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Drug treatment

J Ocul Pharmacol Ther. 2016 May 23. [Epub ahead of print]

Factors Predictive of Visual Outcome 1 Year After Intravitreal Aflibercept Injection for Typical Neovascular Age-Related Macular Degeneration.

Kikushima W, Sakurada Y, Sugiyama A, Tanabe N, Kume A, Iijima H.

PURPOSE: Several factors have been reported to be associated with visual outcomes after intravitreal ranibizumab treatment for neovascular age-related macular degeneration (AMD). In the present study, we investigated the factors associated with visual outcomes after intravitreal aflibercept injection (IAI) for typical neovascular AMD.

METHODS: We retrospectively studied the visual changes in 47 eyes of 51 patients with typical neovascular AMD, who had been initially treated with 3 monthly IAI followed by as-needed IAI.

RESULTS: Mean best-corrected visual acuity (BCVA) improved during the 12-month follow-up period in 40 eyes of 37 patients without reticular pseudodrusen (RPD) in both eyes, whereas it deteriorated in 11 eyes of 10 patients with RPD in either eye. Multiple regression analysis revealed that visual gain at 12 months after the first IAI positively correlated with worse baseline BCVA and thicker baseline subfoveal choroidal thickness ($P = 0.018$, $P = 0.004$, respectively), but not with absence of RPD ($P = 0.13$). Subfoveal choroidal thickness was significantly thinner in eyes with RPD compared with that in eyes without RPD ($P = 0.003$).

CONCLUSIONS: Visual gain after IAI in eyes with typical neovascular AMD appears to be limited in patients with RPD, which may reflect the poor visual outcome after IAI in eyes with a thinner subfoveal choroid that is seen predominately in patients with RPD.

PMID: 27213222 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 May 26. [Epub ahead of print]

Twelve-month outcomes of treatment using ranibizumab or aflibercept for neovascular age-related macular degeneration: a comparative study.

Kim JH, Lee DW, Chang YS, Kim JW, Kim CG.

PURPOSE: To compare the 12-month treatment outcome of ranibizumab with that of aflibercept in cases of neovascular age-related macular degeneration (AMD).

METHODS: This retrospective single-institution study included patients who had been diagnosed with treatment-naïve neovascular AMD and treated using either ranibizumab (ranibizumab group, $n = 30$) or aflibercept (aflibercept group, $n = 21$) monotherapy over a 12-month follow-up period. Patients initially received three monthly injections, and were re-treated when neovascularization recurred. The best-

corrected visual acuity (BCVA) at diagnosis and at 12 months, as well as the number of injections, were compared between the two groups.

RESULTS: In the ranibizumab group, the mean logarithm of the minimum angle of resolution BCVA values at diagnosis and at 12 months were 0.86 ± 0.45 and 0.72 ± 0.56, respectively. The equivalent values were 0.73 ± 0.37 and 0.58 ± 0.41 in the aflibercept group. The mean number of injections was 4.5 ± 1.3 in the ranibizumab group and 4.3 ± 0.9 in the aflibercept group. There was no difference in BCVA between the two groups at either diagnosis (P = 0.560) or 12 months (P = 0.702). There was also no difference between the two groups in the number of injections (P = 0.847).

CONCLUSION: The 12-month treatment outcome of intravitreal ranibizumab was similar to that of intravitreal aflibercept, with a comparable injection frequency. Further prospective studies with a more controlled design are needed to confirm our findings.

PMID: 27230919 [PubMed - as supplied by publisher]

Angiogenesis. 2016 May 27. [Epub ahead of print]

Aflibercept exhibits VEGF binding stoichiometry distinct from bevacizumab and does not support formation of immune-like complexes.

MacDonald DA, Martin J, Muthusamy KK et al.

Abstract: Anti-vascular endothelial growth factor (VEGF) therapies have improved clinical outcomes for patients with cancers and retinal vascular diseases. Three anti-VEGF agents, pegaptanib, ranibizumab, and aflibercept, are approved for ophthalmic indications, while bevacizumab is approved to treat colorectal, lung, and renal cancers, but is also used off-label to treat ocular vascular diseases. The efficacy of bevacizumab relative to ranibizumab in treating neovascular age-related macular degeneration has been assessed in several trials. However, questions persist regarding its safety, as bevacizumab can form large complexes with dimeric VEGF165, resulting in multimerization of the Fc domain and platelet activation. Here, we compare binding stoichiometry, Fcγ receptor affinity, platelet activation, and binding to epithelial and endothelial cells in vitro for bevacizumab and aflibercept, in the absence or presence of VEGF. In contrast to bevacizumab, aflibercept forms a homogenous 1:1 complex with each VEGF dimer. Unlike multimeric bevacizumab:VEGF complexes, the monomeric aflibercept:VEGF complex does not exhibit increased affinity for low-affinity Fcγ receptors, does not activate platelets, nor does it bind to the surface of epithelial or endothelial cells to a greater degree than unbound aflibercept or control Fc. The latter finding reflects the fact that aflibercept binds VEGF in a unique manner, distinct from antibodies not only blocking the amino acids necessary for VEGFR1/R2 binding but also occluding the heparin-binding site on VEGF165.

PMID: 27234973 [PubMed - as supplied by publisher]

Cornea. 2016 May 24. [Epub ahead of print]

Mycobacterium chelonae Scleral Abscess After Intravitreal Ranibizumab Injection.

Sluch IM, Siatkowski RL, Shah VA.

PURPOSE: To report a case of Mycobacterium chelonae scleral abscess after an intravitreal injection of ranibizumab.

METHODS: A 54-year-old female received an intravitreal ranibizumab injection for diabetic macular edema. Two weeks postinjection, a scleral abscess developed at the injection site. The patient was treated with incision and drainage of the abscess, subconjunctival injection of amikacin, topical clarithromycin and amikacin, and oral clarithromycin.

RESULTS: After 4 weeks of treatment, the inflammation and infection resolved, and the patient returned to

best-corrected preinjection visual acuity.

CONCLUSIONS: Injection-site scleral abscesses are very rare and serious complications of intravitreal injections. Once the abscess is drained, it is possible to identify the organism and treat the infection with appropriate combination antibiotic therapy.

PMID: 27227391 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2016 May 26. [Epub ahead of print]

Three-month outcomes of ziv-aflibercept in the treatment of diabetic macular oedema.

Ashraf M, Souka AA, El Kayal H, El Manhaly M, Abdallah MH.

PMID: 27227354 [PubMed - as supplied by publisher]

Eye Sci. 2015 Dec;30(4):198-200.

Approved pharmacotherapy for myopic choroidal neovascularization: a review of randomized controlled trials in ranibizumab and aflibercept.

Wang JK, Huang TL, Su PY, Chang PY.

Abstract: Myopic choroidal neovascularization (mCNV) can cause severe visual impairment in highly myopic patients. We review the randomized trials of two approved pharmacotherapy for treating mCNV, including intravitreal injections of ranibizumab and aflibercept. These two vascular endothelial growth factor (VEGF) antagonists show superior ability to improve vision and reduce macular thickness, comparing with sham injections or verteporfin photodynamic therapy (vPDT). There is no severe ocular or systemic adverse reaction reported in studies associated with ranibizumab and aflibercept for mCNV. Prompt treatment with these agents can lead to a better outcome.

PMID: 27215011 [PubMed - in process]

Eye Sci. 2015 Dec;30(4):176-83.

An updated review of long-term outcomes from randomized controlled trials in approved pharmaceuticals for diabetic macular edema.

Wang JK, Huang TL, Su PY, Chang PY.

Abstract: Diabetic macular edema (DME) is a major sight-threatening cause in diabetic patients. We review the long-term outcome of four approved pharmacotherapy for treating DME, including intravitreal injections of corticosteroids (dexamethasone implants and fluocinolone acetonide inserts) and anti-vascular endothelial growth factor (VEGF) (ranibizumab and aflibercept). They all show superior ability to improve vision and reduce macular thickness, comparing with sham injections or macular focal/grid laser treatment. Anti-VEGF agents result in low incidence of severe ocular or systemic adverse effects, but glaucoma and cataract should be aware after intravitreal corticosteroids. Prompt treatment with these agents can lead to a better outcome

PMID: 27215008 [PubMed - in process]

Ophthalmology. 2016 May 24. [Epub ahead of print]

The Impact of Systemic Factors on Clinical Response to Ranibizumab for Diabetic Macular Edema.

Singh RP, Habbu K, Ehlers JP, Lansang MC, Hill L, Stoilov I.

PURPOSE: To evaluate the effect of systemic factors on best-corrected visual acuity (BCVA) achieved with ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA) for treatment of diabetic macular edema (DME) in the RIDE and RISE phase 3 studies.

DESIGN: Exploratory, post hoc analysis of 2 randomized, double-masked, sham-injection controlled studies.

PARTICIPANTS: Adults with DME, BCVA of 20/40 to 20/320 Snellen equivalent, and central foveal thickness of 275 μm or more.

METHODS: Analysis of RIDE (clinicaltrials.gov identifier, NCT00473382) and RISE (clinicaltrials.gov identifier, NCT00473330) pooled ranibizumab data through month 24. Change in BCVA was assessed for association with the following covariates: age, body mass index (BMI), blood pressure, serum glucose, glycosylated hemoglobin (HbA1c), blood urea nitrogen, serum creatinine, estimated glomerular filtration rate, and blood chemistry variables. Change in BCVA at month 24 was assessed according to the following categories of diabetes medication use history: insulin only (n = 193), insulin plus other medications (n = 221), or other noninsulin medications (n = 331).

MAIN OUTCOME MEASURES: Change in BCVA from baseline assessed by randomized treatment group in pooled 0.3- and 0.5-mg monthly ranibizumab groups.

RESULTS: In patients with DME, vision improvement with ranibizumab was not influenced by systemic factors such as diabetes medication history, serum glucose, HbA1c, renal function, BMI, and blood pressure. Patients taking insulin with or without other medications at baseline had longer diabetes disease duration (mean, 17.4 and 20.9 years, respectively) compared with those taking other noninsulin medications (mean, 11.9 years). At month 24, among ranibizumab-treated patients, the mean BCVA change from baseline (Early Treatment Diabetic Retinopathy Study letters ± standard deviation) was not different between patients taking only insulin (12.6±11.2 letters), insulin plus other medications (12.2±12.4 letters), or other noninsulin medications (14.0±13.7 letters). Mean BCVA change also was comparable among patients taking thiazolidinediones (12.9±9.7 letters) and those not taking thiazolidinediones (13.2±13.3 letters).

CONCLUSIONS: There were no associations between systemic factors (baseline values or change from baseline) and mean change of BCVA at month 24. These results suggest that visual response to ranibizumab therapy in DME was not influenced by nonocular factors related to systemic management of diabetes in the RIDE and RISE studies.

PMID: 27234930 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2016;132(2):80-84.

[Combination surgery for wet age-related macular degeneration and chronic peripheral uveitis]. [Article in Russian]

Zapuskalov IV, Krivosheina OI, Khoroshikh YI.

AIM: To develop a combination surgery for wet age-related macular degeneration and concurrent chronic peripheral uveitis that would include intravitreal injection of Lucentis and cryocerclage of the peripheral retina.

MATERIAL AND METHODS: A total of 75 patients were examined and divided into 2 groups: the main group (37 patients) and the controls (38 patients). Patients from the main group underwent the new combination surgery, while the controls received intravitreal Lucentis alone (peripheral uveitis was managed therapeutically).

RESULTS: It has been found that the new combination method provides a significant and stable improvement in visual acuity (by a factor of 10) and a decrease in the area of central scotoma (by a factor of 2.95) in the postoperative period. The period needed for recovery in the central retinal thickness is also 1.6 times shorter.

CONCLUSION: The new combination surgery for wet age-related macular degeneration and concurrent chronic peripheral uveitis provides rapid reduction of inflammation in the extreme periphery of the fundus and a 1.5 times faster (as compared to traditional methods) primary restoration of topographic anatomy of the retina in the macular region.

PMID: 27213803 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2016 May 23. [Epub ahead of print]

Five-year visual acuity outcomes and injection patterns in patients with pro-re-nata treatments for AMD, DME, RVO and myopic CNV.

Wecker T, Ehlken C, Bühler A, Lange C, Agostini H, Böhringer D, Stahl A.

BACKGROUND: Anti vascular endothelial growth factor (VEGF) therapy is an established treatment for various retinal diseases. Long-term data on injection frequencies and visual acuity (VA), however, are still rare.

METHODS: Five-year analysis of real-life VA developments and injection patterns from 2072 patients (2577 eyes; 33 187 injections) with chronically active disease undergoing pro-re-nata treatment for age-related macular degeneration (AMD), diabetic macular oedema (DME), retinal vein occlusion (RVO) and myopic choroidal neovascularisation (CNV).

RESULTS: Maximum mean VA gain in year 1 was+5.2 letters in AMD, +6.2 in DME, +10 in RVO and+7.2 in myopic CNV. Over 5 years, however, VA in patients with AMD declined. By year 5, 34% of patients with AMD had experienced VA loss of >15 letters, 56% had remained stable and 10% had gained >15 letters. Long-term VA developments in DME and RVO were more favourable with 81% of DME and 79% of patients with RVO gaining or maintaining vision at 5 years. In AMD, median injection frequency was six in year 1 and between four and five in consecutive years. In DME and RVO, median injection frequency was six in year 1 but lower compared with AMD in consecutive years. Injection frequency in DME was weakly associated with patient age (rs=0.1; p=0.03).

CONCLUSIONS: In AMD, the initial VA gain was not maintained long term despite higher injection numbers compared with DME, RVO and myopic CNV. The presented real-world data provide a peer-group-based estimate of VA developments and injection frequencies for counselling patients undergoing long-term anti-VEGF therapy.

PMID: 27215744 [PubMed - as supplied by publisher]

Med Monatsschr Pharm. 2016 Apr;39(4):148-56;

[Diabetic retinopathy--Current aspects of therapy]. [Article in German]

Tost F, Kempin R, Grossjohann R, Herfurth S.

Abstract: Pathological changes of the small blood vessels are the main risk for diabetic retinopathy. A distinction is made between proliferative and non-proliferative processes. The diabetic macular edema can manifest itself at any stage of the diabetic retinopathy and poses a serious threat to vision and quality of life. Evidence based therapy primarily focuses on laser coagulation. Laser coagulation suspends progression of the disease and is used particularly for extrafoveolar edema. Especially a pathological swelling, such as the cystoid edema, in this central part of the retina, can cause a rapid deterioration of vision. The treatment of cystoid macular edema with intravitreal application of drugs is a widespread therapeutical approach. Invasive therapeutical drug application into the vitreous cavity has to be sterile in order to prevent infection. The usage of VEGF (Vascular endothelial growth factor) antagonists is an

effective treatment for the diabetic macular edema. Several drugs are now available for intravitreal injection. Nevertheless a small number of medical drugs regularly administered to patients still have to be approved by the authorities (off-label use). One can distinguish mainly between VEGF antagonist (growth factor antagonist) like ranibizumab, aflibercept and bevacizumab and steroid therapy which includes dexamethasone, fluocinolone and triamcinolone.

PMID: 27209895 [PubMed - in process]

Ophthalmology. 2016 May 18. [Epub ahead of print]

Predictors of Diabetic Macular Edema Treatment Frequency with Ranibizumab During the Open-Label Extension of the RIDE and RISE Trials.

Wykoff C, Elman MJ, Regillo C, Ding B, Lu N, Stoilov I.

PURPOSE: To investigate the role of baseline demographics, disease characteristics, and treatment responses to ranibizumab during RIDE/RISE in predicting long-term treatment frequency with a criteria-based pro re nata (PRN) regimen during the open-label extension (OLE).

DESIGN: Pooled, retrospective, post hoc analysis from the phase III, randomized RIDE/RISE studies and subsequent OLE.

PARTICIPANTS: Five hundred patients enrolled in the OLE after completion of the 36-month RIDE/RISE studies.

METHODS: Summary statistics of RIDE/RISE baseline characteristics and treatment responses were generated by PRN ranibizumab 0.5 mg annualized injection frequency in the OLE (0 and >7 annualized injections). Univariable regression and analysis of variance, and multivariable analysis of covariance were performed on the annualized number of ranibizumab injections administered during the OLE versus baseline characteristics and response to treatment during the RIDE/RISE studies.

MAIN OUTCOME MEASURES: Association of patient characteristics and responses to treatment during RIDE/RISE with the observed ranibizumab treatment burden during the OLE.

RESULTS: During the OLE, 121 patients required no treatment, 132 required >0 to ≤3 annualized injections, 159 required >3 to ≤7 annualized injections, and 88 required >7 annualized injections. Parameters identified in the multivariable analysis as related to the annualized number of injections included the total number of rescue focal macular lasers received during the core studies ($P = 0.0203$), central foveal thickness at baseline ($P = 0.0002$) and month 36 ($P < 0.0001$), fluorescein leakage area at month 36 ($P = 0.0137$), and glycated hemoglobin (HbA1c) levels at month 36 ($P = 0.0054$). Patients receiving 0 versus >7 annualized injections during the OLE had, on average, a shorter duration of diabetes and diabetic macular edema (DME) at baseline, were less likely to have proliferative diabetic retinopathy at baseline, received fewer rescue focal macular laser treatments, and were more likely to experience diabetic retinopathy severity scale improvement of ≥2 steps.

CONCLUSIONS: Patients who received less frequent injections during the RIDE/RISE OLE tended to have less advanced disease at baseline and responded better to initial ranibizumab treatment, suggesting that earlier anti-vascular endothelial growth factor treatment of center-involving DME with visual acuity loss may decrease long-term treatment burden.

PMID: 27208982 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Acta Ophthalmol. 2016 May 26. [Epub ahead of print]

Mesopic Pelli-Robson contrast sensitivity and MP-1 microperimetry in healthy ageing and age-

related macular degeneration.

Maynard ML, Zele AJ, Feigl B.

PURPOSE: To determine whether decreasing illumination of the Pelli-Robson contrast sensitivity (CS) chart and MP-1 microperimeter to low mesopic conditions is more sensitive to vision changes occurring with healthy ageing and in early and intermediate age-related macular degeneration (AMD) and whether these mesopic tests can differentiate visual function between healthy older participants with and without AMD risk genotypes.

METHODS: Retinal sensitivity was measured in 98 healthy participants (19-85 years) and 21 AMD (AREDS Grade 2/3) patients (73.9 ± 6.5 years) using the Pelli-Robson CS chart and MP-1 microperimeter under low mesopic and standard illumination. The effect of ageing and AMD on retinal sensitivity was estimated using regression analysis. Healthy older participants (>50 years; n = 24) were genotyped for AMD risk genes CFH and/or ARMS2 and retinal sensitivity was compared between genotypes.

RESULTS: With healthy ageing, photopic and mesopic Pelli-Robson CS showed a similar decline (-0.004 log CS/year). In AMD, photopic CS showed a similar decline to healthy ageing (-0.004 log CS/year) while mesopic CS was significantly reduced (-0.007 log CS/year). Both standard and low mesopic microperimetry showed a significant decline (-0.51 and -0.73% contrast/year) with healthy ageing and greater decline (-0.73 and -0.99% contrast/year) with AMD onset. Pelli-Robson CS and microperimetry sensitivity did not differ between AMD risk genotypes in healthy participants.

CONCLUSIONS: Mesopic Pelli-Robson CS detects functional deficits before photopic CS in early and intermediate AMD that can be differentiated from ageing. This test can be easily administered in clinical practice and may provide a means for early detection of retinal dysfunction.

PMID: 27225020 [PubMed - as supplied by publisher]

Biomed Opt Express. 2016 Feb 2;7(3):709-25. eCollection 2016.

Automatic differentiation of color fundus images containing drusen or exudates using a contextual spatial pyramid approach.

van Grinsven MJ, Theelen T, Witkamp L, van der Heijden J, van de Ven JP, Hoyng CB, van Ginneken B, Sánchez CI.

Abstract: We developed an automatic system to identify and differentiate color fundus images containing no lesions, drusen or exudates. Drusen and exudates are lesions with a bright appearance, associated with age-related macular degeneration and diabetic retinopathy, respectively. The system consists of three lesion detectors operating at pixel-level, combining their outputs using spatial pooling and classification with a random forest classifier. System performance was compared with ratings of two independent human observers using human-expert annotations as reference. Kappa agreements of 0.89, 0.97 and 0.92 and accuracies of 0.93, 0.98 and 0.95 were obtained for the system and observers, respectively.

PMID: 27231583 [PubMed]

Pathogenesis

Mol Biol Rep. 2016 May 26. [Epub ahead of print]

Osmotic induction of placental growth factor in retinal pigment epithelial cells in vitro: contribution of NFAT5 activity.

Hollborn M, Reichmuth K, Prager P, Wiedemann P, Bringmann A, Kohen L.

Abstract: One risk factor of neovascular age-related macular degeneration is systemic hypertension;

hypertension is mainly caused by extracellular hyperosmolarity after consumption of dietary salt. In retinal pigment epithelial (RPE) cells, high extracellular osmolarity induces vascular endothelial growth factor (VEGF)-A (Hollborn et al. in Mol Vis 21:360-377, 2015). The aim of the present study was to determine whether extracellular hyperosmolarity and chemical hypoxia trigger the expression of further VEGF family members including placental growth factor (PlGF) in human RPE cells. Hyperosmotic media were made up by addition of 100 mM NaCl or sucrose. Chemical hypoxia was induced by CoCl2. Gene expression was quantified by real-time RT-PCR, and secretion of PlGF-2 was investigated with ELISA. Nuclear factor of activated T cell 5 (NFAT5) was depleted using siRNA. Extracellular hyperosmolarity triggered expression of VEGF-A, VEGF-D, and PlGF genes, and secretion of PlGF-2. Hypoosmolarity decreased PlGF gene expression. Hypoxia induced expression of VEGF-A, VEGF-B, VEGF-D, and PlGF genes. Extracellular hyperosmolarity and hypoxia produced additive PlGF gene expression. Both hyperosmolarity and hypoxia induced expression of KDR and FLT-4 receptor genes, while hyperosmolarity caused neuropilin-2 and hypoxia neuropilin-1 gene expression. The hyperosmotic, but not the hypoxic, PlGF gene expression was in part mediated by NFAT5. The expression of PlGF in RPE cells depends on the extracellular osmolarity. The data suggest that high consumption of dietary salt may exacerbate the angiogenic response of RPE cells in the hypoxic retina via transcriptional activation of various VEGF family member genes.

PMID: 27230578 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2016 May 1;57(6):2864-2875.

NADPH Oxidase Contributes to Photoreceptor Degeneration in Constitutively Active RAC1 Mice.

Song H, Vijayasarathy C, Zeng Y, Marangoni D, Bush RA, Wu Z, Sieving PA.

PURPOSE: The active form of small GTPase RAC1 is required for activation of NADPH oxidase (NOX), which in turn generates reactive oxygen species (ROS) in nonphagocytic cells. We explored whether NOX-induced oxidative stress contributes to rod degeneration in retinas expressing constitutively active (CA) RAC1.

METHODS: Transgenic (Tg)-CA-RAC1 mice were given apocynin (10 mg/kg, intraperitoneal), a NOX inhibitor, or vehicle daily for up to 13 weeks. Superoxide production and oxidative damage were assessed by dihydroethidium staining and by protein carbonyls and malondialdehyde levels, respectively. Outer nuclear layer (ONL) cells were counted and electroretinogram (ERG) amplitudes measured in Tg-CA-RAC1 mice. Outer nuclear layer cells were counted in wild-type (WT) mice after transfer of CA-Rac1 gene by subretinal injection of AAV8-pOpsin-CA Rac1-GFP.

RESULTS: Transgenic-CA-RAC1 retinas had significantly fewer photoreceptor cells and more apoptotic ONL cells than WT controls from postnatal week (Pw) 3 to Pw13. Superoxide accumulation and protein and lipid oxidation were increased in Tg-CA-RAC1 retinas and were reduced in mice treated with apocynin. Apocynin reduced the loss of photoreceptors and increased the rod ERG a- and b-wave amplitudes when compared with vehicle-injected transgenic controls. Photoreceptor loss was also observed in regions of adult WT retina transduced with AAV8-pOpsin-CA Rac1-GFP but not in neighboring regions that were not transduced or in AAV8-pOpsin-GFP-transduced retinas.

CONCLUSIONS: Constitutively active RAC1 promotes photoreceptor cell death by oxidative damage that occurs, at least partially, through NOX-induced ROS. Reactive oxygen species are likely involved in multiple forms of retinal degenerations, and our results support investigating RAC1 inhibition as a therapeutic approach that targets this disease pathway.

PMID: 27233035 [PubMed - as supplied by publisher]

Free Radic Res. 2016 May 25:1-31. [Epub ahead of print]

Inhibition of phagocytic activity of ARPE-19 cells by free radical mediated oxidative stress.

Olchawa MM, Pilat AK, Szewczyk GM, Sarna TJ.

Abstract: Oxidative stress is a main factor responsible for key changes leading to the onset of age-related macular degeneration (ARMD) that occur in the retinal pigment epithelium (RPE), which is involved in phagocytosis of photoreceptor outer segments (POS). In this study hydrogen peroxide (H2O2), H2O2 and iron ions (Fe) or rose Bengal (RB) in the presence of NADH and Fe were used to model free radical mediated oxidative stress to test if free radicals and singlet oxygen have different efficiency to inhibit phagocytosis of ARPE-19 cells. Free radical mediated oxidative stress was confirmed by HPLC-EC(Hg) measurements of cholesterol hydroperoxides in treated cells. Electron Paramagnetic Resonance (EPR) spin trapping was employed to detect superoxide anion. Cell survival was analyzed by the MTT assay. Specific phagocytosis of fluorescein-5-isothiocyanate-labeled POS and non-specific phagocytosis of fluorescent beads were measured by flow cytometry. HPLC analysis of cells photosensitized with RB in the presence of NADH and Fe indicated substantial increase in formation of free radical-dependent 7α/7β-hydroperoxides. EPR spin trapping confirmed the photogeneration of superoxide anion in samples enriched with RB, NADH and Fe. For all three protocols sub-lethal oxidative stress induced significant inhibition of the specific phagocytosis of POS. In contrast, non-specific phagocytosis was inhibited only by H2O2 or H2O2 and Fe treatment. Inhibition of phagocytosis was transient and recoverable by 24 hours. These results suggest that free radicals may exert similar to singlet oxygen efficiency in inhibiting phagocytosis of RPE cells, and that the effect depends on the location where initial reactive species are formed.

PMID: 27225587 [PubMed - as supplied by publisher]

Zhonghua Yan Ke Za Zhi. 2016 May 11;52(5):386-90.

[The immunomodulatory role of retinal microglial cells in age-related macular degeneration]. [Article in Chinese]

Zhang PF, Sun XD.

Abstract: Age-related macular degeneration (AMD) is one of the major causes of visual impairment in the elder population. Recent studies have revealed that retinal microgliacytes may play an important role in the pathogenesis of AMD, and the activation of retinal microglia could regulate the progress of AMD. The immunomodulatory role of retinal microglial cells is reviewed in this article, so as to investigate the mechanism and provide new insight for prevention and treatment of AMD.(Chin J Ophthalmol, 2016, 52: 386-390).

PMID: 27220713 [PubMed - in process]

Genetics

Mol Vis. 2016 May 16;22:472-90. eCollection 2016.

Gene expression changes in the retina following subretinal injection of human neural progenitor cells into a rodent model for retinal degeneration.

Jones MK, Lu B, Saghizadeh M, Wang S.

PURPOSE: Retinal degenerative diseases (RDDs) affect millions of people and are the leading cause of vision loss. Although treatment options for RDDs are limited, stem and progenitor cell-based therapies have great potential to halt or slow the progression of vision loss. Our previous studies have shown that a single subretinal injection of human forebrain derived neural progenitor cells (hNPCs) into the Royal College of Surgeons (RCS) retinal degenerate rat offers long-term preservation of photoreceptors and visual function. Furthermore, neural progenitor cells are currently in clinical trials for treating age-related macular degeneration; however, the molecular mechanisms of stem cell-based therapies are largely unknown. This is the first study to analyze gene expression changes in the retina of RCS rats following subretinal injection of hNPCs using high-throughput sequencing.

METHODS: RNA-seq data of retinas from RCS rats injected with hNPCs (RCS(hNPCs)) were compared to

sham surgery in RCS (RCS(sham)) and wild-type Long Evans (LE(sham)) rats. Differential gene expression patterns were determined with in silico analysis and confirmed with qRT-PCR. Function, biologic, cellular component, and pathway analyses were performed on differentially expressed genes and investigated with immunofluorescent staining experiments.

RESULTS: Analysis of the gene expression data sets identified 1,215 genes that were differentially expressed between RCS(sham) and LE(sham) samples. Additionally, 283 genes were differentially expressed between the RCS(hNPCs) and RCS(sham) samples. Comparison of these two gene sets identified 68 genes with inverse expression (termed rescue genes), including Pdc, Rp1, and Cdc42ep5. Functional, biologic, and cellular component analyses indicate that the immune response is enhanced in RCS(sham). Pathway analysis of the differential expression gene sets identified three affected pathways in RCS(hNPCs), which all play roles in phagocytosis signaling. Immunofluorescent staining detected the increased presence of macrophages and microglia in RCS(sham) retinas, which decreased in RCS(hNPCs) retinas similar to the patterns detected in LE(sham).

CONCLUSIONS: The results from this study provide evidence of the gene expression changes that occur following treatment with hNPCs in the degenerating retina. This information can be used in future studies to potentially enhance or predict responses to hNPC and other stem cell therapies for retinal degenerative diseases.

PMID: 27217715 [PubMed - in process] PMCID: PMC4872275 Free PMC Article

Vestn Oftalmol. 2016;132(2):8-13.

[Cytokine gene polymorphisms in patients with age-related macular degeneration]. [Article in Russian]

Shevchenko AV, Prokof'ev VF, Konenkov VI, Chernykh VV, Eremina AV, Dudnikova LV, Kashkina NY, Trunov AN.

AIM: To establish possible association between age-related macular degeneration (AMD) and cytokine genotype polymorphisms; for that promoter regions of a number of cytokine genes were studied, namely, TNF-A863C, TNF-A308G, TNF-A238G, IL1β-C-31T, IL4-C590T, IL6-C174G, and IL10A-1082G.

MATERIAL AND METHODS: A total of 102 AMD and 100 non-AMD participants in the same age range were examined at the Novosibirsk branch of the Academician S.N. Fyodorov IRTC «Eye Microsurgery». In all cases restriction fragment length polymorphism analysis was performed.

RESULTS: The frequency of TNF-308 GA and IL10-1082 GG genotypes was higher in AMD patients than in the controls, while the TNF-308 AA minor genotype has proved protective against the disease. Moreover, AMD has been found to be positively related to 48 genotypic combinations and negatively - to 32 (with specificity as high as 98-99%). The odds ratio was also higher in combination analysis as compared to monogenotypes.

CONCLUSION: Complex genetic analysis of cytokines gives an idea of the balance of proinflammatory and anti-inflammatory cytokines in AMD and, therefore, plays an important role in studying the disease pathogenesis and exploring therapeutic options.

PMID: 27213791 [PubMed - as supplied by publisher]

Diet, lifestyle & low vision

Dtsch Arztebl Int. 2016 May 6;113(18):323-7.

The Prevalence of Visual Impairment in Retirement Home Residents.

Thederan L, Steinmetz S, Kampmann S, Koob-Matthes AM, Grehn F, Klink T.

BACKGROUND: Elderly persons often have eye diseases causing either reversible or irreversible visual loss. The prevalence of such problems among retirement home residents is unknown.

METHODS: 203 residents of retirement homes in and around Würzburg, Germany, were examined. Clinical histories were taken, including information on prior ophthalmological care, and ophthalmological examinations were performed, including visual acuity, slit-lamp examination of the anterior segment of the eye, fundoscopy (with optical coherence tomography), and measurement of the intraocular pressure.

RESULTS: 119 women and 84 men aged 55 to 101 were examined in 6 retirement homes. 44 (21.7%) had ophthalmological findings that required acute treatment. The most common diagnoses in the anterior segment of the eye were keratoconjunctivitis sicca (160; 78.8%), cataract (88; 43.3%), secondary cataract (15; 7.4%), glaucoma (33; 12.3%), and eyelid malpositions (25; 12.3%). In the fundus, 45 residents (22.2%) had dry age-related macular degeneration (AMD), 7 (3.4%) had fresh wet AMD, and 7 (3.4%) had epiretinal gliosis. 81 (39.9%) could give no information about earlier ophthalmologic examinations, and 42 (20.7%) had not been to an ophthalmologist for at least 5 years. After correction of refractive errors, their mean decimal visual acuity improved from 0.25 to 0.33.

CONCLUSION: The retirement home residents that we examined were not receiving adequate ophthalmological care; in particular, some of them had irreversible eye diseases that were not being treated. The ophthalmological care of retirement home residents needs to be improved through better collaboration of all types of personnel taking care of them.

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Fixation Improvement through Biofeedback Rehabilitation in Stargardt Disease.

Scuderi G, Verboschi F, Domanico D, Spadea L.

Abstract: Stargardt disease is the most common hereditary macular degeneration in juveniles. It is characterized by macular dystrophy associated with loss of central vision in the first or second decade of life, a "beaten-metal" appearance in the fovea or parafoveal region, yellowish flecks around the macula or in posterior area of the retina, progressive atrophy of the bilateral foveal retinal pigment epithelium, and the "dark choroid" sign on fundus fluorescein angiography in most cases. We report a case of Stargardt disease in a 26-year-old Caucasian female submitted to rehabilitative training with microperimetry MP-1 to find a new preferred retinal locus (PRL) and to train her to better her quality of life. Best corrected visual acuity, mean retinal sensitivity, fixation, bivariate contour ellipse area, and speed reading were evaluated before and after the training and results were discussed.

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