

Issue 146

Monday 2 September, 2013

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term "macular degeneration".

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Drug treatment

Drug Des Devel Ther. 2013 Aug 5;7:711-22. doi: 10.2147/DDDT.S40215.

Aflibercept in wet AMD: specific role and optimal use.

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BACKGROUND:Vascular endothelial growth factor (VEGF) is a naturally occurring glycoprotein in the body that acts as a growth factor for endothelial cells. It regulates angiogenesis, enhances vascular permeability, and plays a major role in wet age-related macular degeneration. The consistent association between choroidal neovascularization and increased VEGF expression provides a strong reason for exploring the therapeutic potential of anti-VEGF agents in the treatment of this disorder. Blockade of VEGF activity is currently the most effective strategy for arresting choroidal angiogenesis and reducing vascular permeability, which is frequently the main cause of visual acuity deterioration. In recent years, a number of other molecules have been developed to increase the efficacy and to prolong the durability of the anti-VEGF effect. Aflibercept (EYLEA®; Regeneron Pharmaceutical Inc and Bayer), also named VEGF Trap-eye, is the most recent member of the anti-VEGF armamentarium that was approved by the US Food and Drug Administration in November 2011. Because of its high binding affinity and long duration of action, this drug is considered to be a promising clinically proven anti-VEGF agent for the treatment of wet maculopathy.

OBJECTIVE:This article reviews the current literature and clinical trial data regarding the efficacy and the pharmacological properties of VEGF-Trap eye and describes the possible advantages of its use over the currently used "older" anti-VEGF drugs.

METHODS:For this review, a search of PubMed from January 1989 to May 2013 was performed using the following terms (or combination of terms): vascular endothelial growth factors, VEGF, age-related macular degeneration, VEGF-Trap eye in wet AMD, VEGF-Trap eye in diabetic retinopathy, VEGF-Trap eye in retinal vein occlusions, aflibercept. Studies were limited to those published in English.

RESULTS AND CONCLUSION:Two Phase III clinical trials, VEGF Trap-eye Investigation of Efficacy and Safety in Wet AMD (VIEW) 1 and 2, comparing VEGF Trap-eye to ranibizumab demonstrated the noninferiority of this novel compound. The clinical equivalence of this compound against ranibizumab is maintained even when the injections are administered at 8-week intervals, which indicates the potential to reduce the risk of monthly intravitreal injections and the burden of monthly monitoring.

PMID: 23990705 [PubMed - in process]

Am J Ophthalmol. 2013 Aug 20. pii: S0002-9394(13)00422-4. doi: 10.1016/j.ajo.2013.06.024. [Epub ahead of print]

Mechanism of Retinal Pigment Epithelium Tear Formation Following Intravitreal Anti-Vascular Endothelial Growth Factor Therapy Revealed by Spectral-Domain Optical Coherence Tomography.

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PURPOSE: To demonstrate the mechanism by which retinal pigment epithelium (RPE) tears occur in eyes with neovascular age-related macular degeneration (AMD) treated with intravitreal anti-vascular endothelial growth factor (VEGF) agents using spectral-domain optical coherence tomography (OCT).

DESIGN: Retrospective observational case series.

METHODS: OCT images of 8 eyes that developed RPE tears following the administration of intravitreal anti-VEGF agents for neovascular AMD were evaluated. Pretear and posttear images were compared in order to elucidate the mechanism by which RPE tears occur in this setting.

RESULTS: In all eyes, pretear images revealed a vascularized pigment epithelial detachment (PED) containing hyperreflective material consistent with choroidal neovascularization (CNV). This CNV was adherent to the undersurface of the RPE and created contractile folds in the RPE contour. In 6 eyes, contractile neovascular tissue spanned the PED, causing outward bowing of the Bruch membrane and a peaked appearance to the overlying RPE monolayer. RPE tears occurred after the first anti-VEGF injection in 6 of 8 eyes. The posttear OCT images showed a discontinuity in the RPE with the CNV adherent to the retracted RPE. In all eyes, the RPE ruptured along a segment of bare RPE not in contact with the CNV or Bruch membrane.

CONCLUSIONS: Eyes with vascularized PEDs secondary to AMD may show specific OCT findings that increase the risk for RPE tear following intravitreal anti-VEGF injection. Rapid involution and contraction of neovascular tissue adherent to the undersurface of the RPE may impart a substantial contractile force that tears this already-strained tissue layer.

PMID: 23972309 [PubMed - as supplied by publisher]

Expert Rev Clin Pharmacol. 2013 Aug 24. [Epub ahead of print]

Update on current and future novel therapies for dry age-related macular degeneration.

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Abstract: Age-related macular degeneration (ARMD) is the leading cause of irreversible blindness in developed countries. There are currently no cures, but there are promising potential therapies that target the underlying disease mechanisms of dry ARMD. Stem cells, ciliary neurotrophic factor, rheopheresis, ozonated autohemotherapy and prostaglandins show promise in stabilizing or improving visual acuity. Age-Related Eye Disease Study vitamins may reduce progression to severe ARMD. Adjuvant therapy like low vision rehabilitation and implantable miniature telescopes may help patients adjust to the sequelae of their disease, and herbal supplementation with saffron, zinc monocyteine and phototrop may be helpful. Therapies that are currently in clinical trials include brimonidine, doxycycline, anti-amyloid antibodies (GSK933776 and RN6G), RPE65 inhibitor (ACU-4429), complement inhibitors (ARC1905, FCFD4514S), hydroxychloroquine, intravitreal fluocinolone acetate and vasodilators like sildenafil, moxaverine and MC-1101. Therapies that have not been shown to be effective include POT-4, eculizumab, tandospirone,

anecortave acetate, the antioxidant OT-551, sirolimus and vitamin E.

PMID: 23971874 [PubMed - as supplied by publisher]

Vojnosanit Pregl. 2013 Jul;70(7):660-3.

The effect of intravitreal administration of bevacizumab on macular edema and visual acuity in age-related macular degeneration with subfoveal choroidal neovascularisation.

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BACKGROUND/AIM: Age-related macular degeneration (AMD) is a leading cause of the loss of central visual acuity in population older than 70 years. We can distinguish wet and dry form of AMD. The aim of the study was to present our early results in treatment of the wet (neovascular) form of AMD with intravitreal administration of bevacizumab.

METHODS: The study included 39 patients. Each patient underwent a complete ophthalmological examination, fluorescein angiography (FA) and optical coherence tomography (OCT). All the patients received 1.25 mg of intravitreal bevacizumab (0.05 mL of commercial phial of Avastin). The total of three doses was given with a one-month interval between doses.

RESULTS: Among 39 patients, 24 were women and 15 men. The average best corrected visual acuity (BCVA) was improved from 0.09 before the therapy to 0.24 after the administration of all the three doses of bevacizumab ($p < 0.001$). The average central macular thickness (CMT) measured by OCT was improved from 474 microm in the beginning to 341 microm after the administration of all the three doses of the drug ($p < 0.001$). There were no side effects.

CONCLUSIONS: Our short-term experience indicates that intravitreal administration of three doses of bevacizumab in one-month intervals between the doses leads to a significant reduction of macular edema and improvement of BCVA in patients with neovascular AMD.

PMID: 23984614 [PubMed - in process]

JAMA Ophthalmol. 2013 Aug 22. doi: 10.1001/jamaophthalmol.2013.4592. [Epub ahead of print]

Patient-Reported Visual Function Outcomes Improve After Ranibizumab Treatment in Patients With Vision Impairment Due to Diabetic Macular Edema: Randomized Clinical Trial.

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IMPORTANCE: Few data are available on relative changes in vision-related function after treatment for diabetic macular edema (DME).

OBJECTIVE: To determine the impact of intravitreal ranibizumab, 0.5 mg, compared with laser on patient-reported visual function.

DESIGN: Phase 3, randomized, double-masked, 12-month study. **SETTING** Outpatient retina practices in Australia, Canada, and Europe.

PARTICIPANTS: Patients 18 years or older with type 1 or 2 diabetes mellitus and visual impairment due to DME.

INTERVENTIONS: Patients were randomized to ranibizumab plus sham laser (n = 116), ranibizumab plus laser (n = 118), or sham injections plus laser (n = 111). Ranibizumab and sham injections were given for 3 consecutive months then as needed; laser plus sham laser treatment was given at baseline then as needed.

MAIN OUTCOMES AND MEASURES: National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) scores at 0, 3, and 12 months for patients receiving 1 or more study treatments with 1 or more postbaseline NEI VFQ-25 assessments and last observation carried forward for missing data.

RESULTS: Mean baseline NEI VFQ-25 composite scores were 72.8, 73.5, and 74.1 in the ranibizumab, laser, and ranibizumab plus laser groups, respectively. At 12 months, the mean composite scores (95% CIs) improved by 5.0 (ranibizumab vs laser, 2.6 to 7.4; P = .01 vs laser) and 5.4 (ranibizumab plus laser vs laser alone, 3.3 to 7.4; P = .004 vs laser) from baseline in the ranibizumab and ranibizumab plus laser groups, respectively, compared with 0.6 (-1.8 to 3.0) for the laser group. Near activities scores improved by 9.0 (ranibizumab vs laser, 5.0 to 13.0; P = .01) and 9.1 (ranibizumab plus laser vs laser, 5.6 to 12.6; P = .006) compared with 1.1 (-3.0 to 5.2) for the laser group, whereas distance activities scores improved by 5.3 (ranibizumab vs laser, 1.8 to 8.9; P = .04) and 5.6 (ranibizumab plus laser vs laser, 2.3 to 9.0; P = .03) compared with 0.4 (-3.1 to 3.8) for the laser group. Patients with better baseline visual acuity or lower central retinal thickness had greater improvements with ranibizumab treatment compared with laser in composite and some subscale scores compared with patients with worse visual acuity or higher central retinal thickness.

CONCLUSIONS AND RELEVANCE: These data provide vision-related, patient-reported outcome evidence that mirrors visual acuity outcomes and supports benefits from ranibizumab or ranibizumab plus laser treatment for patients with DME and characteristics similar to those enrolled in this randomized clinical trial.

PMID: 23974915 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2013 Aug 27. pii: iovs.13-12653v1. doi: 10.1167/iov.13-12653. [Epub ahead of print]

Comparison of macular choroidal thickness among patients over age 65 with early atrophic age-related macular degeneration and normals.

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Purpose: To compare macular choroidal thickness between patients with early atrophic age-related macular degeneration (AMD), and normals in patients over 65 years of age.

Methods: Consecutive, cross-sectional observational study. Enhanced depth imaging spectral domain optical coherence tomography using horizontal raster scanning at 12 locations throughout the macula was performed in one eye of consecutive patients presenting with large soft drusen alone, drusen with additional features of early AMD, or a normal fundus. Choroidal thickness was measured at 7 points for each raster scan in the central 3 mm of the macula (total 84 points/eye). In addition, a single sub-foveolar measurement was obtained for each eye.

Results: 150 eyes of 150 patients were included. There was no significant difference between mean refractive error for each diagnosis category via one-way ANOVA (p=0.451). Mean macular CT for normals was 235±49 µm (range=125-334 µm; median 222 µm), 161±39 µm (range=89-260 µm; median=158 µm) for the drusen group, and 115±40 µm (range=22-256 µm; median=112 µm) for patients with AMD. Mean

macular CT was significantly different via one-way ANOVA among all diagnosis categories ($p < 0.001$).

Conclusions: The presence of features of early AMD without geographic atrophy and/or soft drusen alone is associated with decreased mean macular CT in vivo compared to patients with no chorioretinal pathology. Using enhanced depth imaging, measurement of a single sub-foveolar choroidal thickness is highly correlated to mean central macular CT.

PMID: 23982844 [PubMed - as supplied by publisher]

Cell Death Dis. 2013 Aug 29;4:e781. doi: 10.1038/cddis.2013.303.

Hyperactivation of retina by light in mice leads to photoreceptor cell death mediated by VEGF and retinal pigment epithelium permeability.

Cachafeiro M, Bemelmans AP, Samardzija M, Afanasieva T, Pournaras JA, Grimm C, Kostic C, Philippe S, Wenzel A, Arsenijevic Y.

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Abstract: Light toxicity is suspected to enhance certain retinal degenerative processes such as age-related macular degeneration. Death of photoreceptors can be induced by their exposure to the visible light, and although cellular processes within photoreceptors have been characterized extensively, the role of the retinal pigment epithelium (RPE) in this model is less well understood. We demonstrate that exposition to intense light causes the immediate breakdown of the outer blood-retinal barrier (BRB). In a molecular level, we observed the slackening of adherens junctions tying up the RPE and massive leakage of albumin into the neural retina. Retinal pigment epithelial cells normally secrete vascular endothelial growth factor (VEGF) at their basolateral side; light damage in contrast leads to VEGF increase on the apical side - that is, in the neuroretina. Blocking VEGF, by means of lentiviral gene transfer to express an anti-VEGF antibody in RPE cells, inhibits outer BRB breakdown and retinal degeneration, as illustrated by functional, behavioral and morphometric analysis. Our data show that exposure to high levels of visible light induces hyperpermeability of the RPE, likely involving VEGF signaling. The resulting retinal edema contributes to irreversible damage to photoreceptors. These data suggest that anti-VEGF compounds are of therapeutic interest when the outer BRB is altered by retinal stresses.

PMID: 23990021 [PubMed - in process]

Dev Ophthalmol. 2013;52:114-23. doi: 10.1159/000351088. Epub 2013 Aug 26.

Radiation therapy: posterior segment complications.

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Abstract: Therapeutic radiation to the posterior segment of the eye is a common option for posterior segment tumors. Such tumors are often malignant, but sometimes, benign neoplasms are treated with ionizing radiation. Also, non-neoplastic intraocular lesions like wet age-related macular degeneration may be treated with radiotherapy. Orbital disease, both neoplastic lesions like optic nerve sheath meningioma and non-neoplastic entities like Graves' ophthalmopathy may be treated with radiotherapy and this may include radiation of the optic nerve and posterior segment of the eye. Occasionally, radiotherapy of extraocular malignant disease, involving, e.g. the paranasal sinuses, may cause significant radiation damage to the eye. Complications after radiation to the posterior segment of the eye are largely related to the radiation dose to the posterior segment. The amount of irradiated volume of normal tissue and

fractionation are also important for the development of radiation complications to the posterior segment. Radiation retinopathy is the most common complication of the posterior segment, but radiation optic neuropathy also occurs frequently. Radiation scleral necrosis is less frequent probably due to the radioresistance of the scleral collagen. These complications have the potential to cause blindness (radiation retinopathy and optic neuropathy) or enucleation of the eye (scleral necrosis). Although numerous treatments have been advocated, management of radiation-induced damage remains controversial. Efficacy for any treatment still needs to be proven and, if possible, the best option by far is to minimize radiation changes to normal tissue.

PMID: 23989132 [PubMed - in process]

Dev Ophthalmol. 2013;52:75-84. doi: 10.1159/000351061. Epub 2013 Aug 26.

Radiation therapy: age-related macular degeneration.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of severe irreversible vision loss in patients over the age of 50 years in the developed world. Neovascular AMD (NVAMD) is responsible for 90% of the cases with severe visual loss. In the last decade, the treatment paradigm for NVAMD has been transformed by the advent of anti-vascular endothelial growth factor therapy. Despite the excellent results of anti-vascular endothelial growth factor therapy, frequent injections remain a necessity for most patients. The burden of these frequent visits as well as the cumulative risks of indefinite intravitreal injections demand continued pursuit of more enduring therapy that provides similar functional results. Radiotherapy has been studied for two decades as a potential therapy for NVAMD. Because of its antiangiogenic properties, radiation therapy remains a promising potential adjunctive resource for the treatment of choroidal neovascularization secondary to NVAMD. This review considers the past, present and future of radiation as a treatment or combination treatment of NVAMD.

PMID: 23989128 [PubMed - in process]

Ophthalmologica. 2013 Aug 24. [Epub ahead of print]

The Vitreous, the Retinal Interface in Ocular Health and Disease.

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Abstract: The vitreous is a complex structure whose composition and appearance change with age. Anomalous adhesions between the posterior vitreous face and the retinal surface are the cause of numerous vitreoretinal complications, while the presence of an intact posterior hyaloid provides a scaffold for vascular growth and anteroposterior traction. This review summarizes what is known about the biochemistry of the vitreous, the process of posterior vitreous detachment (PVD) development, and the available clinical approaches to examining the vitreous and its interface. A pooled analysis of studies looking at the presence of a complete, partial or absent PVD in a number of macular and retinal diseases allows us to establish odds ratios for these various states. From this emerge both protective and disease-associated states in conditions such as proliferative diabetic retinopathy, macular edema, and age-related macular degeneration. With the emergence of pharmacological means to separate the posterior hyaloid, a better understanding of the possible role of the vitreous in tractional syndromes is required.

PMID: 23989078 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2013 Sep;88(9):362-364. doi: 10.1016/j.oftal.2012.05.007. Epub 2012 Jul 19.

Charles Bonnet syndrome precipitated by brimonidine.

[Article in English, Spanish]

García-Catalán MR, Arriola-Villalobos P, Santos-Bueso E, Gil-de-Bernabé J, Díaz-Valle D, Benítez-Del-Castillo JM, García-Sánchez J.

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CASE REPORT: An 81-year-old woman with age-related macular degeneration and pseudoexfoliative glaucoma developed visual hallucinations (faces, flowers and frames) shortly after beginning brimonidine drops. Neurologic and psychiatric examination was normal. Visual hallucinations disappeared within 10 days after discontinuing the drug.

DISCUSSION: The Charles Bonnet syndrome (CBS) is characterised by complex visual hallucinations in elderly patients in the setting of significant visual impairment without any psychiatric symptoms. Awareness of CBS among ophthalmologist is essential. Clinicians should treat visual impairment and be aware of possible visual hallucinations in patients treated with brimonidine.

PMID: 23988044 [PubMed - as supplied by publisher]

Pathogenesis

Invest Ophthalmol Vis Sci. 2013 Aug 27. pii: iovs.13-12374v1. doi: 10.1167/iov.13-12374. [Epub ahead of print]

Complement factor C3a alters proteasome function in human RPE cells and in an animal model of age-related RPE degeneration.

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Purpose: Complement activation plays an unequivocal role in the pathogenesis of age-related macular degeneration (AMD). More recent evidence suggests an additional role in AMD for the ubiquitin proteasome pathway (UPP), a protein-degradation nanomachinery present in all types of eukaryotic cells. The purpose of this study was to elaborate on these findings and investigate whether the complement system directly contributes to derangements in the UPP through the activated complement components C3a and C5a.

Methods: In retinal pigment epithelium (RPE) of monocyte chemoattractant protein-1 (Ccl2)-deficient mice, a mouse model for AMD, proteasome function was investigated by immunohistochemistry of household ($\beta 5$) and immune ($\beta 5i$) subunit expression. Subsequently, proteasome overall activity was determined using the BodipyFl-Ahx3L3VS probe in primary cultured human RPE cells that were exposed to different stimuli including C3a and C5a, using confocal laser scanning microscopy and flow cytometry. Gene expression and protein levels of proteasome subunits $\alpha 7$, PA28 α , $\beta 5$ and $\beta 5i$ were also studied in RPE cells after exposure to γ -interferon, C3a and C5a by real-time PCR and western blotting.

Results: RPE cells of Ccl2-deficient mice showed immunoproteasome up-regulation. C3a but not C5a supplementation induced a decreased proteasome overall activity in human RPE cells, whereas mRNA and protein levels of household proteasome and immunoproteasome subunits were unaffected.

Conclusions: In human RPE cells, C3a induces decreased proteasome-mediated proteolytic activity,

whereas in a mouse model of AMD, the immunoproteasome was up-regulated, indicating a role for complement-driven alterations in proteasome activity in the cascade of pathological events that result in AMD.

PMID: 23982842 [PubMed - as supplied by publisher]

PLoS One. 2013 Aug 16;8(8):e72935. doi: 10.1371/journal.pone.0072935.

Myeloid cells expressing VEGF and arginase-1 following uptake of damaged retinal pigment epithelium suggests potential mechanism that drives the onset of choroidal angiogenesis in mice.

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Unit of Ophthalmology, School of Clinical Sciences, University of Bristol, Bristol, United Kingdom.

Abstract: Whilst data recognise both myeloid cell accumulation during choroidal neovascularisation (CNV) as well as complement activation, none of the data has presented a clear explanation for the angiogenic drive that promotes pathological angiogenesis. One possibility that is a pre-eminent drive is a specific and early conditioning and activation of the myeloid cell infiltrate. Using a laser-induced CNV murine model, we have identified that disruption of retinal pigment epithelium (RPE) and Bruch's membrane resulted in an early recruitment of macrophages derived from monocytes and microglia, prior to angiogenesis and contemporaneous with lesional complement activation. Early recruited CD11b(+) cells expressed a definitive gene signature of selective inflammatory mediators particularly a pronounced Arg-1 expression. Accumulating macrophages from retina and peripheral blood were activated at the site of injury, displaying enhanced VEGF expression, and notably prior to exaggerated VEGF expression from RPE, or earliest stages of angiogenesis. All of these initial events, including distinct VEGF (+) Arg-1(+) myeloid cells, subsided when CNV was established and at the time RPE-VEGF expression was maximal. Depletion of inflammatory CCR2-positive monocytes confirmed origin of infiltrating monocyte Arg-1 expression, as following depletion Arg-1 signal was lost and CNV suppressed. Furthermore, our in vitro data supported a myeloid cell uptake of damaged RPE or its derivatives as a mechanism generating VEGF (+) Arg-1(+) phenotype in vivo. Our results reveal a potential early driver initiating angiogenesis via myeloid-derived VEGF drive following uptake of damaged RPE and deliver an explanation of why CNV develops during any of the stages of macular degeneration and can be explored further for therapeutic gain.

PMID: 23977372 [PubMed - in process] PMCID: PMC3745388

PLoS One. 2013 Aug 20;8(8):e71808. doi: 10.1371/journal.pone.0071808.

VEGF Receptor Blockade Markedly Reduces Retinal Microglia/Macrophage Infiltration into Laser-Induced CNV.

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Abstract: Although blocking VEGF has a positive effect in wet age-related macular degeneration (AMD), the effect of blocking its receptors remains unclear. This was an investigation of the effect of VEGF receptor (VEGFR) 1 and/or 2 blockade on retinal microglia/macrophage infiltration in laser-induced choroidal neovascularization (CNV), a model of wet AMD. CNV lesions were isolated by laser capture microdissection at 3, 7, and 14 days after laser and analyzed by RT-PCR and immunofluorescence staining for mRNA and protein expression, respectively. Neutralizing antibodies for VEGFR1 or R2 and the microglia inhibitor minocycline were injected intraperitoneally (IP). Anti-CD11b, CD45 and Iba1 antibodies were used to confirm the cell identity of retinal microglia/macrophage, in the RPE/choroidal flat mounts or

retinal cross sections. CD11b(+), CD45(+) or Iba1(+) cells were counted. mRNA of VEGFR1 and its three ligands, PlGF, VEGF-A (VEGF) and VEGF-B, were expressed at all stages, but VEGFR2 were detected only in the late stage. PlGF and VEGF proteins were expressed at 3 and 7 days after laser. Anti-VEGFR1 (MF1) delivered IP 3 days after laser inhibited infiltration of leukocyte populations, largely retinal microglia/macrophage to CNV, while anti-VEGFR2 (DC101) had no effect. At 14 days after laser, both MF1 and DC101 antibodies markedly inhibited retinal microglia/macrophage infiltration into CNV. Therefore, VEGFR1 and R2 play differential roles in the pathogenesis of CNV: VEGFR1 plays a dominant role at 3 days after laser; but both receptors play pivotal roles at 14 days after laser. In vivo imaging demonstrated accumulation of GFP-expressing microglia into CNV in both CX3CR1(gfp/gfp) and CX3CR1(gfp/+) mice. Minocycline treatment caused a significant increase in lectin(+) cells in the sub-retinal space anterior to CNV and a decrease in dextran-perfused neovessels compared to controls. Targeting the chemoattractant molecules that regulate trafficking of retinal microglia/macrophage appears to be a compelling therapeutic strategy to control CNV and treat wet AMD.

PMID: 23977149 [PubMed - in process] PMCID: PMC3748119

Commun Integr Biol. 2013 Jul 1;6(4):e24474. doi: 10.4161/cib.24474. Epub 2013 May 10.

Let's play a game of chutes and ladders: Lysosome fusion with the epithelial plasma membrane.

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Abstract: In non-polarized cells, calcium-induced exocytosis of "conventional" lysosomes is important in diverse processes like membrane repair after exposure to pore-forming toxins and clearance of cellular debris. Resealing of torn membranes is especially critical for barrier epithelia that directly interact with pathogens and toxins, which can result in membrane microdisruptions and lesions. However, whether lysosomes participate in membrane repair in polarized epithelia has been an open question. We recently reported that in polarized Madin-Darby canine kidney (MDCK) cells, localized influx of calcium induces lysosomes to fuse with the basolateral membrane. This spatial segregation of exocytosis depends on an intact actin cytoskeleton, membrane cholesterol and restricted distribution of fusion machinery such as the t-SNARE syntaxin 4. Our data show that the polarity of syntaxin 4 (which is regulated by the clathrin adaptor protein AP-1) dictates whether lysosomes parachute down to the basolateral membrane or take a ladder up to the apical membrane. Here, we speculate about additional machinery (such as the lysosomal calcium sensor synaptotagmin VII and the v-SNARE VAMP7) that could be involved in polarized fusion of lysosomes with the epithelial membrane. We also discuss the potential importance of lysosome exocytosis in maintaining membrane integrity in the retinal pigment epithelium, the primary tissue affected in blinding diseases such as age-related macular degeneration.

PMID: 23986802 [PubMed]

Epidemiology

Am J Ophthalmol. 2013 Aug 20. pii: S0002-9394(13)00462-5. doi: 10.1016/j.ajo.2013.06.035. [Epub ahead of print]

Identification of Persons With Incident Ocular Diseases Using Health Care Claims Databases.

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PURPOSE: To assess the extent to which incidence rates calculated for common ocular diseases by using claims data may be overestimated according to the length of the disease-free look-back period used in the analysis.

DESIGN: Retrospective longitudinal cohort analysis.

METHODS: Billing records of 2457 persons continuously enrolled for 11 years in a managed-care network were searched for International Classification of Diseases (ICD-9-CM) diagnoses of cataract, open-angle glaucoma (OAG), nonexudative age-related macular degeneration (ARMD), and nonproliferative diabetic retinopathy (NPDR) at eye-care visits in the first half of 2001, the second half of 2010, and 2011. For each condition, incidence rates calculated by using "look-back" periods ranging from 0.5-9 years were compared with best estimates from a gold-standard period of 9.5 years.

RESULTS: With a 1-year disease-free look-back period, incidence was overestimated by 260% for cataract, 135% for OAG, 209% for ARMD, and 300% for NPDR. Expanding the disease-free look-back period to 3 years resulted in a reduction of incidence overestimation to 40% for cataract, 14% for OAG, 45% for ARMD, and 100% for NPDR. A 5-year look-back period yielded incidence rates that were overestimated by <30% for all 4 conditions.

CONCLUSIONS: In our claims-data analysis of 4 common ocular conditions, a disease-free interval ≤ 1 year insufficiently distinguished newly diagnosed from pre-existing disease, resulting in grossly overestimated incidence rates. Using look-back periods of 3-5 years, depending on the specific diagnosis, yielded considerably more accurate estimates of disease incidence.

PMID: 23972306 [PubMed - as supplied by publisher]

Ophthalmic Epidemiol. 2013 Aug 29. [Epub ahead of print]

Eye Care Use Among Rural Adults in China: The Handan Eye Study.

Peng Y, Tao QS, Liang YB, Friedman DS, Yang XH, Jhanji V, Duan XR, Sun LP, Wang NL.

Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology & Visual Science Key Lab, Beijing, China.

Abstract Purpose: To assess the use of eye care services in a rural population in North China and to analyze the factors associated with underuse of these services.

Methods: In a cross-sectional population-based study, demographic, health and vision-related information including use of eye care services were determined during a face-to-face interview. A single visit to an eye care provider qualified as "use" of eye care services.

Results: Of 6612 participants, 754 (11.4%, 95% confidence interval, CI, 8.7-14.1%) had used eye care services. The most common reason cited for not seeing an eye care provider was "no need" (n = 5754). Of the 5754 who thought that there was no need to see an ophthalmologist, 3458 (60.1%) were found to have one or more type of eye disease, including glaucoma (56, 1.0%), cataract (1056, 18.4%), age-related macular degeneration (AMD; 164, 2.9%) and refractive error (3048, 53.0%). Also, 74 (1.3%) and 409 (7.1%) of the 5754 participants had visual impairment (<20/60) according to best-corrected visual acuity and presenting visual acuity, respectively. In a multiple regression model, participants who had glaucoma (adjusted odds ratio, OR, 4.0, 95% CI 3.0-5.4), AMD (adjusted OR 1.6, 95% CI 1.2-2.3) or refractive error (adjusted OR 1.4, 95% CI 1.1-1.8), were more likely to visit an eye care provider.

Conclusion: A high proportion of the Chinese rural population had never used eye care services although three fifths had eye diseases. Further efforts towards better education of the general population about common eye problems as well as increasing the number of ocular health providers would be necessary in future.

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Genetics

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VEGF A (rs699947 and rs833061) and VEGFR2 (rs2071559) Gene Polymorphisms are not Associated with AMD Susceptibility in a Spanish Population.

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Abstract Purpose: Age-related macular degeneration (AMD) is a multifactorial disease due to interaction between genetic and environmental factors. Increased angiogenesis plays a central role in AMD development. Previous studies on the potential link between AMD and vascular endothelial growth factor (VEGFA) and vascular endothelial growth factor receptor (VEGFR) have yielded conflicting results. We have analysed if polymorphisms in genes coding for VEGFA and VEGFR are associated to susceptibility to suffer AMD in a cohort of Spanish subjects.

Patients and Methods: We obtained peripheral blood samples from 151 patients with diagnosis of exudative AMD. We also studied 91 healthy subjects matched by age. We studied VEGFA rs699947 and rs833061, and VEGFR2 rs2071559 polymorphisms using real-time PCR with TaqMan probes.

Results: We did not find statistically significant differences in genotypic distribution of VEGF rs699947 and rs833061 polymorphisms between patients and controls. However, analysis of VEGFR2 rs2071559 polymorphism shows that carriers of GG genotype are more frequent in subjects with AMD (p: 0.032; Odds Ratio(OR): 1.933; confidence interval (CI): 1.053-3.549), but, when corrected by Bonferroni testing, the result was found to be not significant.

Conclusion: Our study shows that VEGFA rs699947 and rs833061 and VEGFR2 rs2071559 polymorphisms do not modify the risk of suffering AMD in a Spanish population.

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Subretinal Transplantation of RMSCs and Erythropoietin Gene Modified RMSCs for Protecting and Rescuing Degenerative Retina in Rats.

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Abstract: For degenerative retina, like the acquired form exemplified by age-related macular degeneration (AMD), there is currently no cure. This study was to explore a stem cell therapy and a stem cell-based gene therapy for sodium iodate (SI)-induced retinal degeneration in rats. Three cell types, i.e., rat mesenchymal stem cells (rMSCs) alone, erythropoietin (EPO) gene modified rMSC (EPO-rMSCs) or doxycycline (DOX) inducible EPO expression rMSCs (Tet-on EPO-rMSCs), were transplanted into the subretinal spaces of SI-treated rats. The rMSCs, after isolated, were prepared for transplantation after 3 to 5 passages or modified with EPO gene. During the 8 weeks after the transplantation, the rats treated with rMSCs alone or with two types of EPO-rMSCs were all monitored by fundus examination, fluorescent fundus angiography and electroretinogram. The transplantation efficiency of donor cells was examined for their survival, integration and differentiation. Following the transplantation, labeled donor cells were observed in subretinal space and adopted RPE morphology. EPO concentration in vitreous and retina of SI-treated rats which were also

transplanted with EPO-rMSCs or Tet-on EPO-rMSCs were markedly increased, in parallel with the improvement of retinal morphology and function. These findings suggest that rMSCs transplantation could be a new therapy for degenerative retinal diseases since it can protect and rescue RPE and retinal neurons, while EPO gene modification to rMSCs could be an even better option.

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Nanoceria inhibit expression of genes associated with inflammation and angiogenesis in the retina of Vldlr null mice.

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Abstract: Oxidative stress and inflammation are important pathological mechanisms in many neurodegenerative diseases, including age-related macular degeneration (AMD). The Very Low-Density Lipoprotein Receptor knockout mouse (Vldlr^{-/-}) has been identified as a model for AMD and in particular for Retinal Angiomatous Proliferation (RAP). In this study we examined the effect of cerium oxide nanoparticles (nanoceria) that have been shown to have catalytic antioxidant activity, on expression of 88 major cytokines in the retinas of Vldlr^{-/-} mice using a PCR array. A single intravitreal injection of nanoceria at P28 caused inhibition of pro-inflammatory cytokines and pro-angiogenic growth factors including Tslp, Lif, Il-3, Il-7, Vegfa, Fgf1, Fgf2, Fgf7, Egf, Efna 3, Lep, and up-regulation of several cytokines and anti-angiogenic genes in the Vldlr^{-/-} retina within one week. We used the Ingenuity Pathway Analysis software to search for biological functions, pathways, and interrelationships between gene networks. Many of the genes whose activities were affected are involved in cell signaling, cellular development, growth and proliferation, and tissue development. Western blot analysis revealed that nanoceria inhibit the activation of ERK 1/2, JNK, p38 MAP kinase, and Akt. These data suggest that nanoceria may represent a novel therapeutic strategy to treat AMD, RAP, and other neurodegenerative diseases.

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Diet

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CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration.

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OBJECTIVE: The Age-Related Eye Disease Study (AREDS) demonstrated that antioxidant and zinc supplementation decreases progression to advanced age-related macular degeneration (AMD) in patients with moderate to severe disease. We evaluated the interaction of genetics and type of nutritional supplement on progression from moderate to advanced AMD.

DESIGN: Genetic analysis of a randomized, prospective clinical trial.

PARTICIPANTS: White patients with AREDS category 3 AMD in 1 eye and AREDS categories 1 through 4

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AMD in the fellow eye enrolled in the AREDS with available peripheral blood-derived DNA (995).

METHODS: Subjects were evaluated for known AMD genetic risk markers and treatment category. The progression rate to advanced AMD was analyzed by genotypes and AREDS treatment group using Cox regression.

MAIN OUTCOME MEASURES: The effect of inherited gene polymorphisms on treatment group-specific rate of progression to advanced AMD.

RESULTS: Over an average of 10.1 years, individuals with 1 or 2 complement factor H (CFH) risk alleles derived maximum benefit from antioxidants alone. In these patients, the addition of zinc negated the benefits of antioxidants. Treatment with zinc and antioxidants was associated with a risk ratio (RR) of 1.83 with 2 CFH risk alleles ($P = 1.03E-02$), compared with outcomes for patients without CFH risk alleles. Patients with age-related maculopathy sensitivity 2 (ARMS2) risk alleles derived maximum benefit from zinc-containing regimens, with a deleterious response to antioxidants in the presence of ARMS2 risk alleles. Treatment with antioxidants was associated with an RR of 2.58 for those with 1 ARMS2 risk allele and 3.96 for those with 2 ARMS2 risk alleles ($P = 1.04E-6$), compared with patients with no ARMS2 risk alleles. Individuals homozygous for CFH and ARMS2 risk alleles derived no benefit from any category of AREDS treatment.

CONCLUSIONS: Individuals with moderate AMD could benefit from pharmacogenomic selection of nutritional supplements. In this analysis, patients with no CFH risk alleles and with 1 or 2 ARMS2 risk alleles derived maximum benefit from zinc-only supplementation. Patients with one or two CFH risk alleles and no ARMS2 risk alleles derived maximum benefit from antioxidant-only supplementation; treatment with zinc was associated with increased progression to advanced AMD. These recommendations could lead to improved outcomes through genotype-directed therapy.

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Use of Complementary and Alternative Medicine for Eye-related Diseases and Conditions.

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Abstract Aim: To determine the prevalence, types and characteristics associated with complementary and alternative medicine (CAM) use to treat eye-related diseases and conditions.

Materials and Methods: The 2002 and 2007 National Health Interview Survey (NHIS) was used to identify participants, 18 years of age and older, who completed the Adult Alternative Health/Complementary and Alternative Medicine questionnaire. Characteristics for those who reported CAM use for eye diseases and conditions and those who did not were compared; the types of CAM and the eye diseases and conditions for their use were also reported.

Results: In 2002, an estimated 0.1% of US adults reported using at least one of eight CAM therapies for eye-related problems; in 2007 the prevalence of CAM use for eye diseases and conditions had increased to 0.3%. In both 2002 and 2007, those who reported CAM use for eye diseases and conditions were more likely to be older, female, white and married. In both 2002 and 2007, the most common types of CAM therapies used were natural herbs and vitamin supplements. Macular degeneration was the most common condition for which CAM therapies were used.

Conclusions: The study suggests that there is a small and perhaps increasing proportion of the US population that uses CAM for eye diseases and conditions. Further research is needed to determine the

use and effectiveness of CAM for ophthalmologic purposes.

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