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MD Research News

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Drug treatment

Invest Ophthalmol Vis Sci. 2013 Jul 2. pii: iovs.13-11993v1. doi: 10.1167/iovs.13-11993. [Epub ahead of print]

Prospective Audit of Exudative Age-Related Macular Degeneration: 12-month Outcomes in Treatment-Naive eyes.

Gillies MC, Walton R, Simpson JM, Arnold J, Guymer RH, McAllister IL, Hunyor AP, Essex RW, Morlet N, Barthelmes D.

Clinical Ophthalmology and Eye Health, Save Sight institute, 8 Macqurie st, Sydney, NSW, 2000, Australia.

PURPOSE: To report the 12-month outcomes of 1,140 treatment-naïve eyes with exudative age-related macular degeneration (wet AMD) who were treated for 12 months with intravitreal anti-VEGF drugs in routine clinical practice.

METHODS: Index visit characteristics, such as lesion type and size, visual acuity (VA in logMAR [Logarithm of the Minimal Angle of Resolution] letters), as well as treatments, outcomes (VA, lesion activity status) and ocular adverse events were recorded in a prospectively designed electronic database. Index visit characteristics associated with the 12-month VA outcome were identified using mixed effects linear regression.

RESULTS: Mean change in VA in the cohort after 12 months was +4.7 logMAR letters (95%CI: 3.4 to 6.1) with a mean of 7.0 injections. No significant difference was found in change in VA or number of injections by type or size of the lesion. Median time to inactivation of lesions was 194 days. VA at the index visit was the strongest predictor for the 12-month outcomes. Infectious endophthalmitis occurred in 2 cases, retinal detachment in 1 case from a total of 9,162 injections.

CONCLUSIONS: These findings indicate that VEGF inhibitors can achieve reasonably good outcomes for wet AMD when used in routine clinical practice.

PMID: 23821201 [PubMed - as supplied by publisher]

Discov Med. 2013 Jun;15(85):343-8.

Current therapeutic approaches in neovascular age-related macular degeneration.

Nguyen DH, Luo J, Zhang K, Zhang M.

Department of Ophthalmology, University of California San Diego, La Jolla, California 92093, USA.

Abstract: Age-related macular degeneration (AMD) is the leading eye disease to cause visual impairment in the elderly. Neovascular AMD is a type of advanced AMD that is characterized by pathologic proliferation and leakage of abnormal blood vessels in the eye. While the pathogenesis of neovascular AMD is not completely known, one of the important milestones in neovascular AMD research was the identification of vascular endothelial growth factor (VEGF) as a major stimulus of abnormal angiogenesis that can be targeted for intravitreal treatment. Anti-VEGF therapies that neutralize or block the induction of angiogenesis by VEGF have recently revolutionized the therapeutic approach to neovascular AMD. The scientific literature regarding the efficacy and safety of anti-VEGF treatment has been hugely enriched with results from various recent randomized clinical trials involving the three most commonly utilized anti-VEGF pharmacologic agents -- ranibizumab, bevacizumab, and aflibercept. The potential to stop and reverse the progressive loss of vision due to neovascular AMD is evident. Continued investigation into inhibiting VEGF as well as targeting other crucial factors that contribute to neovascular AMD is an active field of research that is expected to accelerate the progress of neovascular AMD therapy.

PMID: 23819948 [PubMed - in process]

Drug Des Devel Ther. 2013 Jun 17;7:485-90. doi: 10.2147/DDDT.S43470. Print 2013.

Resistance to antivascular endothelial growth factor treatment in age-related macular degeneration.

Tranos P, Vacalis A, Asteriadis S, Koukoula S, Vachtsevanos A, Perganta G, Georgalas I.

Retina Centre, Thessaloniki, Greece.

Abstract: Age-related macular degeneration (AMD) is the main cause of visual impairment and blindness in people aged over 65 years in developed countries. Vascular endothelial growth factor (VEGF) is a positive regulator of angiogenesis and its proven role in the pathological neovascularization in wet AMD has provided evidence for the use of anti-VEGF agents as potential therapies. In this study, we review the literature for the possible causes of failure after treatment with anti-VEGF agents and attempt to propose an algorithm of suggestive actions to increase the chances of successful management of such difficult cases.

PMID: 23818759 [PubMed - in process] PMCID: PMC3692343

Clin Ophthalmol. 2013;7:1171-4. doi: 10.2147/OPTH.S46399. Epub 2013 Jun 13.

Longstanding refractory pseudophakic cystoid macular edema resolved using intravitreal 0.7 mg dexamethasone implants.

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BACKGROUND: Refractory pseudophakic cystoid macular edema (PCME) following cataract surgery has long posed a challenge to clinicians, but intravitreal injections with a sustained delivery 0.7 mg dexamethasone implant has emerged as a promising therapy for this condition.

OBJECTIVE: To present a case of longstanding and refractory PCME with complete remission through 189 days of follow-up after two successive injections with intravitreal dexamethasone implants.

CASE REPORT: A 59-year-old male had experienced metamorphopsia for approximately 4 years and had been diagnosed with PCME 15 months earlier. Since the time of the diagnosis, the condition had been refractory to both subtenon triamcinolone acetonide and a total of five injections with intravitreal ranibizumab. After the last injection with ranibizumab, central subfield mean thickness was 640 µm, and the best corrected visual acuity was 78 Early Treatment Diabetic Retinopathy Study letters. Following an

intravitreal injection with a dexamethasone implant, the macular edema resolved at the next follow-up. The macular edema returned 187 days after the first injection and was treated with another intravitreal dexamethasone implant. Again, the macular edema subsided completely, and best corrected visual acuity improved to 84 Early Treatment Diabetic Retinopathy Study letters, a condition which was maintained through an additional 189 days of follow-up.

CONCLUSION: Chronic PCME is traditionally a difficult condition to treat, but we are encouraged by the optimal response experienced with intravitreal sustained release dexamethasone implants in our patient whose longstanding PCME had been refractory to previous treatments with both subtenon triamcinolone and intravitreal ranibizumab. In this case, the condition appeared to be fully reversible once inflammation was controlled, but the need for monitoring and repeated injections remains an issue of concern.

PMID: 23818753 [PubMed] PMCID: PMC3693843

Eur J Ophthalmol. 2013 Jun 28:0. doi: 10.5301/ejo.5000333. [Epub ahead of print]

High-dose (2.0 mg) intravitreal ranibizumab for recalcitrant radiation retinopathy.

Finger PT, Chin KJ.

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Purpose: To evaluate the safety and tolerability and treatment efficacy of high-dose (2.0 mg) intravitreal ranibizumab for recalcitrant radiation retinopathy.

Methods: A phase I to II open-label, nonrandomized prospective clinical trial was performed on 10 eyes of 10 patients with recalcitrant radiation retinopathy who were failing standard dose anti-vascular endothelial growth factor (VEGF) therapy. External beam or plaque brachytherapy-associated retinopathy was characterized by persistent macular edema or leakage on optical coherence tomography or fluorescein angiography. Intravitreal 2.0 mg ranibizumab was given monthly up to 12 months and monitored for tolerability and change in best-corrected visual acuity (BCVA), central foveal thickness, and clinical signs of radiation retinopathy.

Results: Seven patients completed the 1-year study and received all 12 injections; 3 withdrew from the study due to worsening retinopathy (1 after external beam, 2 following plaque). Treatment was well-tolerated with no severe adverse reactions. A total of 70% had stable (n = 3) or improved (n = 4) BCVA. Mean change in BCVA was +3.3 letters at 6 months and +0.7 letters at 1 year. Mean improvement in central foveal thickness (CFT) was -19.3% (range -57 to +15%) at 1 year. Initial mean CFT was 428 µm (range 192-776); final mean CFT was 333 µm (range 190-532). A total of 80% demonstrated a statistically significant ($p<0.05$) reduction in CFT.Conclusions: Regardless of radiation source, intravitreal injections of 2.0 ranibizumab induced significant reductions in macular edema and maintained or improved BCVA in most patients who were failing standard dose anti-VEGF therapy.

PMID: 23813109 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2013 Jun 23:0. doi: 10.5301/ejo.5000337. [Epub ahead of print]

Intravitreal Lucentis for myopic choroidal neovascularization after pars plana vitrectomy and silicone oil tamponade.

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Department of Ophthalmology, Vita-Salute University, San Raffaele Scientific Institute, Milan - Italy.

Purpose: To report on intravitreal Lucentis for intervening myopic choroidal neovascularization (CNV) in a

case of retinal detachment successfully repaired with pars plana vitrectomy and silicone oil tamponade.

Methods: Intravitreal ranibizumab was performed in a 67-year-old woman with CNV complicating pathologic myopia. The patient had previously undergone vitrectomy and silicone oil tamponade for retinal detachment.

Results: At 2 months from intravitreal ranibizumab, best-corrected visual acuity (BCVA) improved from count fingers to 20/100, and intraocular pressure (IOP) was 16 mm Hg. Fluorescein angiography (FA) and spectral-domain optical coherence tomography (SD-OCT) showed resolution of late leakage and subretinal/ intraretinal fluid, respectively.

Conclusions: Administration of intravitreal anti-VEGF in patients with silicone oil as intraocular tamponade may represent an intriguing treatment option. Our results suggest that intravitreal injections of Lucentis may lead to a rapid improvement in both functional (BCVA) and morphologic (FA and SD-OCT) parameters of CNV activity, without significant rise in IOP, in eyes with silicone oil as intraocular tamponade.

PMID: 23813105 [PubMed - as supplied by publisher]

Arq Bras Oftalmol. 2013 Feb;76(1):18-20.

Panretinal photocoagulation versus intravitreal injection retreatment pain in high-risk proliferative diabetic retinopathy.

Lucena CR, Ramos Filho JA, Messias AM, Silva JA, Almeida FP, Scott IU, Ribeiro JA, Jorge R.

PURPOSE: To compare pain related to intravitreal injection and panretinal photocoagulation in the management of patients with high-risk proliferative diabetic retinopathy.

METHODS: Prospective study including patients with high-risk proliferative diabetic retinopathy and no prior laser treatment randomly assigned to receive panretinal photocoagulation (PRP group) or panretinal photocoagulation plus intravitreal ranibizumab (PRPplus group). In all patients, panretinal photocoagulation was administered in two sessions (weeks 0 and 2), and intravitreal ranibizumab was administered at the end of the first laser session in the PRPplus group. Retreatment was performed at weeks 16 and 32 if active new vessels were detected at fluorescein angiography. Patients in the PRPplus group received intravitreal ranibizumab and patients in the PRP group received 500-µm additional spots per quadrant of active new vessels. After the end of retreatment, a 100-degree Visual Analog Scale was used for pain score estimation. The patient was asked about the intensity of pain during the whole procedure (retinal photocoagulation session or intravitreal ranibizumab injection). Statistics for pain score comparison were performed using a non-parametric test (Wilcoxon rank sums).

RESULTS: Seventeen patients from PRPplus and 14 from PRP group were evaluated for pain scores. There were no significant differences between both groups regarding gender, glycosylated hemoglobin and disease duration. Mean intravitreal injection pain (±SEM) was 4.7 ± 2.1 and was significantly lower ($p<0.0001$) than mean panretinal photocoagulation pain (60.8 ± 7.8). Twelve out of 17 patients from the PRPplus group referred intensity pain score of zero, while the minimal score found in PRP group was found in one patient with 10.5.

CONCLUSION: In patients with high-risk proliferative diabetic retinopathy who needed retreatment for persistent new vessels, there was more comfort for the patient when retreatment was performed with an intravitreal injection in comparison with retinal photocoagulation. Further larger studies are necessary to confirm our preliminary findings.

PMID: 23812521 [PubMed - in process]

Am J Ophthalmol. 2013 Jun 27. pii: S0002-9394(13)00285-7. doi: 10.1016/j.ajo.2013.03.041. [Epub ahead of print]

Choroidal Thickness Changes After Intravitreal Ranibizumab and Photodynamic Therapy in Recurrent Polypoidal Choroidal Vasculopathy.

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PURPOSE: To evaluate subfoveal choroidal thickness changes in cases with recurrent polypoidal choroidal vasculopathy (PCV) after combination therapy with intravitreal ranibizumab and photodynamic therapy (PDT).

DESIGN: Retrospective observational case series study.

METHODS: We measured subfoveal choroidal thickness in PCV using optical coherence tomography (OCT) before and after PDT. In recurrent cases, the choroidal thickness was measured at the time of the recurrence. In nonrecurrent cases, choroidal thickness was measured 1 year after PDT.

RESULTS: Combination therapy was performed in 27 eyes (27 patients). Polypoidal lesions regressed within 3 months after initial treatment in all eyes. Retreatment was needed in 10 of 27 eyes (37.0%) after more than 3 months of follow-up. In recurrent cases, subfoveal choroid decreased from 188 μm at baseline to 157 μm 3 months after PDT ($P < .01$); however, choroidal thickness increased to 179 μm with recurrence ($P = .54$ compared to baseline; average, 8.0 months). In nonrecurrent cases, subfoveal choroid decreased from 257 μm at baseline to 210 μm 3 months after PDT and 212 μm 1 year after PDT ($P < .01$, respectively).

CONCLUSION: Subfoveal choroidal thickness in PCV at the time of recurrence returned to the baseline level after choroidal thinning as a result of PDT treatment. Choroidal thickness changes after PDT examined using OCT may reflect disease activity in PCV.

PMID: 23810474 [PubMed - as supplied by publisher]

Other treatment and diagnosis

Acta Ophthalmol. 2013 Jul 2. doi: 10.1111/aos.12234. [Epub ahead of print]

Prediction of retinal pigment epithelial tear in serous vascularized pigment epithelium detachment.

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Purpose: The aim of the study was to identify predictive factors for detection of impending retinal pigment epithelium (RPE) tears in patients under anti-VEGF therapy for treatment of retinal pigment epithelial detachment (PED) due to exudative age-related macular degeneration (AMD) using near-infrared reflectance imaging (NIR), spectral-domain optical coherence tomography (SD-OCT) and fluorescein angiography (FLA).

Methods: We retrospectively evaluated NIR, SD-OCT and FLA images, number of intravitreal injections as well as demographical data of 103 eyes of 98 patients with vascularized PED [48.5% fibrovascular PED (fPED), 51.5% serous vascularized PED (svPED)] secondary to AMD.

Results: Fifteen eyes with svPED of 103 included eyes (14.6%) developed an RPE tear under anti-VEGF

therapy. Prior to RPE tear formation, we could identify radial hyperreflective lines spreading in a funnel-like pattern across the PED lesion in NIR images in 11 eyes correlating with folds in the RPE on corresponding SD-OCT scans (mean observation period: 115.4 ± 66.6 days; mean number of injections: 3.2 ± 1.5; mean PED height 828.2 ± 356.5 µm). In nine RPE tears (81.8%), the edge of the tear could be clearly localized on the opposite side of the PED lesion in relation to the origin of hyperreflective lines. None of the fPED patients showed the described signal.

Conclusions: Patients under anti-VEGF therapy for treatment of svPED due to AMD frequently show radial hyperreflective lines in NIR images prior to RPE tear development that correspond to wrinkled changes in the RPE. Hyperreflective lines may serve as an indicator for an impending RPE tear in svPED patients.

PMID: 23819839 [PubMed - as supplied by publisher]

Optom Vis Sci. 2013 Jun 27. [Epub ahead of print]

Patient and Public Preferences for Health States Associated with AMD.

Butt T, Dunbar HM, Morris S, Orr S, Rubin GS.

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PURPOSE: Health utility values suitable for calculating quality-adjusted life-years are increasingly used to assess the cost-effectiveness of treatments for age-related macular degeneration (AMD). In the United States, health utilities are usually derived from the patients' own valuation or modeled using visual acuity as a surrogate outcome. In the United Kingdom and throughout Europe, health utilities are derived from public valuations. Our aim was to test if utility values for health states associated with AMD elicited directly from patients were different from those calculated from public tariffs for health-related quality of life (HRQoL) questionnaires.

METHODS: Generic preference-based HRQoL questionnaires (EQ-5D and SF-6D) and the time trade-off (TTO) and visual analog scale (VAS) valuation techniques were administered to a sample of UK patients with AMD (N = 60). Health utilities were calculated using standard general population tariffs for the patient EQ-5D and SF-6D health states and directly from patient TTO and VAS scores.

RESULTS: Mean utilities derived from the public tariffs were significantly higher than from patients' valuation (mean [±SD], 0.613 (±0.275) for the EQ-5D and 0.628 (±0.114) for the SF-6D compared with 0.481 [±0.411] for the TTO and 56.7 [±21.8] for the VAS score; $p < 0.001$). The EQ-5D was not significantly different from the SF-6D ($p > 0.6$). Visual acuity in the better seeing eye was not associated with any utility measure (all $r < 0.08$; $p > 0.2$).

CONCLUSIONS: Patient and public preferences for health states associated with AMD are different, with patients valuing their health state more severely than the public tariffs of commonly used HRQoL questionnaires. Visual acuity did not predict health utility using any measure, and therefore, care should be taken when using visual acuity as a surrogate measure for utility in health economic analyses.

PMID: 23811607 [PubMed - as supplied by publisher]

Photomed Laser Surg. 2013 Jun 29. [Epub ahead of print]

Laser Photobiomodulation as a Potential Multi-Hallmark Therapy for Age-Related Macular Degeneration.

Rodríguez-Santana E, Santana-Blank L.

Fundalas, Foundation for Interdisciplinary Research and Development , Caracas, Venezuela .

PMID: 23808767 [PubMed - as supplied by publisher]

Pathogenesis

PLoS One. 2013 Jun 27;8(6):e68173. Print 2013.

A Novel Platelet-Activating Factor Receptor Antagonist Inhibits Choroidal Neovascularization and Subretinal Fibrosis.

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Abstract: Choroidal neovascularization (CNV) is a critical pathogenesis in age-related macular degeneration (AMD), the most common cause of blindness in developed countries. To date, the precise molecular and cellular mechanisms underlying CNV have not been elucidated. Platelet-activating factor (PAF) has been previously implicated in angiogenesis; however, the roles of PAF and its receptor (PAF-R) in CNV have not been addressed. The present study reveals several important findings concerning the relationship of the PAF-R signaling with CNV. PAF-R was detected in a mouse model of laser-induced CNV and was upregulated during CNV development. Experimental CNV was suppressed by administering WEB2086, a novel PAF-R antagonist. WEB2086-dependent suppression of CNV occurred via the inhibition of macrophage infiltration and the expression of proangiogenic (vascular endothelial growth factor) and proinflammatory molecules (monocyte chemotactic protein-1 and IL-6) in the retinal pigment epithelium-choroid complex. Additionally, WEB2086-induced PAF-R blockage suppresses experimentally induced subretinal fibrosis, which resembles the fibrotic subretinal scarring observed in neovascular AMD. As optimal treatment modalities for neovascular AMD would target the multiple mechanisms of AMD-associated vision loss, including neovascularization, inflammation and fibrosis, our results suggest PAF-R as an attractive molecular target in the treatment of AMD.

PMID: 23826375 [PubMed - as supplied by publisher]

PLoS One. 2013 Jun 25;8(6):e67894. doi: 10.1371/journal.pone.0067894. Print 2013.

Alternative complement pathway deficiency ameliorates chronic smoke-induced functional and morphological ocular injury.

Woodell A, Coughlin B, Kunchithapautham K, Casey S, Williamson T, Ferrell WD, Atkinson C, Jones BW, Rohrer B.

Division of Research, Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina, United States of America.

BACKGROUND: Age-related macular degeneration (AMD), a complex disease involving genetic variants and environmental insults, is among the leading causes of blindness in Western populations. Genetic and histologic evidence implicate the complement system in AMD pathogenesis; and smoking is the major environmental risk factor associated with increased disease risk. Although previous studies have demonstrated that cigarette smoke exposure (CE) causes retinal pigment epithelium (RPE) defects in mice, and smoking leads to complement activation in patients, it is unknown whether complement activation is causative in the development of CE pathology; and if so, which complement pathway is required.

METHODS: Mice were exposed to cigarette smoke or clean, filtered air for 6 months. The effects of CE

were analyzed in wildtype (WT) mice or mice without a functional complement alternative pathway (AP; CFB(-/-)) using molecular, histological, electrophysiological, and behavioral outcomes.

RESULTS: CE in WT mice exhibited a significant reduction in function of both rods and cones as determined by electroretinography and contrast sensitivity measurements, concomitant with a thinning of the nuclear layers as measured by SD-OCT imaging and histology. Gene expression analyses suggested that alterations in both photoreceptors and RPE/choroid might contribute to the observed loss of function, and visualization of complement C3d deposition implies the RPE/Bruch's membrane (BrM) complex as the target of AP activity. RPE/BrM alterations include an increase in mitochondrial size concomitant with an apical shift in mitochondrial distribution within the RPE and a thickening of BrM. CFB(-/-) mice were protected from developing these CE-mediated alterations.

CONCLUSIONS: Taken together, these findings provide clear evidence that ocular pathology generated in CE mice is dependent on complement activation and requires the AP. Identifying animal models with RPE/BrM damage and verifying which aspects of pathology are dependent upon complement activation is essential for developing novel complement-based treatment approaches for the treatment of AMD.

PMID: 23825688 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2013 Jul 2. pii: iovs.13-12194v1. doi: 10.1167/iovs.13-12194. [Epub ahead of print]

Subjects with unilateral neovascular AMD have bilateral delays in rod-mediated phototransduction activation kinetics and in dark adaptation recovery.

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PURPOSE: To assess the impact of both dry and wet (neovascular) age-related macular degeneration (AMD) on panretinal function.

METHODS: Light- and dark-adapted full-field electroretinogram (ERG) recordings were obtained over a 5-log-unit intensity range from both eyes of 25 patients with unilateral wet AMD. Fellow eyes showed various signs of dry AMD ranging from multiple medium-sized drusen to non-central geographic atrophy. The leading edges of rod-isolated ERG a-waves were fitted to a quantitative model of phototransduction. ERG a - and b-wave amplitudes and implicit times were compared between wet and dry AMD eyes and from non-AMD eyes of age-matched subjects. A quantitative and objective assessment of dark adaptation was achieved by recording the recovery of the pure rod b-wave (post-synaptic depolarization of rod bipolar cells); b-wave amplitudes were measured at 120-second intervals for 20 min. and normalized to the amplitude recorded at t=20 min.

RESULTS: Delays in mixed a- and b-waves implicit times were recorded in both wet and dry AMD eyes. Time required to reach 50% of fully recovered responses was delayed in all wet and dry AMD eyes independently of dry AMD severity in the fellow eye. Generalized cone dysfunction and slower activation of the rod phototransduction cascade was noted in a subgroup of patients with advanced features of dry AMD in the fellow eye.

CONCLUSIONS: Patients with unilateral wet AMD display rod dysfunction in both their wet and dry AMD eyes. A subset of these patients display, in addition, bilateral cone dysfunction and delayed rod phototransduction activation, which may either reflect extensive morphologic change in advanced stages of AMD and/or represent a distinct phenotypic manifestation within the heterogeneous context of AMD as a disease.

PMID: 23821195 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Jul 2. pii: iovs.13-12122v1. doi: 10.1167/iovs.13-12122. [Epub ahead of print]

Age-dependent changes in FasL (CD95L) modulate macrophage function in a model of age-related macular degeneration.

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PURPOSE: Examine the effect of aging on FasL function in a mouse model of choroidal neovascularization (CNV).

METHODS: Young and aged mice were laser treated to induce CNV. Bone marrow chimeras were performed between young and aged mice. FasL protein expression was examined in the eye and soluble FasL (sFasL) was measured in the blood. Young and aged mice were treated with a matrix metalloprotease (MMP) inhibitor and systemic sFasL was neutralized by antibody treatment. Macrophages from young and aged mice were tested for sFasL mediated cytokine production and migration.

RESULTS: The elevated CNV response observed with aging was dependent on bone marrow derived cells. FasL expression in the eye was increased with age but decreased following laser treatment. Aged mice had higher levels of sFasL in the blood compared to young mice. Systemic treatment with an MMP inhibitor decreased blood-borne sFasL and reduced CNV in young and aged mice. Systemic neutralization of sFasL reduced CNV only in aged mice. sFasL increased cytokine production in aged macrophages and proangiogenic M2 macrophages. Aged M2 macrophages had elevated Fas (CD95) expression and displayed increased migration in response to sFasL compared to M1 macrophages derived from young animals.

CONCLUSIONS: Age modulates FasL function where increased MMP cleavage leads to a loss of function in the eye. The released form of FasL (sFasL) preferentially induces the migration of proangiogenic M2 macrophages into the laser lesions and increases pro-angiogenic cytokines promoting CNV. FasL may be a viable target for therapeutic intervention in aged-related neovascular disease.

PMID: 23821188 [PubMed - as supplied by publisher]

Epidemiology

Br J Ophthalmol. 2013 Jun 28. [Epub ahead of print]

Incidence and baseline clinical characteristics of treated neovascular age-related macular degeneration in a well-defined region of the UK.

Keenan TD, Kelly SP, Sallam A, Mohamed Q, Tufail A, Johnston RL.

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AIMS: To analyse the incidence and baseline clinical characteristics of patients with neovascular age-related macular degeneration (nAMD) treated with intravitreal anti-vascular endothelial growth factor (VEGF) injections in a defined UK region.

METHODS: A standardised dataset was collected prospectively using an electronic medical record (EMR) system from 1 January 2008 to 21 June 2012 for all patients living in Gloucestershire who received intravitreal anti-VEGF injections for nAMD.

RESULTS: Over the study period, 1207 eyes from 1033 patients began intravitreal anti-VEGF injections for

nAMD. The annual incidence in the years after National Institute for Health and Care Excellence (NICE) technology appraisal 155 implementation was stable at 120 (95% CI 110 to 138) eyes or 100 (89 to 115) people per 100 000 population. The most common indication was occult choroidal neovascularisation (51%). Median baseline visual acuity (VA) was significantly higher for second treated than first treated eyes (66 and 56 letters, respectively; p<0.0001). Median baseline VA of fellow eyes increased from 47 (2008) to 67 letters (2012; p<0.005). The proportion of patients with baseline VA in the better eye ≥70 letters increased from 27.6% (2008) to 51.4% (2012; p<0.0001), while the proportion eligible at baseline for full or partial certificate of visual impairment decreased from 13.8% (2008) to 7.1% (2012; p<0.05).

CONCLUSIONS: The incidence of patients undergoing anti-VEGF therapy for nAMD increased substantially following NICE approval of ranibizumab (August 2008), and has been stable since 2009. This equates to an annual UK incidence of 26 850 (21 320 to 32 440) eyes, similar to NICE estimates. Patients eligible for blindness certification before treatment decreased by half from 2008-2012. Prospective data collection using an EMR system is invaluable for efficient monitoring of real-world clinical care.

PMID: 23813420 [PubMed - as supplied by publisher]

Front Aging Neurosci. 2013 Jun 28;5:24. doi: 10.3389/fnagi.2013.00024. Print 2013.

Retinal iron homeostasis in health and disease.

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Abstract: Iron is essential for life, but excess iron can be toxic. As a potent free radical creator, iron generates hydroxyl radicals leading to significant oxidative stress. Since iron is not excreted from the body, it accumulates with age in tissues, including the retina, predisposing to age-related oxidative insult. Both hereditary and acquired retinal diseases are associated with increased iron levels. For example, retinal degenerations have been found in hereditary iron overload disorders, like aceruloplasminemia, Friedreich's ataxia, and pantothenate kinase-associated neurodegeneration. Similarly, mice with targeted mutation of the iron exporter ceruloplasmin and its homolog hephaestin showed age-related retinal iron accumulation and retinal degeneration with features resembling human age-related macular degeneration (AMD). Post mortem AMD eyes have increased levels of iron in retina compared to age-matched healthy donors. Iron accumulation in AMD is likely to result, in part, from inflammation, hypoxia, and oxidative stress, all of which can cause iron dysregulation. Fortunately, it has been demonstrated by in vitro and in vivo studies that iron in the retinal pigment epithelium (RPE) and retina is chelatable. Iron chelation protects photoreceptors and retinal pigment epithelial cells (RPE) in a variety of mouse models. This has therapeutic potential for diminishing iron-induced oxidative damage to prevent or treat AMD.

PMID: 23825457 [PubMed]

Arq Bras Oftalmol. 2013 Apr;76(2):80-4.

Risk factors of age-related macular degeneration in Argentina.

Nano ME, Lansingh VC, Pighin MS, Zarate N, Nano H, Carter MJ, Furtado JM, Nano CC, Vernengo LF, Luna JD, Eckert KA.

PURPOSES: To assess the risk factors of age-related macular degeneration in Argentina using a case-control study.

METHODS: Surveys were used for subjects' antioxidant intake, age/gender, race, body mass index,

hypertension, diabetes (and type of treatment), smoking, sunlight exposure, red meat consumption, fish consumption, presence of age-related macular degeneration and family history of age-related macular degeneration. Main effects models for logistic regression and ordinal logistic regression were used to analyze the results.

RESULTS: There were 175 cases and 175 controls with a mean age of 75.4 years and 75.5 years, respectively, of whom 236 (67.4%) were female. Of the cases with age-related macular degeneration, 159 (45.4%) had age-related macular degeneration in their left eyes, 154 (44.0%) in their right eyes, and 138 (39.4%) in both eyes. Of the cases with age-related macular degeneration in their left eyes, 47.8% had the dry type, 40.3% had the wet type, and the type was unknown for 11.9%. The comparable figures for right eyes were: 51.9%, 34.4%, and 13.7%, respectively. The main effects model was dominated by higher sunlight exposure (OR [odds ratio]: 3.3) and a family history of age-related macular degeneration (OR: 4.3). Other factors included hypertension (OR: 2.1), smoking (OR: 2.2), and being of the Mestizo race, which lowered the risk of age-related macular degeneration (OR: 0.40). Red meat/fish consumption, body mass index, and iris color did not have an effect. Higher age was associated with progression to more severe age -related macular degeneration.

CONCLUSION: Sunlight exposure, family history of age-related macular degeneration, and an older age were the significant risk factors. There may be other variables, as the risk was not explained very well by the existing factors. A larger sample may produce different and better results.

PMID: 23828466 [PubMed - in process]

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Unrecognized and unregistered blindness in people 70 or older in Jing'an district, Shanghai, China.

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AIM: To evaluate the efficacy of a registration system for the blind people and to monitor the blindness due to uncorrected refractive error and cataract in Jing'an district, Shanghai, China.

METHODS: Five hundred and ten blind people, based on visual acuity screening in a population aged 70 or older were enrolled into the study. Four hundred and forty subjects were interviewed. The following data were collected on each patient: demographic data, number of hospital visits for eye related problems, distance visual acuity, visual fields, ophthalmic diagnoses, education and registration status. If the eligible subject was not registered as blind, the reason for non-registration was recorded.

RESULTS: Ten point nine one percent blindness was due to cataract, 27.5% due to uncorrected refractive error, and only 61.59% met the eligible blindness criteria (uncorrected refractive error and cataract are not considered as eligible blindness). The first four leading causes of eligible blindness were age related macular degeneration (25.09%), myopic macular degeneration (21.40%), glaucoma (18.82%) and corneal disease (8.12%). Only 68.27% eligible blind people were registered. The patients with macular degeneration and glaucoma tended not to register. Blind people with an above primary school education were 2.59 times more likely to be registered than those who were illiterate or had only a primary school education (OR=2.59, 95%CI: 1.49-4.48, P<0.01). Patients who had 4 or more visits to the hospital requesting eye care services in a year were 2.2 times more likely to be registered than those with less than 4 visits to the hospital (OR=2.54, 95%CI: 1.47-4.38, P<0.001). The first two leading reasons of misregistration were unknowing the registration system (48%) and unwilling to register (21%).

CONCLUSION: Under-registration of the eligible blind people exists in the registry system. Education and the number of hospital visits for eye care services were factors associated with registration levels.

Uncorrected refractive error and cataract are important causes of blindness.

PMID: 23826526 [PubMed]

Mil Med. 2013 Jul;178(7):811-5. doi: 10.7205/MILMED-D-12-00537.

Veteran eye disease after eligibility reform: prevalence and characteristics.

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PURPOSE: To determine the prevalence of eye disease in new "routine" eye patients at the Atlanta Veteran Affairs Medical Center. Design: Retrospective chart review of all new eye patients seen in the Atlanta Veteran Affairs Medical Center Comprehensive Eye Clinic over a 2-month period (January 1, 2008-February 28, 2008).

PARTICIPANTS: 691 charts met inclusion criteria, with 33 charts excluded for insufficient documentation in the medical record. This left a total of 658 charts for the study.

METHODS: Charts were reviewed for the following information: demographic data, vision, ocular diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification codes), and planned minor/laser/incisional surgical procedures. Additional data collected included whether glasses were prescribed and legal blindness.

MAIN OUTCOME MEASURES: Vision-threatening ocular diagnoses and need for minor/laser/incision surgery were tabulated.

RESULTS:There was a very high prevalence of potentially blinding disease in this population of new "routine" eye patients. About 63.4% of veterans were diagnosed with at least one ocular diagnosis other than refractive error; 25% had glaucoma or were suspects, 6% had cataracts, 5% had age-related macular degeneration, and 8% required a surgical procedure.

CONCLUSION: The rate of ocular pathology is high in the veteran population.

PMID: 23820357 [PubMed - in process]

Genetics

Cerebellum. 2013 Jul 5. [Epub ahead of print]

Origin of the Spinocerebellar Ataxia Type 7 Gene Mutation in Mexican Population.

Magaña JJ, Gómez R, Maldonado-Rodríguez M, Velázquez-Pérez L, Tapia-Guerrero YS, Cortés H, Leyva-García N, Hernández-Hernández O, Cisneros B.

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Abstract: Spinocerebellar ataxia type 7 (SCA7) is a neurodegenerative disorder characterized by progressive cerebellar ataxia associated with macular degeneration that leads, in the majority of patients, to loss of autonomy and blindness. The cause of the disease has been identified as (CAG) n repeat expansion in the coding sequence of the ATXN7 gene on chromosome 3p21.1. SCA7 is one of the least common genetically verified autosomal dominant cerebellar ataxias found worldwide; however, we previously identified the Mexican population showing high prevalence of SCA7, suggesting the occurrence

of a common founder effect. In this study, haplotype analysis using four SCA7 gene-linked markers revealed that all 72 SCA7 carriers studied share a common haplotype, A-254-82-98, for the intragenic marker 3145G/A and centromeric markers D3S1287, D3S1228, and D3S3635, respectively. This multiloci combination is uncommon in healthy relatives and Mexican general population, suggesting that a single ancestral mutation is responsible for all SCA7 cases in this population. Furthermore, genotyping using 17 short tandem repeat markers from the non-recombining region of the Y chromosome and further phylogenetic relationship analysis revealed that Mexican patients possess the Western European ancestry, which might trace the SCA7 ancestral mutation to that world region.

PMID: 23828024 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2013 Mar-Apr;129(2):86-90.

[Molecular genetic basis of age-related macular degeneration].[Article in Russian]

Abstract: Visual loss due to age-related macular degeneration (AMD) is caused by one or both forms of advanced disease: "wet" (neovascular) or "dry" (geographic atrophy). Immune system plays a central role in pathogenesis and progression of both AMD forms. Main genetic polymorphisms associated with risk of AMD development and progression were found to be genes that regulate inflammation especially in complement factor H gen (1q31 locus) and 10q26 locus (PLEKHAI/ARMS2/HTRA1). Association of response to treatment and genotype was shown in patients with AMD. Complete characterization of both common and rare alleles that influence AMD risk is necessary for accurate determination of individual genetic risk as well as identification of new targets for therapeutic intervention.

PMID: 23808188 [PubMed - in process]

Diet

Nutrients. 2013 Jul 2;5(7):2405-56. doi: 10.3390/nu5072405.

Diminishing risk for age-related macular degeneration with nutrition: a current view.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly. Clinical hallmarks of AMD are observed in one third of the elderly in industrialized countries. Preventative interventions through dietary modification are attractive strategies, because they are more affordable than clinical therapies, do not require specialists for administration and many studies suggest a benefit of micro- and macro-nutrients with respect to AMD with few, if any, adverse effects. The goal of this review is to provide information from recent literature on the value of various nutrients, particularly omega-3 fatty acids, lower glycemic index diets and, perhaps, some carotenoids, with regard to diminishing risk for onset or progression of AMD. Results from the upcoming Age-Related Eye Disease Study (AREDS) II intervention trial should be particularly informative.

PMID: 23820727 [PubMed - in process]

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Prevention of retinal light damage by zinc oxide combined with rosemary extract.

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PURPOSE: Zinc oxide effectively reduces visual cell loss in rats exposed to intense visible light and is known to slow the rate of disease progression in advanced stages of age-related macular degeneration. Our goal was to determine the efficacy of zinc oxide in combination with novel and well-established antioxidants in an animal model of light-induced oxidative retinal damage.

METHODS: One group of male Sprague-Dawley rats was pretreated with zinc oxide with or without a detergent extract of rosemary powder and then exposed to intense visible light for 4-24 h. Another group of animals received zinc oxide combined with rosemary oil diluted with a mixture of polyunsaturated fatty acids (ROPUFA) and a third group was given an antioxidant mineral mix containing zinc oxide, as recommended by the Age Related Eye Disease Study group's first clinical trial (AREDS1). Visual cell survival was determined 2 weeks after intense light treatment by measuring rhodopsin and photoreceptor cell DNA levels and confirmed by retinal histology and agarose gel electrophoresis of DNA. Western analysis was used to determine the effects of zinc and antioxidants on the oxidative stress markers, glial fibrillary acidic protein (GFAP), heme-oxygenase-1 (HO-1), and carboxyethylpyrrole (CEP). Rod and cone opsin and arrestin levels were used as markers of photoreceptor cell function.

RESULTS: Dark-reared rats treated with 1.3 mg/kg zinc oxide and 17 mg/kg rosemary extract, or with one-half those doses, and exposed to moderate intensity green light retained 75%-85% of the rhodopsin and retinal DNA measured in unexposed rats. These levels were significantly higher than found for zinc oxide or rosemary treatment alone. Rosemary oil was also effective when combined with zinc oxide, but ROPUFA alone was no more effective than the detergent vehicle. Prolonged intense green light led to increases in retinal GFAP and HO-1 levels and to decreases in cone cell opsin and rod and cone arrestins. Rosemary plus zinc treatment reduced the expression of oxidative stress protein markers and enhanced visual cell survival, as shown by improved photoreceptor cell morphology and by decreased retinal DNA degradation. Using higher intensity white light for exposures in cyclic light-reared rats, treatment with an AREDS antioxidant/mineral mixture was found to be ineffective, whereas rosemary extract plus an equivalent dose of zinc oxide was significantly more effective in preserving visual cells. CEP protein adduct formation was reduced by all antioxidant treatments, but rosemary plus zinc oxide also prevented the loss of cone cell opsin and arrestin more effectively than AREDS.

CONCLUSIONS: In the rat model of acute retinal light damage, zinc oxide combined with a detergent extract of rosemary powder or rosemary oil is more effective than treatment with either component alone and significantly more effective than an AREDS mixture containing a comparable dose of zinc oxide. Light-induced oxidative stress in animal models of retinal degeneration can be a useful preclinical paradigm for screening novel antioxidants and for testing potential therapeutics designed to slow the progression of age-related ocular disease.

PMID: 23825923 [PubMed - as supplied by publisher]

Arq Bras Oftalmol. 2013 Feb;76(1):1-5.

[Increased VEGFR-1 immunoreactivity in the choroid-scleral complex in hypercholesterolemia experimental model].[Article in Portuguese]

Torres RJ, Noronha Ld, Casella AM, Torres Rdo R, Martins Ide C, Zotz R, Luchini A, Hoffmann Filho CR, Précoma DB.

PURPOSE: The aim of this study is to investigate the expression of vascular endothelial growth factor (VEGF) in the choroid and sclera using hypercholesterolemia experimental model.

METHODS: New Zealand rabbits were divided into two groups: 8 rabbits (8 eyes), in the normal diet group (NG), were fed by a standard diet for 4 weeks; and 13 rabbits (13 eyes), in the hypercholesterolemic group (HG), were fed by a 1% cholesterol-enriched diet for 8 weeks. Total serum cholesterol, triglyceride, HDL cholesterol and fasting blood glucose exams were performed at the initiation of the experiment and at the euthanasia time. After hypercholesterolemic group 8th week and NG 4th week, animals were euthanized and their eyes underwent immunohistochemical analysis with the RAM-11 and VEGFR-1).

RESULTS: The diet has induced a significant increase in total cholesterol and triglyceride levels in HG when compared with NG ($p<0.001$). There was a significant increase in the RAM-11 and VEGFR-1 expressions in hypercholesterolemic group choroid and sclera in relation to NG ($p<0,001$).

CONCLUSION: This study has revealed that the hypercholesterolemic diet in rabbits induces an increase in the macrophage concentration and immunoreactivity to VEGFR-1 in the choroid and sclera, resembling human age-related macular degeneration (ARMD).

PMID: 23812517 [PubMed - in process]

Vestn Oftalmol. 2013 Mar-Apr;129(2):74-8, 80.

[Efficacy of vitamin mineral complex "Focus forte" in combined treatment of primary open-angle glaucoma and age-related macular degeneration]. [Article in Russian]

[No authors listed]

Abstract: The efficacy of Focus forte is proved in patients with primary open-angle glaucoma (POAG) and age-related macular degeneration (AMD) in terms of improvement of functional retinal activity, oxygenation, metabolism normalization as well as morphometric retinal and optic nerve indices. Principles of evidence based pharmacotherapy in this study allow advising Focus forte in the treatment of patients with POAG and AMD.

PMID: 23808186 [PubMed - in process]