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MD Research News

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Drug Treatment

J Ocul Pharmacol Ther. 2012 Jul 9. [Epub ahead of print]

Evaluation of Very High- and Very Low-Dose Intravitreal Aflibercept in Patients with Neovascular Age-Related Macular Degeneration.

Nguyen QD, Campochiaro PA, Shah SM, Browning DJ, Hudson HL, Sonkin PL, Hariprasad SM, Kaiser PK, Slakter J, Haller JA, Do DV, Mieler W, Chu K, Ingerman A, Vitti R, Berliner AJ, Cedarbaum And The Clear-It 1 Investigators J.

1 The Wilmer Eye Institute, The Johns Hopkins University School of Medicine , Baltimore, Maryland.

Abstract Purpose: To determine bioactivity and duration of effect of intravitreal aflibercept injection (also known as vascular endothelial growth factor Trap-Eye) for neovascular age-related macular degeneration (AMD).

Methods: In this double-masked, phase 1 study, 28 patients with lesions ≤12 disc areas, ≥50% active choroidal neovascularization (CNV), and best corrected visual acuity (BCVA)≤20/40 were randomized 1:1 to a single intravitreal injection of aflibercept 0.15 or 4 mg. The primary end point was the change from baseline in central retinal/lesion thickness (CR/LT) at week-8. Secondary outcomes were the change from baseline BCVA, the change in CNV lesion size and area of leakage, and proportion of patients requiring repeat injection at 8 weeks.

Results: Mean percent decrease in CR/LT for the 4-mg and 0.15-mg groups was, respectively, 34.2 versus 13.3 at week 4 (P=0.0065), 23.8 versus 5.9 at week 6 (P=0.0380), and 25.2% versus 11.3% at week 8 (P=0.150). The 4-mg group gained a mean of 4.5 letters in BCVA (6/14 patients gaining ≥10 letters) versus 1.1 letters in 0.15-mg group (1/14 gaining ≥10 letters) at week 8. Fewer patients needed retreatment in the 4-mg group at week 8. No serious adverse event or ocular inflammation was reported in either group.

Conclusions: Intravitreal aflibercept 4 mg had a safety profile similar to that of the very low dose 0.15 mg, and was well-tolerated. The 4-mg dose significantly reduced foveal thickening at weeks 4 and 6, significantly improved BCVA at weeks 6, and reduced the need for repeat injection after 8 weeks compared with intravitreal aflibercept 0.15 mg in neovascular AMD patients.

PMID: 22775078 [PubMed - as supplied by publisher]

Retina. 2012 Jul 5. [Epub ahead of print]

CORRELATION OF INDOCYANINE GREEN ANGIOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY FINDINGS AFTER INTRAVITREAL RANIBIZUMAB FOR POLYPOIDAL CHOROIDAL VASCULOPATHY.

Ueno C, Gomi F, Sawa M, Nishida K.

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PURPOSE: To evaluate findings in eyes with polypoidal choroidal vasculopathy on indocyanine green angiography (ICGA) and optical coherence tomography (OCT) over 3 months after ranibizumab treatment.

METHOD: Fifty-one eyes from 51 patients with treatment-naive polypoidal choroidal vasculopathy received intravitreal ranibizumab injections. We evaluated changes in polypoidal lesions on ICGA and OCT and their correlation over 3 months. Ranibizumab was injected again based on the presence of residual fluid on OCT.

RESULTS: Indocyanine green angiography detected 75 polypoidal lesions. All corresponding OCT lesions showed baseline protrusion of the retinal pigment epithelium. At 3 months, 26 lesions (35%) resolved on ICGA: retinal pigment epithelium protrusion on OCT resolved in 10 lesions (38%), 10 lesions (38%) decreased in height, and 6 lesions (24%) remained unchanged. Forty-nine lesions persisted on ICGA, retinal pigment epithelium protrusion resolved in 2 lesions (4%), decreased in 4 lesions (8%), were stable in 36 lesions (73%), and increased in 7 lesions (15%). Three lesions newly developed. Six eyes (12%) had resolved lesions, and 33 eyes (67%) had persistent lesions on ICGA and OCT. Residual exudative changes were associated with persistent lesions on OCT.

CONCLUSION: Indocyanine green angiography and OCT baseline findings of polypoidal lesions in polypoidal choroidal vasculopathy were well correlated; however, a discrepancy was seen during treatment. Polypoidal lesions persisted more often on OCT, although ICGA and OCT showed the efficacy of ranibizumab for some polypoidal lesions.

PMID: 22772392 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2012;6:865-869. Epub 2012 Jun 7.

Treatment of peripheral exudative hemorrhagic chorioretinopathy by intravitreal injections of ranibizumab.

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Abstract

Peripheral exudative hemorrhagic chorioretinopathy (PEHCR) is a rare disorder that sometimes causes sudden subretinal and/or vitreous hemorrhage. Choroidal neovascularization is involved in the pathogenesis, but the etiology is unknown. Treatments with photocoagulation, cryopexy, and intravitreal bevacizumab injection have been reported. However, the therapeutic effect of intravitreal injection with ranibizumab for PEHCR is unclear. A 70-year-old woman visited our department because of sudden loss of superior visual field in her left eye. She had a history of surgical removal of hematoma due to subretinal hemorrhage associated with age-related macular degeneration 5 years ago. Peripheral subretinal hemorrhage was observed in the left eye, and fluorescein and indocyanine green angiography revealed choroidal neovascularization in the subretinal hemorrhagic region. PEHCR was diagnosed. Considering her past history, intravitreal ranibizumab injection was used for treatment. After three injections in the left eye, subretinal hemorrhage and choroidal neovascularization resolved completely. No recurrence was observed during 1 year of follow-up. This case demonstrates that intravitreal injection of ranibizumab is an effective treatment for PEHCR with subretinal hemorrhage.

PMID: 22791965 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2012 Jul 10. [Epub ahead of print]

[Intravitreal ranibizumab injection for the treatment of idiopathic choroidal neovascularisation in young patients.] [Article in French]

Ouhadj O, Degheb N, Idir S, Nebab A, Nouri MT.

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PURPOSE: To evaluate the safety and efficacy of intravitreal injection of ranibizumab 0.5mg in the treatment of idiopathic choroidal neovascularisation in young patients, which is the second most common cause of macular CNV in patients under 50 years of age.

PATIENTS AND METHODS: This single-center, prospective, interventional, uncontrolled, nonrandomized clinical case series study included 13 eyes of 13 consecutive young patients with idiopathic macular choroidal neovascularisation treated with monthly intravitreal injections of 0.5mg ranibizumab. Prior to treatment, measurement of best-corrected visual acuity (BCVA), fundus examination, fluorescein angiography (FA) and macular optical coherence tomography (OCT) were performed. Measurement of visual acuity, fundus exam and OCT were repeated each month. A repeated monthly injection was performed in the event of persistence or recurrence of neovascular activity.

RESULTS: Ten women and three men, mean age 34±7.88 years at time of diagnosis, were included in the study. Mean best-corrected visual acuity improved dramatically throughout the study, going from 0.74 LogMar at enrolment to 0.45 LogMar at 13 months (P<10(-6)). On average, two intravitreal injections of ranibizumab (0.5mg) were required during this year. Mean follow-up was 13±7.6 months.

DISCUSSION: Management of idiopathic CNV in young patients is difficult, due to frequent recurrences despite treatment. Argon laser photocoagulation, photodynamic therapy, and subretinal surgery offer limited results in terms of visual recovery and recurrence.

CONCLUSION: Intravitreal ranibizumab injection appears to be safe and effective for treatment of idiopathic macular CNV in young patients. A longer-term prospective trial is required to corroborate these results.

PMID: 22789650 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2012 May;27(3-4):61-4.

Intravitreal Ranibizumab for Treatment of Choroidal Neovascularization Secondary to Angioid Streaks in Pseudoxanthoma Elasticum: Five-year Follow-up.

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Purpose: To report on the five-year follow-up of ranibizumab therapy for choroidal neovascularization (CNV) secondary to angioid streaks (AS) in pseudoxanthoma elasticum (PXE).

Methods: A 51-year-old patient with PXE presenting with macular CNV secondary to AS was treated with a series of intravitreal ranibizumab (0.5 mg) injections and followed for five years with fundoscopy, optical coherence tomography (OCT), and fluorescein angiography (FA).

Results: Fluorescein leakage resolved and OCT evidence of subretinal and intraretinal fluid disappeared one year after presentation following an initial 12 injections. There was mild recurrent neovascular activity on two occasions resulting in two injections in the four years subsequent to resolution. Though peripapillary scar formation occurred, the fovea was preserved with 20/20 visual acuity in the affected eye at five years.

Conclusions: This case provides further evidence for the long-term effectiveness of ranibizumab in the treatment of CNV secondary to AS in PXE. Though multiple initial injections were required to control the disease, once stabilization of the CNV was achieved, recurrent neovascular activity was minimal.

PMID: 22784267 [PubMed - in process]

Expert Opin Pharmacother. 2012 Jul 12. [Epub ahead of print]

Intraocular corticosteroids for posterior segment disease: 2012 update.

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Introduction: Diabetic macular edema (DME), cystoid macular edema (CME), age-related macular degeneration (AMD), retinal vascular occlusion (RVO) and uveitis are responsible for severe visual impairment worldwide. In

some patients with these conditions, treatment with intraocular corticosteroids may be beneficial. Although off-label use of these agents has occurred for many years, novel agents including preservative-free and sustained-release intravitreal implants are currently being studied in clinical trials (CTs).

Areas covered: This paper reviews the use of CTs for vitreoretinal (VR) diseases including choroidal neovascularization, CME, DME, RVO and posterior uveitis. It also discusses the use of corticosteroids for treating VR disease, including dexamethasone, fluocinolone acetonide, intravitreal implants and triamcinolone acetonide.

Expert opinion: Used alone, intravitreal corticosteroids may benefit disorders such as DME, RVO and uveitis compared with standard therapy. Cases of exudative AMD non-responsive to standard treatment may benefit from combination therapy, including usage of intravitreal corticosteroid injections. Intraoperative use of these agents may aid visualization of retinal structures. Sustained-release intraocular implants have been approved for posterior uveitis and RVO associated with macular edema. In spite of this, most intraocular corticosteroids have a limited duration of action along with significant side effects, including cataract and glaucoma. Currently, intravitreal corticosteroid usage for DME is considered off-label.

PMID: 22783878 [PubMed - as supplied by publisher]

Klin Oczna. 2012;114(1):79-83.

[Comparison of the biological principles underlying the action of monoclonal antibody (mAb) and decoy receptor anti-VEGF agents--on the example of ranibizumab (anti-VEGF-A mAb) and aflibercept (decoy VEGFR1-2 receptor)]. [Article in Polish]

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Abstract

Current state-of-the-art anti-angiogenic therapies target the VEGF pathway, which is the main essential signaling pathway for angiogenesis, including pathological angiogenesis in cancer and eye disease. Ranibizumab (Lucentis) and VEGF-Trap (aflibercept) represent two different approaches to inhibiting angiogenesis by targeting VEGF family signaling. The former is a relatively short monoclonal antibody fragment, which binds VEGF-A on the basis of antigen recognition by the variable region of an antibody, while aflibercept is not an monoclonal antibody, but a decoy receptor, binding VEGF-A on the basis of the molecular interaction between the ligand (VEGF) and its cognate cellular receptor (VEGFR-1 and VEGFR-2). VEGF-Trap has therefore a broader specificity, recognizing and binding VEGF-B and PIGF in addition to VEGF-A, following the specificity of VEGFR-1 and VEGFR-2. This broader specificity is considered as beneficial in cancer treatment and could be also beneficial in treatment of nAMD, this claim should, however, be backed by clinical studies. The presence of an Fc fragment in VEGF-Trap is also an important difference; even though this fragment does not participate in the recognition of the target molecule, it can influence the biological properties of the fusion protein. The relative merits of both approaches will become clear only after long-term laboratory and clinical testing, as their biological activity is also likely to differ. Given the clear differences in the mechanism of target molecule recognition, biochemical and biophysical properties (including molecular weight) and specificity, they cannot be considered as equivalent, unless extensive long-term clinical studies prove otherwise.

PMID: 22783753 [PubMed - in process]

Klin Oczna. 2012;114(1):63-7.

[The impact of locally administrated VEGF inhibitors on vascular homeostasis--controversies concerning safety of intravitreal therapy in AMD patients]. [Article in Polish]

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Abstract

Intravitreal vascular endothelial growth factor (VEGF) inhibitors constitutes currently the first-line treatment in neovascular age-related macular degeneration (AMD). By intravitreal application of the drug, the dosage can be kept low while maximizing its effect on choroidal neovascularization and minimizing potential adverse systemic effects. However, the eye-blood barrier is often disrupted in ophthalmic neovascular disorders and the drugs can be detected in circulating blood despite being administered as an intraocular injection. As patients with AMD constitute a high-risk population for cardiovascular events, the safety of anti-VEGF therapies must be precisely and thoroughly assessed. In the present work, the recent reports documenting systemic safety of intravitreal VEGF inhibitors have been reviewed. Moreover, the novel methods to assess the potential systemic effect on vascular homeostasis as the consequence of such therapy have been also discussed.

PMID: 22783749 [PubMed - in process]

Arch Ophthalmol. 2012 Jul 1;130(7):934-5.

Intravitreal bevacizumab in advanced-stage neovascular age-related macular degeneration with visual acuity lower than 20/200.

Parodi MB, Cascavilla M, Papayannis A, Kontadakis DS, Bandello F, Iacono P.

PMID: 22776937 [PubMed - in process]

Other treatment & diagnosis

Int J Ophthalmol. 2012;5(3):377-83. Epub 2012 Jun 18.

Low-fluence photodynamic therapy combinations in the treatment of exudative age-related macular degeneration.

Ozturk T, Oner H, Saatci AO, Kaynak S.

Department of Ophthalmology, Dr. Behçet Uz Children's Hospital, Izmir, Turkey.

AIM: To compare the efficacy of low-fluence photodynamic therapy (PDT) combinations in the treatment of age-related macular degeneration (AMD).

METHODS: Forty-five previously untreated eyes of 45 patients with exudative AMD whose best-corrected visual acuity (BCVA) was ≥0.3 (Snellen) were enrolled. 15 patients in Group I underwent low-fluence PDT (25J/cm(2)-300mW/cm(2)-83sec) and intravitreal pegaptanib combination, 15 patients in Group II underwent PDT (50J/cm(2)-600mW/cm(2)-83sec) and intravitreal pegaptanib combination while, 15 patients in Group III underwent intravitreal pegaptanib monotherapy. Complete ophthalmologic examinations were performed in pre and post treatment visits, and the results were statistically analised. A clinical activity score (CAS) was calculated by using changes in lesion size, amount of hemorrhage, staining pattern in FA and OCT measurement of intra/subretinal fluid. ≤ 3 logMAR lines of decrease in BCVA and decrease in CAS were considered as successful treatment.

RESULTS: The mean age of 19 female (42.2%) and 26 male (57.8%) patients was 72.82±8.02 years. Mean follow-up was 13.93±5.87 months. Lesion type was occult in 28 eyes (62.2%). Treatment success rates according to BCVA assessments were 86.7%, 80%, 60% and mean BCVA decrease were 0.3, 1.0, 2.2 logMAR lines in Group I, II and III, respectively (P>0.05). According to the changes in central macular thickness and CAS, no difference was found among the study groups (P=0.850 and P=0.811, respectively). Patients treated with combination regimens had lower intravitreal injection frequencies (P=0.015).

CONCLUSION: Combination regimen with intravitreal pegaptanib and low-fluence PDT seems to be safe and effective in stabilizing the clinical activity and BCVA in exudative AMD.

PMID: 22773992 [PubMed - in process] PMCID: PMC3388412

Ophthalmic Surg Lasers Imaging. 2012 Jul 1;43(4):328-34. doi: 10.3928/15428877-20120618-01.

Glaucoma Filtration Surgery Following Sustained Elevation of Intraocular Pressure Secondary to Intravitreal Anti-VEGF Injections.

Skalicky SE, Ho I, Agar A, Bank A.

Abstract

BACKGROUND AND OBJECTIVE: To document cases of sustained elevation of intraocular pressure (IOP) while receiving intravitreal anti-vascular endothelial growth factor (VEGF) agents and subsequent management.

PATIENTS AND METHODS: A retrospective series of all cases managed by the authors and colleagues was performed.

RESULTS: Six patients developed sustained elevated IOP; five received ranibizumab and one bevacizumab. Four received unilateral and two received bilateral injections. Two had preexisting primary open-angle glaucoma and one had pseudoexfoliative glaucoma, all with stable IOP prior to anti-VEGF treatment. Angles were open in all cases. Peak IOP averaged 43 mm Hg (range: 34 to 60 mm Hg). The mean number of injections preceding the IOP increase was 10 (range: 1 to 20). Four patients required trabeculectomy, one selective laser trabeculoplasty, and one multiple topical medications.

CONCLUSION: A sustained increase in IOP requiring glaucoma filtering surgery is a rare but important treatment complication for patients receiving intravitreal anti-VEGF therapy, especially those with preexisting glaucoma or glaucoma risk factors.

PMID: 22788585 [PubMed - in process]

Prog Retin Eye Res. 2012 Jul 4. [Epub ahead of print]

Cell replacement and visual restoration by retinal sheet transplants.

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Abstract

Retinal diseases such as age-related macular degeneration (ARMD) and retinitis pigmentosa (RP) affect millions of people. Replacing lost cells with new cells that connect with the still functional part of the host retina might repair a degenerating retina and restore eyesight to an unknown extent. A unique model, subretinal transplantation of freshly dissected sheets of fetal-derived retinal progenitor cells, combined with its retinal pigment epithelium (RPE), has demonstrated successful results in both animals and humans. Most other approaches are restricted to rescue endogenous retinal cells of the recipient in earlier disease stages by a 'nursing' role of the implanted cells and are not aimed at neural retinal cell replacement. Sheet transplants restore lost visual responses in several retinal degeneration models in the superior colliculus (SC) corresponding to the location of the transplant in the retina. They do not simply preserve visual performance - they increase visual responsiveness to light.Restoration of visual responses in the SC can be directly traced to neural cells in the transplant, demonstrating that synaptic connections between transplant and host contribute to the visual improvement. Transplant processes invade the inner plexiform layer of the host retina and form synapses with presumable host cells. In a Phase II trial of RP and ARMD patients, transplants of retina together with its RPE improved visual acuity. In summary, retinal progenitor sheet transplantation provides an excellent model to answer questions about how to repair and restore function of a degenerating retina. Supply of fetal donor tissue will always be limited but the model can set a standard and provide an informative base for optimal cell replacement therapies such as embryonic stem cell (ESC)-derived therapy.

PMID: 22771454 [PubMed - as supplied by publisher]

Optom Vis Sci. 2012 Jul 5. [Epub ahead of print]

Aging and Cone Dark Adaptation.

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PURPOSE: Following exposure to a bright light that bleaches a significant portion of photopigment, the eyes take several minutes to regain sensitivity. This slow process, known as dark adaptation, is impaired in patients with age-related macular degeneration and is an important candidate biomarker for this disease. The aim of this study was to evaluate the effect of age on cone dark adaptation.

METHODS: Data were obtained from 41 healthy adults aged between 20 and 83 years. Pupils were dilated and 96% of cone photopigment was "bleached," before threshold was monitored continuously for 5 min in the dark, using a 4° diameter achromatic spot centered on the fovea. Threshold recovery data were modeled, and the time constant of cone recovery (τ), initial cone thresholds, and final cone thresholds were determined. Regression analysis was used to determine the relationship between age and cone dark adaptation parameters.

RESULTS: Cone τ increased by 16.4 s/decade of life, indicating a progressive slowing of dark adaptation with increasing age. This change in cone τ throughout adulthood was significant ($p < 0.0005$). There was no significant relationship between increasing age and initial cone threshold ($p = 0.84$) or final cone threshold ($p = 0.82$).

CONCLUSIONS: Our results provide evidence for age-related slowing of cone dark adaptation after a full bleach in healthy adults, which is likely to contribute to visual difficulties when moving from bright to dim photopic light levels. We propose that the sensitivity and specificity of cone τ as a biomarker for early age-related macular disease could be improved by taking into account the significant age-related decline in this parameter.

PMID: 22773176 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2012 Jul 6. [Epub ahead of print]

Clinical features of reticular pseudodrusen according to the fundus distribution.

Lee MY, Yoon J, Ham DI.

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BACKGROUND: To evaluate the morphological features and prevalence of accompanying late age-related macular degeneration (AMD) according to the fundus distribution of reticular pseudodrusen (RPD).

METHODS: According to the involved area in the fundus, the distribution of RPD was classified as localised, intermediate, or diffuse type. Morphology of RPD was classified as discrete, branching, or confluent pattern. The presence of late AMD was evaluated.

RESULTS: 233 eyes of 121 patients with RPD were included. The distribution of RPD was localised, intermediate and diffuse type in 30.9%, 40.3% and 28.8% of eyes, respectively. The discrete, branching and confluent morphological patterns were found in 45.8%, 44.8% and 9.7% of the localised type, and in 0%, 13.8% and 86.2% of the intermediate type, respectively. In contrast, the diffuse type showed only the confluent morphological pattern. The prevalence of accompanying late AMD was 13.9%, 13.8% and 56.7% in the localised, intermediate and diffuse type, respectively, and it was significantly higher in the diffuse type ($p<0.05$).

CONCLUSION: RPD with diffuse distribution showed a confluent morphological pattern and a high prevalence of late AMD. RPD can be classified by the fundus distribution for the assessment of visual prognosis.

PMID: 22773089 [PubMed - as supplied by publisher]

Ophthalmic Epidemiol. 2012 Aug;19(4):190-5.

Computer Use among Patients with Age-Related Macular Degeneration.

Brody BL, Field LC, Roch-Levecq AC, Depp C, Edland SD, Minasyan L, Brown SI.

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Purpose: Age-related macular degeneration (AMD) is the leading cause of incurable vision loss in older adults in industrialized countries and is on a trajectory to disable a growing number of persons as societies age. To assess

the potential of using telemedicine for expansion of an in-person AMD self-management program, we examined the extent of computer use in a sample of older adults with AMD.

Methods: 160 older adult volunteers (mean age = 76 years; female = 51%) with AMD (mean visual acuity in better eye: 20/40; worse eye: 20/90) were randomly selected from members of the San Diego County AMD Registry. Computer use was assessed with a Health and Impact Questionnaire. Dependent measures were Snellen visual acuity, National Eye Institute-Visual Function Questionnaire, the AMD Self-Efficacy Questionnaire, and the Geriatric Depression Scale.

Results: Overall 70.6% reported computer use at least once per month. By age and gender stratum, 76.5% of men aged 60-74 years, 73.3% of men aged 75 years and over, 74.3% of women aged 60-74 years, and 60.9% of women aged 75 years and over used computers. In logistic regression analyses controlling for age and gender, computer use was associated with better visual acuity (P = 0.029), higher education (P = 0.002), and self-efficacy for communication (P = 0.027).

Conclusion: The majority of older adults with AMD in our sample used computers, with use highest among more educated and visually intact patients. Computer use to access the Internet is feasible in AMD patients and should be encouraged. The inclusion of computer use in measures of AMD-related functioning appears warranted.

PMID: 22775273 [PubMed - in process]

Rev Invest Clin. 2012 Jan-Feb;64(1):89-101.

[Vision abnormalities associated to smoking. A systematic review related to a clinical case]. [Article in Spanish]

Sansores RH, Ramírez-Venegas A, Pérez-Bautista O, Bustos M.

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PMID: 22690534 [PubMed - indexed for MEDLINE]

Pathogenesis

Free Radic Biol Med. 2012 Jul 7. [Epub ahead of print]

Deficiency of αB crystallin augments ER stress-induced apoptosis by enhancing mitochondrial dysfunction.

Dou G, Sreekumar PG, Spee C, He S, Ryan SJ, Kannan R, Hinton DR.

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Abstract

Endoplasmic reticulum (ER) stress is linked to several pathological conditions including age-related macular degeneration. Excessive ER stress initiates cell death cascades which are mediated, in part, through mitochondrial dysfunction. Here, we identify αB crystallin as an important regulator of ER stress-induced cell death. Retinal pigment epithelial (RPE) cells from αB crystallin (-/-) mice, and human RPE cells transfected with αB crystallin siRNA, are more vulnerable to ER stress induced by tunicamycin. ER stress-mediated cell death is associated with increased levels of reactive oxygen species, depletion of glutathione in mitochondria, decreased superoxide dismutase activity, increased release of cytochrome c and activation of caspases 3 and 4. The ER stress signaling inhibitors, salubrinal and 4-(2-aminoethyl) benzenesulfonyl fluoride, decrease mitochondrial damage and reduce RPE apoptosis induced by ER stress. Prolonged ER stress decreases levels of αB crystallin, thus exacerbating mitochondrial dysfunction. Overexpression of αB crystallin protects RPE cells from ER stress-induced apoptosis by attenuating increases in Bax, CHOP, mitochondrial permeability transition, and cleaved caspase 3. Thus, these data collectively demonstrate that αB crystallin provides critical protection of mitochondrial function during ER stress-induced RPE apoptosis.

PMID: 22781655 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2012;5(3):307-11. Epub 2012 Jun 18.

Transforming growth factor-β neutralizing antibodies inhibit subretinal fibrosis in a mouse model.

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Department of Ophthalmology, the First Hospital of China Medical University, Shenyang 110001, Liaoning Province, China.

AIM: To determine the involvement of the transforming growth factor (TGF)-β with the development of experimental subretinal fibrosis in a mouse model.

METHODS: Subretinal fibrosis was induced by subretinal injection of macrophage-rich peritoneal exudate cells (PECs) and the local expression of TGF-β isoforms was assessed by quantitative real-time reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) at various time points. In addition, we investigated the effect of TFG-β-neutralizing antibodies (TGF-β NAb) on subretinal fibrosis development.

RESULTS: TGF-β1 and TGF-β2 mRNA level was significantly elevated at day 2 after subretinal fibrosis induction and increased further to 5 and 6.5-fold respectively at day 5, reaching the peak. TGF-β3 mRNA was not detected in the present study. The result of ELSIA showed that active TGF-β1 and TGF-β2 levels were upregulated to 10-fold approximately, while total TGF-β1 and TGF-β2 levels were even upregulated more than 10-fold and more than 20-fold respectively in subretinal fibrosis mice in comparison with naïve mice at day 5. TGF-β NAb resulted in a reduced subretinal fibrosis areas by 65% compared to animals from control group at day 7.

CONCLUSION: Our results indicate that TGF-β signaling may contribute to the pathogenesis of subretinal fibrogenesis and TGF-β inhibition may provide an effective, novel treatment of advanced and late-stage neovascular age-related macular degeneration.

PMID: 22773978 [PubMed - in process] PMCID: PMC3388398

Mol Vis. 2012;18:1658-67. Epub 2012 Jun 20.

Sequential in-office vitreous aspirates demonstrate vitreous matrix metalloproteinase 9 levels correlate with the amount of subretinal fluid in eyes with wet age-related macular degeneration.

Ecker SM, Pfahler SM, Hines JC, Lovelace AS, Glaser BM.

PURPOSE: To evaluate levels of 37 native pathway proteins of the vitreous proteome from a subset of wet age-related macular degeneration (AMD) patients with and without subretinal fluid (SRF).

METHODS: A total of 62 consecutive samples were aspirated from 12 patients with AMD, six who had SRF at baseline, and six who did not have SRF at any point during the study. Vitreous levels of the 37 native pathway proteins were analyzed in these patients using reverse phase protein microarray technology. At each visit, at which the 62 samples were taken, SRF and central retinal thickness were measured. These values were then compared to the relative intensity level of the 37 proteins screened.

RESULTS: In the subset of AMD patients with SRF, the average matrix metalloproteinase 9 (MMP-9), interleukin (IL)-12, Abelson murine leukemia viral oncogene homolog 1 (cABL) Thr735, heme oxygenase-1, Musashi, platelet-derived growth factor receptor beta Tyr751 (PDGFRβ), IL-8, and BCL-2 associated death promoter (BAD) Ser112 levels in the vitreous were found to be significantly different with a 21%-82% increase in expression compared to those without SRF ($p<0.0001$). Within the SRF group, there was a positive correlation between the vitreous MMP-9 levels and the SRF level. MMP-9 levels in the vitreous proteome varied with the level of SRF but not retinal edema. Compared to patients without SRF, the patients with initial SRF had persistent or progressive disease.

CONCLUSIONS: This is the first prospective case series sequentially monitoring the vitreous proteome in patients with wet AMD. The results suggest that MMP-9 is a proteomic biomarker of SRF accumulation, separate from macular edema.

PMID: 22773904 [PubMed - in process] PMCID: PMC3388986

Mol Vis. 2012;18:1640-8. Epub 2012 Jun 20.

Effects of melatonin and its receptor antagonist on retinal pigment epithelial cells against hydrogen peroxide damage.

Rosen RB, Hu DN, Chen M, McCormick SA, Walsh J, Roberts JE.

PURPOSE: Recently, we reported finding that circulating melatonin levels in age-related macular degeneration patients were significantly lower than those in age-matched controls. The purpose of this study was to investigate the hypothesis that melatonin deficiency may play a role in the oxidative damage of the retinal pigment epithelium (RPE) by testing the protective effect of melatonin and its receptor antagonist on RPE cells exposed to H(2)O(2) damage.

METHODS: Cultured human RPE cells were subjected to oxidative stress induced by 0.5 mM H(2)O(2). Cell viability was measured using the microculture tetrazoline test (MTT) assay. Cells were pretreated with or without melatonin for 24 h. Luzindole (50 μM), a melatonin membrane-receptor antagonist, was added to the culture 1 h before melatonin to distinguish direct antioxidant effects from indirect receptor-dependent effects. All tests were performed in triplicate.

RESULTS: H(2)O(2) at 0.5 mM decreased cell viability to 20% of control levels. Melatonin showed dose-dependent protective effects on RPE cells against H(2)O(2). Cell viability of RPE cells pretreated with 10(-10), 10(-8), 10(-6), and 10(-4) M melatonin for 24 h was 130%, 160%, 187%, and 230% of cells treated with H(2)O(2) alone (all $p<0.05$). Using cells cultured without H(2)O(2) as the control, cell viability of cells treated with H(2)O(2) after pretreatment with 10(-10)-10(-4) M melatonin was still significantly lower than that of the controls, suggesting that melatonin significantly decreased but did not completely abolish the in vitro cytotoxic effects of H(2)O(2). Luzindole completely blocked melatonin's protective effects at low concentrations of melatonin (10(-10)-10(-8) M) but not at high concentrations (10(-6)-10(-4) M).

CONCLUSIONS: Melatonin has a partial protective effect on RPE cells against H(2)O(2) damage across a wide range of concentrations (10(-10)-10(-4) M). This protective effect occurs through the activation of melatonin membrane receptors at low concentrations (10(-10)-10(-8) M) and through both the direct antioxidant and indirect receptor activation effects at high concentrations (10(-6)-10(-4) M).

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Microbubble-conjugated vascular endothelial growth factor receptor 2 binding peptide.

Nunn A, Pochon S, Tardy I, Tranquart F, Chopra A.

Molecular Imaging and Contrast Agent Database (MICAD) [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2004-2011.
2012 Feb 14 [updated 2012 Jul 11].

Excerpt

The vascular endothelial growth factor receptor 2 (VEGFR2; also known as the kinase insert domain receptor) is a primary signal transducer for angiogenesis and the development of pathological conditions such as cancer, diabetic retinopathy, and neovascular age-related macular degeneration (1-3). This receptor is expressed mainly by endothelial cells, and in order to meet the increased nutritional demands of neoplastic lesions its expression is upregulated in the tumor vasculature to promote angiogenesis (2, 4, 5). Therefore, the inhibition of VEGFR2 activity and its downstream signaling pathways are important targets for the treatment of diseases involving angiogenesis (for an illustration of angiogenesis, see Deshpande et al. (6)). The United States Food and Drug Administration (FDA) has approved several drugs and monoclonal antibodies that target the VEGFR2 receptor for the treatment of cancerous tumors and other angiogenic diseases (7). In addition, many antiangiogenic agents are under investigation in ongoing clinical trials. For any therapy to be successful, it is important to select patients who are likely to respond to the treatment and to be able to rapidly evaluate the response after initiation of the therapy. In this respect, the evaluation of anti-VEGFR2 therapies has been performed with various molecular imaging modalities, including ultrasound imaging (8). The main advantage of using ultrasound imaging over other modalities to visualize active tumor angiogenesis by targeting VEGFR2 is that ultrasound generates a purely vascular signal that can be viewed in real time because the contrast agents used with this imaging modality are restricted to the vascular compartment due to their size (9). In addition, the equipment used to perform this technique does not require the use of radioactivity, and it is readily available, inexpensive, and easy to operate (9). With the

advancement of ultrasound technology, microbubble (MB)-based contrast agents that target disease-specific receptors or molecules have been developed and used to visualize or monitor angiogenesis and hard-to-detect pathological lesions (6). Previously, biotinylated anti-VEGFR2 antibodies (Abs) coupled to streptavidin-containing MBs through the biotin-strepavidin linkage have been used to assess the expression of VEGFR2 in mouse tumor models, but such contrast agents cannot be used in the clinic because strepavidin and/or the Abs can be immunogenic in humans (10). To circumvent the immunogenicity issues of the Ab-directed biotin-streptavidin–based MB contrast agents, it was necessary to develop contrast agents that would use non-immunogenic molecules to link the VEGFR2-seeking molecules to the MBs. For this, a novel MB contrast agent (BR55) that targets VEGFR2 and has the potential for translation to the clinic was developed (11). A phage display library was used to identify and create a heterodimeric peptide that showed a selective and high affinity for human VEGFR2 (12). The heterodimeric peptide was then used to generate lipopeptides that were inserted into the phospholipid shells of MBs to produce a targeted ultrasound contrast agent (BR55). This agent was then evaluated for the visualization of xenograft or orthotopic tumors that expressed VEGFR2 (11) and to quantify the receptor in tumors of nude mice undergoing antiangiogenic therapy (10).

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Chemokine Receptor Expression in Peripheral Blood Monocytes from Patients with Neovascular Age-Related Macular Degeneration.

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Purpose: Chemokine signaling and monocytes/macrophages were implicated in the pathogenesis of age-related macular degeneration (AMD). We tested the association between chemokines involved in monocyte recruitment and AMD.

Methods: Immunophenotyping for white blood cell (WBC) populations including CD14++CD16- and CD14+CD16+ monocytes, CD19+, CD3+, and CD16+ lymphocytes, and chemokine receptors CCR1, CCR2, CCR5, CX3CR1, and CXCR4 was performed on peripheral blood from treatment-naïve neovascular AMD (NV-AMD) patients and controls. Chemokine receptors' mRNA level in monocytes was measured with quantitative-PCR. Systemic levels of major chemokine ligands CCL2, CCL5, CCL3, and CXCL10 were evaluated by ELISA. Genotyping was performed for risk SNPs for AMD in the CFH, C3, and HTRA1 genes.

Results: The percentage of WBC sub-populations tested was similar between NV-AMD patients (n=18) and controls (n=20). CD14+CD16+ monocyte sub-population showed 3.5-fold increased expression of CCR1 (P=0.039; T-test) and 2.2-fold increased expression of CCR2 (P=0.027) in patients compared to controls. Increased CCR1 and CCR2 expression was correlated with each other in patients (R2=0.64, P<0.0001), but not controls (R2=0.02, P=0.57). Increased mRNA levels of CCR1 (1.6-fold, P=0.037) and CCR2 (1.6-fold, P=0.007) were found in monocytes from NV-AMD patients. Chemokine receptor expression was not correlated with the presence of risk SNPs, and was not associated with blood chemokine levels.

Conclusion: CCR1 and CCR2 are co-upregulated on the CD14+CD16+ monocyte population in NV-AMD patients. This data implicates CD14+CD16+ monocytes and chemokine signaling in AMD. Additional investigation is needed to elucidate the role of these monocytes and their potential as a biomarker or therapeutic target for AMD.

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Genetics

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Relationship Among CFH and ARMS2 Genotypes, Macular Pigment Optical Density, and Neuroretinal Function in Persons Without Age-Related Macular Degeneration.

Feigl B, Morris CP, Brown B, Zele AJ.

OBJECTIVES: To determine whether there is a difference in neuroretinal function and in macular pigment optical density between persons with high- and low-risk gene variants for age-related macular degeneration (AMD) and no ophthalmoscopic signs of AMD, and to compare the results on neuroretinal function to patients with manifest early AMD.

METHODS: Neuroretinal function was assessed with the multifocal electroretinogram for 32 participants (22 healthy persons with no AMD and 10 patients with early AMD). The 22 healthy participants with no AMD had either high- or low-risk genotypes for CFH (rs380390) and/or ARMS2 (rs10490924). Trough-to-peak response densities and peak-implicit times were analyzed in 5 concentric rings. Macular pigment optical density was assessed by use of customized heterochromatic flicker photometry.

RESULTS: Trough-to-peak response densities for concentric rings 1 to 3 were, on average, significantly greater in participants with high-risk genotypes than in participants with low-risk genotypes and in persons with early AMD after correction for age and smoking (P < .05). The group peak-implicit times for ring 1 were, on average, delayed in the patients with early AMD compared with the participants with high- or low-risk genotypes, although these differences were not significant. There was no significant correlation between genotypes and macular pigment optical density.

CONCLUSIONS: Increased neuroretinal activity in persons who carry high-risk AMD genotypes may be due to genetically determined subclinical inflammatory and/or histological changes in the retina. Neuroretinal function in healthy persons genetically susceptible to AMD may be a useful additional early biomarker (in combination with genetics) of AMD before there is a clinical manifestation.

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Diet

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Association between hypovitaminosis d and late stages of age-related macular degeneration: a case-control study.

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Rapid purification method for vitamin A-derived aging pigments A2E and iso-A2E using cation exchange resin.

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Abstract

A2E, known to be involved in the pathogenesis of age-related macular degeneration (AMD), is one of the major compounds that accumulate as fluorescent pigments in retinal pigment epithelial (RPE) cells with age and in some retinal disorders. While the biomimetic synthesis of A2E and its cis-isomer, iso-A2E is as simple as 'one-pot' reaction, the purification of these amphiphillic compounds has been a bottleneck for the mass production of these pathophysiologically important eye pigments. In order to provide a new method of rapid purification of A2E and iso-A2E, we employed a cation exchange resin for the separation of these pigments from crude reaction mixture. The reaction mixture was loaded on a weak acid resin and was eluted with 80% methanol with sodium hydroxide (pH 12), 100% methanol, and 100% methanol with 0.1% trifluoroacetic acid (TFA) in sequence. A2E and isoA2E were eluted only with 100% methanol solution containing TFA. Most of unreacted starting materials and intermediates were removed with 80% methanol containing sodium hydroxide. The new method can be used as a relatively simple and economic way to purify A2E and iso-A2E compared to conventional HPLC technique.

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