMD and PCV. However, the dynamic metabolism of the ECM is closely regulated by matrix metalloproteinases (MMPs) and tissue metalloproteinase inhibitors (TIMPs). Whether MMPs and TIMPs participate in the pathogenesis of AMD and PCV remains unclear. The aim of this study was to investigate the correlation between circulating MMP and TIMP levels and AMD and PCV.

METHODS: The serum levels of MMPs (MMP1, MMP2, MMP3, and MMP9) and TIMPs (TIMP1 and TIMP3) were quantified using enzyme-linked immunosorbent assays in four groups of subjects (n=342):

early AMD (group 1, n=75), neovascular AMD (group 2, n=89), PCV (group 3, n=98), and age- and gender-matched controls (group 4, n=80).

RESULTS: The mean concentrations of the two gelatinases, MMP2 and MMP9, in the PCV group were significantly higher than that of the control (p=0.001, p<0.001, respectively), early AMD (both p<0.001), and neovascular AMD (p=0.005, p=0.001, respectively) groups. Moreover, the serum MMP2 concentration was positively correlated with the serum MMP9 concentration in the PCV group (r=0.822, p<0.001). However, the mean concentrations of MMP2 and MMP9 in the early AMD and neovascular AMD groups were not significantly different from that of the control group (p>0.05). The mean serum levels of MMP1, MMP3, TIMP1, and TIMP3 were not significantly different among the four groups.

CONCLUSIONS: This pilot study first reveals a link between increased levels of circulating gelatinases (MMP2 and MMP9) and PCV but not AMD, which may provide a biologically relevant marker of ECM metabolism in patients with PCV. This finding suggests that the two disorders may have different molecular mechanisms.

PMID: 23559867 [PubMed - in process]

Mol Vis. 2013;19:718-28. Epub 2013 Mar 21.

Altered cytokine profiles of human retinal pigment epithelium: Oxidant injury and replicative senescence.

Cao S, Walker GB, Wang X, Cui JZ, Matsubara JA.

Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, British Columbia, Canada.

PURPOSE: Age-related macular degeneration (AMD) is a local, chronic inflammatory disease of the eye that is influenced by oxidative stress and dysregulation of the retinal pigment epithelium (RPE) associated with aging. The purpose of this study is to characterize the effects of oxidative stress and replicative senescence on the secreted cytokine profiles of RPE in vitro.

METHODS: We used multiple, serial passages of human RPE cells from primary culture as an in vitro model of aging. Responses of early passage 5 (P5) and late passage 21 (P21) RPE cells were compared. Oxidative stress was induced in RPE cells (P5) by exposure to 75 μM hydroquinone (HQ) for 24 h. The secretome profiles of the RPE cells were measured with a multiplex suspension assay that assayed human cytokine, chemokine, and growth factors. Immunohistochemistry on younger (≤55 years old) and older (≥70 years old) human post-mortem donor eyes was used to verify selected cytokines.

RESULTS: Supernatant of HQ-treated RPE cultures exhibited increased secreted levels of vascular endothelial growth factor (VEGF), interleukin (IL)-12, and IL-10 that reached statistical significance (p<0.05). Supernatant of late passage P21 RPE cultures exhibited decreased secreted levels of stromal cell -derived factor (SDF)-1α, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-8, IL-15, IL-6, and an increased level of IL-1ra compared to early passage P5 RPE cultures that reached statistical significance (p<0.05). Immunohistochemical analysis demonstrated increased expression of IL-1ra in RPE cells from older post-mortem donor eyes (≥70 years old) versus younger eyes (≤55 years old).

CONCLUSIONS: Our data demonstrate a unique cytokine secretion profile of primary culture RPE cells at early and late passage. Our in vitro data suggest an age-specific modulation of cytokine secretion in RPE and is consistent with immunohistochemical analysis on post-mortem eyes. The secretion profile associated with RPE under conditions that mimic oxidative stress, another factor associated with the pathogenesis of AMD, emphasizes upregulation of the angiogenic growth factor, vascular endothelial growth factor. Together, these data support the role of advanced age and oxidative stress in inflammatory cytokine modulation in RPE cells.

PMID: 23559866 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2013 Apr 4. pii: iovs.13-11612v1. doi: 10.1167/iovs.13-11612. [Epub ahead of print]

Aβ-induced senescent retinal pigment epithelial cells create a proinflammatory microenvironment in AMD.

Cao L, Wang H, Wang F, Xu D, Liu F, Liu C.

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Purpose: Chronic inflammation is implicated in the pathogenesis of age-related macular degeneration (AMD). The source of chronic inflammation is often attributed to the progressive activation of immune cells over time. However, recent studies have shown that senescent cells can alter tissue microenvironment via secretion of growth factors, proteases and inflammatory cytokines and might be an additional source of chronic inflammation. We hypothesized that altered secretory pattern in Aβ-induced senescent retinal pigment epithelial (RPE) cells may contribute to compromised RPE barrier integrity and chronic inflammation in AMD.

Methods: Senescence was assessed by measuring the SA-β-galactosidase activity, the expressions of p16INK4a and ATM, and cell cycle analysis. Expressions of IL-8 and MMPs were analyzed by RT-PCR, ELISA and Gelatin zymography. The barrier structures of RPE cells were detected by actin-tracker, ZO-1, claudin-19 and occludin immunochemistry and western blot, barrier function was analyzed by measuring transepithelial resistance (TER) and transepithelial diffusion rate of FITC-dextran. For inhibitory studies, MMP-9 was inhibited by RNA interference strategy.

Results: Aβ promotes RPE cells to enter senescence and secrete higher concentrations of IL-8 and MMP-9. Secretion of MMP-9 is associated with compromised barrier integrity and with processing of IL-8 to a more activated form. The degradation of tight junction proteins and barrier dysfunction in senescent cells were reversed by silence of MMP-9.

Conclusions: The altered secretory phenotype of senescent RPE cells may contribute to age-related inflammation in AMD.

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Mol Vis. 2013;19:536-43. Epub 2013 Mar 5.

Specific inhibition of serine/arginine-rich protein kinase attenuates choroidal neovascularization.

Dong Z, Noda K, Kanda A, Fukuhara J, Ando R, Murata M, Saito W, Hagiwara M, Ishida S.

Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo, Japan ; Laboratory of Ocular Cell Biology and Visual Science, Hokkaido University Graduate School of Medicine, Sapporo, Japan.

PURPOSE: To investigate the applicability of serine/arginine-rich protein kinase (SRPK)-specific inhibitor, SRPIN340, for attenuation of choroidal neovascularization (CNV) formation using a mouse model.

METHODS: Laser photocoagulation was performed to induce CNV in C57BL/6J mice, followed by intravitreal injection of SRPIN340 or vehicle. Seven days after the treatment, the CNV size was evaluated using a flatmount technique. Protein levels of vascular endothelial growth factor (VEGF) and inflammation-associated molecules, such as monocyte chemoattractant protein (MCP)-1 and intercellular adhesion molecule (ICAM)-1, in the retinal pigment epithelium-choroid complex were measured with enzyme-linked immunosorbent assay. Expression levels of total Vegf, exon 8a-containing Vegf isoforms, and F4/80 (a specific marker for macrophage) were assessed using real-time PCR.

RESULTS: SRPIN340 inhibited CNV formation in a dose-dependent manner. Compared with the vehicle, SRPIN340 significantly decreased the protein levels of VEGF, MCP-1, ICAM-1, and consequently inhibited macrophage infiltration. Furthermore, SRPIN340 suppressed the gene expression levels of total Vegf and exon 8a-containing Vegf isoforms.

CONCLUSIONS: SRPIN340, a specific inhibitor of SRPK, suppressed Vegf expression and attenuated CNV formation. Our data suggest the possibility that SRPIN340 is applicable for neovascular age-related macular degeneration as a novel chemical therapeutics.

PMID: 23559848 [PubMed - in process]

Epidemiology

Am J Epidemiol. 2013 Apr 1. [Epub ahead of print]

Younger Siblings, C-Reactive Protein, and Risk of Age-Related Macular Degeneration.

Cohn AC, Busija L, Robman LD, Dimitrov PN, Varsamidis M, Lim LL, Baird PN, Guymer RH.

Abstract: In this study, we examined the relationship between exposure to siblings and 1) the risk of age-related macular degeneration (AMD) and 2) C-reactive protein levels. We retrospectively analyzed pooled cross-sectional data from 2 studies: the Cardiovascular Health and Age-Related Maculopathy Study (2001-2002) and the Age-Related Maculopathy Statin Study (2004-2006). Associations between number of siblings and AMD were assessed by using multinomial logistic regression. Associations between number of siblings and C-reactive protein levels were examined by using a generalized linear model for γ distribution. A higher number of younger siblings was associated with significantly lower odds of early AMD in those with a family history of AMD (odds ratio = 0.2, 95% confidence interval: 0.1, 0.8) (P = 0.022) but was unrelated to AMD for those who had no family history of the disease (odds ratio = 1.0, 95% confidence interval: 0.9, 1.2) (P = 0.874). A higher number of younger siblings correlated with lower C-reactive protein levels (β = -0.19, 95% confidence interval: -0.38, -0.01) (P = 0.036). This supports the theory that immune modulation contributes to AMD pathogenesis and suggests that exposure to younger siblings might be protective when there is a family history of AMD.

PMID: 23548752 [PubMed - as supplied by publisher]

Eur J Epidemiol. 2013 Mar 31. [Epub ahead of print]

The synergistic effect of exposure to alcohol, tobacco smoke and other risk factors for age-related macular degeneration.

La Torre G, Pacella E, Saulle R, Giraldi G, Pacella F, Lenzi T, Mastrangelo O, Mirra F, Aloe G, Turchetti P, Brillante C, De Paolis G, Boccia A, Giustolisi R.

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Genetics

Retina. 2013 Mar 30. [Epub ahead of print]

GENETIC AND ENVIRONMENTAL FACTORS ASSOCIATED WITH RETICULAR PSEUDODRUSEN IN AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To analyze the genetic and environmental factors associated with reticular pseudodrusen (RPD) in age-related macular degeneration (AMD).

METHODS: In a large population, AMD patients (n = 519) with and without RPD were assessed with a standardized examination including infrared images and spectral domain optical coherence tomography scans. Three groups were defined: Group 1: AMD patients with RPD (n = 105); Group 2: AMD patients without RPD (n = 414); and Group 3: controls with no AMD and no RPD (n = 430). Four genes associated with AMD (CFH, ARMS2/HTRA1, C3, apolipoprotein E) and environmental factors were assessed between the 3 groups.

RESULTS: None of the environmental factors studied were more significantly associated to either Group 1 or Group 2. The odds ratios and 95% confidence intervals for individuals homozygous for the CFH risk allele were 4.0 (2.1-7.7) ([95% confidence interval: 2.1-7.7]; P < 0.0004) in Group 1 and 4.3 ([2.6-7.1]; P < 0.0004) in Group 2, compared with Group 3. The odds ratios for individuals homozygous for the ARMS2 risk allele for Groups 1 and 2 compared with Group 3 were 16.3 ([7.6-35.4]; P < 0.0004) and 11.9 ([6.3-22.3]; P < 0.0004), respectively. None of the genotypes studied were more significantly associated to Group 1 than Group 2.

CONCLUSION: Genotypes known to be associated with AMD were similarly observed in patients with and without RPD.

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The Benefits of Using Genetic Information to Design Prevention Trials.

Hu Y, Li L, Ehm MG, Bing N, Song K, Nelson MR, Talmud PJ, Hingorani AD, Kumari M, Kivimäki M, Xu CF, Waterworth DM, Whittaker JC, Abecasis GR, Spino C, Kang HM.

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Abstract: Clinical trials for preventative therapies are complex and costly endeavors focused on individuals likely to develop disease in a short time frame, randomizing them to treatment groups, and following them over time. In such trials, statistical power is governed by the rate of disease events in each group and cost is determined by randomization, treatment, and follow-up. Strategies that increase the rate of disease events by enrolling individuals with high risk of disease can significantly reduce study size, duration, and cost. Comprehensive study of common, complex diseases has resulted in a growing list of robustly associated genetic markers. Here, we evaluate the utility-in terms of trial size, duration, and cost-of enriching prevention trial samples by combining clinical information with genetic risk scores to identify individuals at greater risk of disease. We also describe a framework for utilizing genetic risk scores in these trials and evaluating the associated cost and time savings. With type 1 diabetes (T1D), type 2 diabetes (T2D), myocardial infarction (MI), and advanced age-related macular degeneration (AMD) as examples, we illustrate the potential and limitations of using genetic data for prevention trial design. We illustrate settings where incorporating genetic information could reduce trial cost or duration considerably, as well as settings where potential savings are negligible. Results are strongly dependent on the genetic architecture of the

disease, but we also show that these benefits should increase as the list of robustly associated markers for each disease grows and as large samples of genotyped individuals become available.

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Mol Vis. 2013;19:665-74. Epub 2013 Mar 21.

Review: Epigenetic mechanisms in ocular disease.

He S, Li X, Chan N, Hinton DR.

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Abstract: Epigenetics has become an increasingly important area of biomedical research. Increasing evidence shows that epigenetic alterations influence common pathologic responses including inflammation, ischemia, neoplasia, aging, and neurodegeneration. Importantly, epigenetic mechanisms may have a pathogenic role in many complex eye diseases such as corneal dystrophy, cataract, glaucoma, diabetic retinopathy, ocular neoplasia, uveitis, and age-related macular degeneration. The emerging emphasis on epigenetic mechanisms in studies of eye disease may provide new insights into the pathogenesis of complex eye diseases and aid in the development of novel treatments for these diseases.

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A genetic variant in the SKIV2L gene is significantly associated with age-related macular degeneration in a Han Chinese population.

Lu F, Shi Y, Qu C, Zhao P, Liu X, Gong B, Ma S, Zhou Y, Zhang Q, Fei P, Xue Y, Hu J, Fan Y, Lin Y, Zhu X, Yang Z.

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PURPOSE: Previous studies have shown genetic variants in the complement component 2 (C2)/ complement factor B (BF) gene are associated with age-related macular degeneration (AMD) in Caucasians, but not in Han Chinese. Recent studies have indicated that genetic variants in the neighboring superkiller viralicidic activity 2-like (SKIV2L) gene showed significant association with AMD. We conducted this study to investigate whether genetic variants in the SKIV2L gene are associated with AMD in a Han Chinese population.

METHODS: Thirteen single nucleotide polymorphisms (SNPs) in the C2-BF-RDBP-SKIV2L-STK19 region were genotyped by the SNaPshot method in a cohort composed of 449 patients with choriodal neovascularization (CNV) AMD and 1,025 normal controls of Han Chinese descent.

RESULTS: Among the SNPs genotyped, P-values of seven SNPs were less than 0.05; however, only rs429608 was found to be significantly associated with AMD after correction for multiple testing. The minor allele (A) frequency of rs429608 was 0.050 in cases and 0.089 in controls, and the P-value was 3.76x10-4 (0.00489 after Bonfferoni correction), with an odds ratio (OR) of 0.55 (95% confidence interval, 0.40-0.77). The SKIV2L gene was expressed in the human retinal pigment epithelium (RPE), retina and D407 (human RPE) cells, and in mouse retinas and RPE.

CONCLUSIONS: We demonstrated that the rs429608 genetic variant in the SKIV2L gene was significantly associated with AMD in a Han Chinese population. SKIV2L may play an important role in the development of AMD.

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Diet

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Epoxy metabolites of docosahexaenoic acid (DHA) inhibit angiogenesis, tumor growth, and metastasis.

Zhang G, Panigrahy D, Mahakian LM, Yang J, Liu JY, Stephen Lee KS, Wettersten HI, Ulu A, Hu X, Tam S, Hwang SH, Ingham ES, Kieran MW, Weiss RH, Ferrara KW, Hammock BD.

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Abstract: Epidemiological and preclinical evidence supports that omega-3 dietary fatty acids (fish oil) reduce the risks of macular degeneration and cancers, but the mechanisms by which these omega-3 lipids inhibit angiogenesis and tumorigenesis are poorly understood. Here we show that epoxydocosapentaenoic acids (EDPs), which are lipid mediators produced by cytochrome P450 epoxygenases from omega-3 fatty acid docosahexaenoic acid, inhibit VEGF- and fibroblast growth factor 2-induced angiogenesis in vivo, and suppress endothelial cell migration and protease production in vitro via a VEGF receptor 2-dependent mechanism. When EDPs (0.05 mg·kg-1·d-1) are coadministered with a low-dose soluble epoxide hydrolase inhibitor, EDPs are stabilized in circulation, causing ~70% inhibition of primary tumor growth and metastasis. Contrary to the effects of EDPs, the corresponding metabolites derived from omega-6 arachidonic acid, epoxyeicosatrienoic acids, increase angiogenesis and tumor progression. These results designate epoxyeicosatrienoic acids and EDPs as unique endogenous mediators of an angiogenic switch to regulate tumorigenesis and implicate a unique mechanistic linkage between omega-3 and omega-6 fatty acids and cancers.

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