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MD Research News

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Drug treatment

Br J Ophthalmol. 2013 Feb 21. [Epub ahead of print]

Results of 2 years of treatment with as-needed ranibizumab reinjection for polypoidal choroidal vasculopathy.

Hikichi T, Higuchi M, Matsushita T, Kosaka S, Matsushita R, Takami K, Ohtsuka H, Kitamei H, Shioya S.

Ohtsuka Eye Hospital, Sapporo, Japan.

PURPOSE: To investigate the 2-year outcomes of three monthly intravitreal ranibizumab injections followed by as-needed reinjections to treat polypoidal choroidal vasculopathy (PCV).

METHODS: Seventy-five consecutive eyes with naïve symptomatic PCV with 2 years of follow-up after treatment were studied prospectively.

RESULTS: The mean (±SD) numbers of injections were 4.2±1.3 that included three monthly injections in the loading phase and 1.6±1.7 during years 1 and 2, respectively (mean 2-year total, 5.6±1.9). The baseline logarithm of the minimum angle of resolution visual acuity (VA) was 0.59±0.51 that improved significantly (p=0.001 for both comparisons) to 0.37±0.33 and 0.41±0.40 at 1 and 2 years, respectively, after the first injection. Although no significant difference was found between years 1 and 2 after the first injection, the VA tended to decrease slightly during year 2. The improved foveal thickness was maintained during year 2. Thirty (40%) eyes and 19 (25%) eyes, respectively, at years 1 and 2 after the first injection had no polypoidal lesions on indocyanine green angiography. A branching vascular network (BVN) remained in all eyes 2 years after the first injection and tended to increase in size during year 2.

CONCLUSIONS: The 2-year outcomes showed significant VA and foveal thickness improvements in eyes with PCV. During year 2, the magnitude of the improvement was lower compared with year 1. An as-needed reinjection schedule might not prevent polypoidal lesions or BVNs from regrowing. Further investigations should establish a treatment strategy for PCV.

PMID: 23428984 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Feb 22. [Epub ahead of print]

Retreatment by series of three intravitreal injections of ranibizumab in neovascular age-related macular degeneration: long-term outcomes.

Saleh M, Kheliouen M, Tebeanu E, Ballonzoli L, Bourcier T, Speeg-Schatz C, Gaucher D.

Department of Ophthalmology, University Hospital Jean Minjoz of Besançon, Franche-Comté University, 25000, Besançon, France.

BACKGROUND: The purpose of this study was to analyze the results of a retreatment regimen using a series of three monthly intravitreal ranibizumab injections (IVR), instead of one injection, and to determine if this treatment scheme can safely reduce the number of injections and the number of visits compared to the widely used PrONTO study retreatment protocol.

METHODS: >Sixty-six eyes of 60 patients with exudative age-related macular degeneration (AMD) were included. The mean follow-up period was 27 months (range, 11-48 months). The mean age of the patients was 79 years (range, 65-93 years). All patients received three initial IVRs, and were retreated with a new series of three monthly IVRs when needed. The retreatment criteria were: visual loss of ≥5 ETDRS letters and/or signs of retinal exudation on OCT, new macular hemorrhage, expansion of new vessels. Follow-up visits were conducted 1 month after the last IVR of each series, and renewed on a monthly basis when no retreatment was required. Each visit included a comprehensive ophthalmological examination with BCVA measurement and OCT examination.

RESULTS: Mean VA did not improve during follow-up (53.18 letters at the initial visit versus 54.18 at the last visit, $p > 0.05$). However, VA stabilized or improved in 66.6 % of the eyes. A gain of ≥15 letters was observed in 28.8 % of eyes. On average, over 2 years, the number of IVRs was five per year, and the number of follow-up visits was four per year.

CONCLUSION: Even if no gain in VA is observed after 2 years, this treatment regimen reduces the number of IVRs and control visits. The proportion of patients with a VA gain of three lines or more was smaller than the one reported in the original PrONTO study, but higher than the rates reported in other studies implementing the PrONTO recommendations in everyday practice. The benefit of the three IVR retreatment scheme should be prospectively studied and compared to the PRN regimen.

PMID: 23430191 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2013 Feb 21:1-6. doi: 10.1001/jamaophthalmol.2013.2379. [Epub ahead of print]

Antibiotic Resistance of Ocular Surface Flora With Repeated Use of a Topical Antibiotic After Intravitreal Injection.

Yin VT, Weisbrod DJ, Eng KT, Schwartz C, Kohly R, Mandelcorn E, Lam WC, Daneman N, Simor A, Kertes PJ.

IMPORTANCE: Treatment with intravitreal (IVT) injections has increased during the last several years as evidence has accumulated demonstrating the efficacy of anti-vascular endothelial growth factor agents in the treatment of neovascular age-related macular degeneration (AMD) and various retinal vascular diseases. Although IVT injections are generally safe, infectious endophthalmitis is a rare but devastating complication, and the risk of morbidity and vision loss from endophthalmitis is high.

OBJECTIVE: To examine the change in antibiotic resistance of ocular surface flora with repeated prophylactic use of antibiotics after IVT injection for AMD. DESIGN AND SETTING Prospective, nonrandomized cohort study in 2 tertiary academic hospitals.

PARTICIPANTS: Patients 65 years and older with newly diagnosed AMD were recruited by 7 retinal specialists from July 1, 2010, through December 31, 2011. INTERVENTION The study group received topical moxifloxacin hydrochloride for 3 days after each monthly IVT injection.

MAIN OUTCOME MEASURE: Resistance to moxifloxacin and ceftazidime in cultured isolates at baseline and monthly for 3 months by change in minimal inhibitory concentration (MIC) of culture isolates was studied.

RESULTS: The study group consisted of 84 patients, and the control group had 94 patients. In the study group, the baseline adjusted MIC increased (from 1.04 to 1.25 μg/mL; P = .01) as did the MIC for 50% of isolates (MIC50) (from 0.64 to 1.00 μg/mL) and the MIC for 90% of isolates (MIC90) (from 0.94 to 4.00 μg/mL). In both groups, the culture-positive rate did not change significantly when adjusted for baseline. No significant change was found in the MIC level, culture-positive rate, MIC50 level, and MIC90 level in the control group. Subgroup analysis found diabetes mellitus to be noncontributory to both the MIC and culture-positive rate. No endophthalmitis or adverse events were reported.

CONCLUSIONS AND RELEVANCE: Repeated use of topical moxifloxacin after IVT injection significantly increases antibiotic resistance of ocular surface flora. We recommend that routine use of prophylactic antibiotics after IVT injection be discouraged.

PMID: 23430175 [PubMed - as supplied by publisher]

Curr Opin Ophthalmol. 2013 Feb 20. [Epub ahead of print]

Combination therapy for the treatment of neovascular age-related macular degeneration.

Englander M, Kaiser PK.

Cole Eye Institute, Cleveland, Ohio, USA.

PURPOSE OF REVIEW: To discuss the current combination treatments that involve existing as well as novel drugs that show promise for the treatment of neovascular age-related macular degeneration.

RECENT FINDINGS: Photodynamic therapy in combination with antivascular endothelial growth factor (VEGF) and steroids is currently used as a second-line therapy in patients not responding to monotherapy with anti-VEGF agents or in whom the treatment burden of monthly injections is too great. It is used as a primary therapy for idiopathic polypoidal choroidal vasculopathy. Radiation and antiplatelet-derived growth factor therapy show promising results and are currently under investigation.

SUMMARY: Using combination treatments that target other pathways involved in angiogenesis will hopefully improve on the results of current anti-VEGF agents and may result in greater visual improvement and more convenient dosing regimens.

PMID: 23429601 [PubMed - as supplied by publisher]

Ophthalmology. 2013 Feb 14. pii: S0161-6420(12)01090-1. doi: 10.1016/j.ophtha.2012.11.011. [Epub ahead of print]

Predictive Value in Retinal Vein Occlusions of Early Versus Late or Incomplete Ranibizumab Response Defined by Optical Coherence Tomography.

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PURPOSE: To determine if optical coherence tomography (OCT) at baseline or month 3 in the Treatment of Macular Edema following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) and Treatment of Macular Edema following Central Retinal Vein Occlusion: Evaluation of Efficacy and Safety (CRUISE) studies provides information that predicts visual outcome.

DESIGN: Post hoc analysis from 2 prospective, randomized, controlled clinical trials.

PARTICIPANTS: Three hundred ninety-seven patients from the BRAVO study and 392 patients from the

CRUISE study.

METHODS: Time-domain OCT imaging data were analyzed.

MAIN OUTCOME MEASURES: Mean change from baseline best-corrected visual acuity (BCVA) letter score at month 6 and month 12.

RESULTS: Among ranibizumab-treated patients, 71.2% (0.3 mg) and 78.5% (0.5 mg) in the CRUISE study and 79.1% (0.3 mg) and 84.7% (0.5 mg) in the BRAVO study had central foveal thickness (CFT) of 250 μm or less at month 3 and therefore were categorized as early ranibizumab responders. Early ranibizumab responders had excellent visual outcomes regardless of ranibizumab dose; mean improvement in BCVA letter score at 6 and 12 months was 15.0 to 16.5 (central retinal vein occlusion [CRVO]) and 17.4 to 19.1 (branch retinal vein occlusion [BRVO]). Late or incomplete ranibizumab responders with CRVO (CFT >250 μm at month 3) did not fare as well as early responders if they were treated with 0.3 mg ranibizumab (month 6, P = 0.012). At month 6, compared with ranibizumab-treated CRVO patients with resolved cystoid macular edema (CME) at month 3, those with persistent CME did worse, on average, and significantly so for 0.5 mg (13.1 vs. 18.6; P = 0.027). At baseline, subretinal fluid (SRF) was present in 57% of patients with CRVO and in 45% of patients with BRVO; its presence did not portend a poor outcome in patients treated with ranibizumab for whom SRF was eliminated in almost all by month 3.

CONCLUSIONS: At month 3 of ranibizumab treatment, OCT images provide predictive information for patients with CRVO, but not for those with BRVO. Visual outcome at months 6 and 12 was reduced in 0.5 mg ranibizumab-treated patients with CRVO who had persistent CME at month 3. It also was reduced in CRVO for those with CFT of more than 250 μm at month 3 who were treated with 0.3 mg ranibizumab. The findings suggest that late or incomplete responders may need careful follow-up.

PMID: 23415775 [PubMed - as supplied by publisher]

Immunotherapy. 2013 Feb;5(2):121-30. doi: 10.2217/imt.12.158.

Intravitreal aflibercept for neovascular age-related macular degeneration.

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Abstract: Neovascular age-related macular degeneration (AMD) is the leading cause of legal blindness in patients over the age of 50 in the western world. Intravitreally administered anti-VEGF drugs have been developed to halt neovascular growth in AMD. Randomized trials have demonstrated the excellent safety profile and significant benefit of anti-VEGF therapy in maintaining vision. Aflibercept (Eylea(®); Regeneron, NY, USA) is a soluble decoy receptor against VEGF that offers greater potency and binding affinity than other anti-VEGF drugs. Having received US FDA approval for neovascular AMD in November 2011, aflibercept given every 8 weeks after a loading dose was 'clinically equivalent' and statistically noninferior to the current FDA-approved therapy ranibizumab (Lucentis(®); Genentech, CA, USA), given every 4 weeks. This article discusses the clinical background of AMD, development of aflibercept, results of the clinical trials and the future role of aflibercept in ocular neovascular diseases.

PMID: 23413903 [PubMed - in process]

Am J Pathol. 2013 Feb 12. pii: S0002-9440(13)00045-X. doi: 10.1016/j.ajpath.2012.12.032. [Epub ahead of print]

VEGF-A Is Necessary and Sufficient for Retinal Neuroprotection in Models of Experimental Glaucoma.

Foxton R, Finkelstein A, Vijay S, Dahlmann-Noor A, Khaw PT, Morgan J, Shima D, Ng YS.

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Abstract: Vascular endothelial growth factor A (VEGF-A) is a validated therapeutic target in several angiogenic- and vascular permeability-related pathological conditions, including certain cancers and potentially blinding diseases, such as age-related macular degeneration and diabetic retinopathy. We and others have shown that VEGF-A also plays an important role in neuronal development and neuroprotection, including in the neural retina. Antagonism of VEGF-A function might, therefore, present a risk to neuronal survival as a significant adverse effect. Herein, we demonstrate that VEGF-A acts directly on retinal ganglion cells (RGCs) to promote survival. VEGF receptor-2 signaling via the phosphoinositide-3-kinase/Akt pathway was required for the survival response in isolated RGCs. These results were confirmed in animal models of staurosporine-induced RGC death and experimental hypertensive glaucoma. More important, we observed that VEGF-A blockade significantly exacerbated neuronal cell death in the hypertensive glaucoma model. Our findings highlight the need to better define the risks associated with use of VEGF-A antagonists in the ocular setting.

PMID: 23416159 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Feb;48(1):22-30. doi: 10.1016/j.jcjo.2012.11.012.

Evolving strategies in the management of diabetic macular edema: clinical trials and current management.

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Abstract: Diabetic macular edema (DME) is the leading cause of vision loss in the working-age population in developed countries. Management has traditionally consisted of focal/grid macular laser, according to the guidelines established by the Early Treatment of Diabetic Retinopathy Study. More recent prospective clinical trials examining the effect of intravitreal ranibizumab in the treatment of DME-most notably, READ-2, RESOLVE, RESTORE, RISE/RIDE, and DRCR.net protocol I-have demonstrated improved visual outcomes with pharmacologic targeting of vascular endothelial growth factor. Similar treatment benefits have also been noted in clinical trials evaluating intravitreal bevacizumab and aflibercept (BOLT and DA VINCI, respectively). Intravitreal steroids, particularly in refractory cases, continue to have a limited role in the management of DME. In patients with symptomatic visual loss, the treatment paradigm for DME has shifted toward intravitreal pharmacotherapeutics, principally anti-vascular endothelial growth factor therapy, and this review examines the clinical trials leading to this change.

PMID: 23419295 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2013 Jan 1;44(1):25-7. doi: 10.3928/23258160-20121221-08.

Acute anterior uveitis following intravitreal injection of bevacizumab.

Mozayan A, Farah S.

BACKGROUND AND OBJECTIVE: To report five cases of iritis after intravitreal injection of bevacizumab.

PATIENTS AND METHODS: The clinical charts of patients who received intravitreal injections of bevacizumab or ranibizumab from January 2009 to September 2011 by one physician were retrospectively reviewed.

RESULTS: A total of 1,097 injections of bevacizumab and 571 of ranibizumab were administered. Five patients developed acute anterior uveitis and presented with severe pain, photophobia, conjunctival injection, and anterior chamber reaction 2 to 24 hours after intravitreal injection of bevacizumab. All five patients were treated with topical corticosteroids with rapid resolution of the inflammation.

CONCLUSION: Although uncommon, acute iritis is a complication of intravitreal injection of bevacizumab.

PMID: 23418730 [PubMed - in process]

Clin Ophthalmol. 2013;7:321-7. doi: 10.2147/OPTH.S41556. Epub 2013 Feb 13.

Bevacizumab inhibits proliferation of choroidal endothelial cells by regulation of the cell cycle.

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BACKGROUND: The purpose of this study was to evaluate cell cycle changes in choroidal endothelial cells treated with varying doses of bevacizumab in the presence of a range of concentrations of vascular endothelial growth factor (VEGF). Bevacizumab, a drug widely used in the treatment of neovascular age-related macular degeneration, choroidal neovascularization, and proliferative diabetic retinopathy, neutralizes all isoforms of VEGF. However, the effect of intravitreal administration of bevacizumab on the choroidal endothelial cell cycle has not been established.

METHODS: Monkey choroidal endothelial (RF/6A) cells were treated with VEGF 50 ng/mL and escalating doses of bevacizumab 0.1-2 mg/mL for 72 hours. Cell cycle changes in response to bevacizumab were analyzed by flow cytometry and propidium iodide staining. Cell proliferation was measured using the WST-1 assay. Morphological changes were recorded by bright field cell microscopy.

RESULTS: Bevacizumab inhibited proliferation of choroidal endothelial cells by stabilization of the cell cycle in G0/G1 phase. Cell cycle analysis of VEGF-enriched choroidal endothelial cells revealed a predominant increase in the G2/M population (21.84%, P, 0.01) and a decrease in the G0/G1 phase population (55.08%, P, 0.01). Addition of escalating doses of bevacizumab stabilized VEGF-enriched cells in the G0/G1 phase (55.08%, 54.49%, 56.3%, and 64% [P, 0.01]) and arrested proliferation by inhibiting the G2/M phase (21.84%, 21.46%, 20.59%, 20.94%, and 16.1% [P, 0.01]). The increase in G0/G1 subpopulation in VEGF-enriched and bevacizumab-treated cells compared with VEGF-enriched cells alone was dose-dependent.

CONCLUSION: Bevacizumab arrests proliferation of VEGF-enriched choroidal endothelial cells by stabilizing the cell cycle in the G0/G1 phase and inhibiting the G2/M phase in a dose-dependent fashion.

PMID: 23430458 [PubMed - in process]

Other treatment & diagnosis

Curr Opin Ophthalmol. 2013 Feb 20. [Epub ahead of print]

Update on depression and age-related macular degeneration.

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PURPOSE OF REVIEW: This review updates the literature on depression in age-related macular degeneration (AMD). Treatment for AMD has been revolutionized since the 2004 review of depression and

AMD. New data describing the prevalence of depression in AMD, as well as novel interventions for managing depression in AMD, are discussed.

RECENT FINDINGS: Depression continues to be prevalent in AMD and new information is available on the pathways by which impaired vision leads to depression. Strategies for the treatment of depression in patients with impaired vision have evolved.

SUMMARY: AMD is still a major risk factor for depression and people with activity restriction due to vision loss are at greatest risk. An integrated approach to depression management in older adults with impaired vision may be the best course of action.

PMID: 23429599 [PubMed - as supplied by publisher]

Curr Opin Ophthalmol. 2013 Feb 20. [Epub ahead of print]

Optical coherence tomography - current and future applications.

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Department of Ophthalmology, New England Eye Center, Tufts Medical Center, Boston, Massachusetts, USA.

PURPOSE OF REVIEW: Optical coherence tomography (OCT) has revolutionized the clinical practice of ophthalmology. It is a noninvasive imaging technique that provides high-resolution, cross-sectional images of the retina, retinal nerve fiber layer and the optic nerve head. This review discusses the present applications of the commercially available spectral-domain OCT (SD-OCT) systems in the diagnosis and management of retinal diseases, with particular emphasis on choroidal imaging. Future directions of OCT technology and their potential clinical uses are discussed.

RECENT FINDINGS: Analysis of the choroidal thickness in healthy eyes and disease states such as age-related macular degeneration, central serous chorioretinopathy, diabetic retinopathy and inherited retinal dystrophies has been successfully achieved using SD-OCT devices with software improvements. Future OCT innovations such as longer-wavelength OCT systems including the swept-source technology, along with Doppler OCT and en-face imaging, may improve the detection of subtle microstructural changes in chorioretinal diseases by improving imaging of the choroid.

SUMMARY: Advances in OCT technology provide for better understanding of pathogenesis, improved monitoring of progression and assistance in quantifying response to treatment modalities in diseases of the posterior segment of the eye. Further improvements in both hardware and software technologies should further advance the clinician's ability to assess and manage chorioretinal diseases.

PMID: 23429598 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Feb 20. pii: iovs.12-9680v1. doi: 10.1167/iovs.12-9680. [Epub ahead of print]

Implicit processing of scene context in macular degeneration.

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PURPOSE: For normally sighted people, there is a general consensus that objects that appear in a congruent context (e.g. a hair dryer in a bathroom) are processed more accurately and/or more quickly than

objects in an incongruent context (e.g. a hair dryer in a corn field). We investigated whether people with AMD, who have impairments in recognizing objects embedded in complex scenes, can nevertheless take advantage of contextual information for object detection.

METHODS: 22 people with AMD and 18 age-matched, normally sighted controls took part in the study. They were tested in two tasks: (i) an object detection task in which a foreground target object was set within a congruent background or an incongruent background, with no information being given to the participants as to the relationship between the target and its background, and (ii) a task in which the participant had to explicitly state whether or not the foreground object was congruent with its background. A go/nogo paradigm was used in both tasks (i.e., a key press when the target is present and no key press when it is absent). The same participants, stimuli, and presentation conditions were used in both tasks.

RESULTS: In the context task the people with AMD exhibited higher accuracy when the target object was consistent with its background. However, they performed no better than chance in the explicit task. Normally sighted controls benefited from the congruent context in both tasks.

CONCLUSION: Our results suggest that when central vision is impaired (as in AMD), the contextual information captured by peripheral vision provides cues for object categorization.

PMID: 23425698 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2013 Feb;48(1):56-62. doi: 10.1016/j.jcjo.2012.09.017.

Courier: a better font for reading with age-related macular degeneration.

Tarita-Nistor L, Lam D, Brent MH, Steinbach MJ, González EG.

Vision Science Research Program, Toronto Western Hospital; Centre for Vision Research, York University.

OBJECTIVE: This study examines the reading performance of patients with age-related macular degeneration (AMD) using 4 readily available fonts.

DESIGN: Experimental study.

PARTICIPANTS: Twenty-four patients with bilateral AMD participated.

METHODS: Reading performance (reading acuity, critical print size, and maximum reading speed) was measured for all patients, using 4 versions of the MNRead charts. These charts were printed in the following fonts: Times New Roman (serif, proportionally spaced), Arial (sans serif, proportionally spaced), Courier (serif, mono spaced), and Andale Mono (sans serif, mono spaced).

RESULTS: Reading acuity was significantly better on the Courier chart (0.58±0.21 logMAR) and significantly worse on the Arial chart (0.69±0.20 logMAR) than on any of the other charts ($P<0.05$). A larger proportion of patients were able to read≥1 sentences on the Courier chart than on any of the other charts. Reading speed dropped below the limit for fluent reading first with the Arial chart. There was no difference in maximum reading speed with the 4 fonts, and differences in critical print size failed to reach significance ($P = 0.052$).

CONCLUSIONS: Font has an effect on the reading performance of patients with AMD at print sizes close to their reading acuity. Courier was the most advantageous and Arial the worst font for reading smaller print. This is contrary to the advice given by agencies for the blind.

PMID: 23419299 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2013 Feb 22;44(2):1-3. doi: 10.3928/23258160-20130213-01. [Epub ahead of print]

Spontaneous Combined Full-Thickness Retinal and Pigment Epithelium Macular Hole in Age-Related Macular Degeneration.

Panthier C, Querques G, Zerbib J, Souied EH.

Abstract: The authors describe a case of combined full-thickness retinal and pigment epithelium macular hole that spontaneously developed in the right eye of an 86-year-old woman with age-related macular degeneration (AMD). One year prior, the patient had been diagnosed with drusenoid pigment epithelium detachment (PED) in the right eye and geographic atrophy in the left eye. Full-thickness macular hole associated with PED and spontaneous rip of the retinal pigment epithelium (RPE) associated with macular hole have been previously reported in eyes with exudative AMD. However, the authors are unaware of any report of spontaneous full-thickness retinal and pigment epithelium hole at the macula in AMD. The pathogenic mechanisms of this unusual macular hole, which involves the full retinal thickness and RPE, may include stretching forces at the vitreomacular interface and pushing from within the PED.

PMID: 23413892 [PubMed - as supplied by publisher]

Drugs Aging. 2013 Feb 20. [Epub ahead of print]

Do Statins Have a Role in the Prevention of Age-Related Macular Degeneration?

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Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness worldwide for which preventative therapies are few. Evidence suggesting shared common risk factors and mirrored pathophysiology between cardiovascular disease and AMD led to the hypothesis that hydroxymethylglutaryl -CoA reductase inhibitors (statins) could be helpful in preventing AMD. For over a decade, observational studies have repeatedly investigated this hypothesis with conflicting conclusions. Although many reports conclude that statin use has no effect on the risk of AMD, no randomized controlled trial has yet been completed. Furthermore, relatively few studies factor characteristics of statin use into their analysis. A few studies have observed an incompletely explained protective effect against drusen, a funduscopic finding associated with AMD. Although there is insufficient evidence for a preventive effect of statins on dry AMD, there does seem to be stronger evidence against any effect on the development of exudative AMD. Overall, we find that there is insufficient evidence to conclude whether statin use is helpful in preventing AMD.

PMID: 23423861 [PubMed - as supplied by publisher]

Pathogenesis

Pigment Cell Melanoma Res. 2013 Feb 19. doi: 10.1111/pcmr.12078. [Epub ahead of print]

Photoaging of human retinal pigment epithelium is accompanied by oxidative modifications of its eumelanin.

Ito S, Pilat A, Gerwat W, Skumatz CM, Ito M, Kiyono A, Zadlo A, Nakanishi Y, Kolbe L, Burke JM, Sarna T, Wakamatsu K.

Department of Chemistry, Fujita Health University School of Health Sciences, Toyoake, Aichi, Japan.

Abstract: Although photodegradation of the retinal pigment epithelium (RPE) melanin may contribute to the etiology of age-related macular degeneration, the molecular mechanisms of this phenomenon and the structural changes of the modified melanin remain unknown. Recently, we found that the ratio of pyrrole-2,3,4,5-tetracarboxylic acid (PTeCA) to pyrrole-2,3,5-tricarboxylic acid (PTCA) is a marker for the heat-induced cross-linking of eumelanin. In this study, we examined UVA-induced changes in synthetic eumelanins to confirm the usefulness of the PTeCA/PTCA ratio as an indicator of photo-oxidation and compared changes in various melanin markers and their ratios in human melanocytes exposed to UVA, in isolated bovine RPE melanosomes exposed to strong blue light and in human RPE cells from donors of various ages. The results indicate that the PTeCA/PTCA ratio is a sensitive marker for the oxidation of eumelanin exposed to UVA or blue light and that eumelanin and pheomelanin in human RPE cells undergo extensive structural modifications due to the life-long exposure to blue light.

PMID: 23421783 [PubMed - as supplied by publisher]

Proteomics Clin Appl. 2013 Feb 18. doi: 10.1002/prca.201200012. [Epub ahead of print]

Proteomic analysis of the aqueous humor in patients with wet age-related macular degeneration.

Yao J, Liu X, Yang Q, Zhuang M, Wang F, Chen X, Hang H, Zhang W, Liu Q.

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PURPOSE: A number of studies have shown that the levels of some proteins in the aqueous humor (AH) are altered and correlate with the mechanisms or prognosis of many eye diseases. To identify the possible mechanisms that lead to the development of wet age-related macular degeneration (AMD), a proteomic analysis of the AH composition from wet AMD patients was performed and compared with that from non-AMD cataract patients.

EXPERIMENTAL DESIGN: Six wet AMD and 6 non-AMD cataract patients were enrolled. A proteomic approach which included two-dimensional electrophoresis (2-DE) coupled with mass spectrometry and bioinformatics methods were used to identify AH proteins with altered expression in wet AMD compared with non-AMD patients. An enzyme-linked immunosorbent assay was used to validate the proteomic results.

RESULTS: We separated 78 protein spots and identified 68 that were differently expressed in the wet AMD group and controls. Numerous proteins identified in this study are implicated in inflammation, apoptosis, angiogenesis and oxidative stress.

CONCLUSIONS AND CLINICAL RELEVANCE: The AH protein composition was significantly different between wet AMD and non-AMD patients. The proteins identified in this study may be potential biomarkers of wet AMD development and might play a role in the mechanisms of wet AMD.

PMID: 23418058 [PubMed - as supplied by publisher]

Prog Retin Eye Res. 2013 Feb 12. pii: S1350-9462(13)00014-1. doi: 10.1016/j.preteyeres.2013.02.001. [Epub ahead of print]

Molecular basis of the inner blood-retinal barrier and its breakdown in diabetic macular edema and other pathological conditions.

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Abstract: Breakdown of the inner endothelial blood-retinal barrier (BRB), as occurs in diabetic retinopathy, age-related macular degeneration, retinal vein occlusions, uveitis and other chronic retinal diseases, results in vasogenic edema and neural tissue damage, causing loss of vision. The central mechanism of altered BRB function is a change in the permeability characteristics of retinal endothelial cells caused by elevated levels of growth factors, cytokines, advanced glycation end products, inflammation, hyperglycemia and loss of pericytes. Subsequently, paracellular but also transcellular transport across the retinal vascular wall increases via opening of endothelial intercellular junctions and qualitative and quantitative changes in endothelial caveolar transcellular transport, respectively. Functional changes in pericytes and astrocytes, as well as structural changes in the composition of the endothelial glycocalyx and the basal lamina around BRB endothelium further facilitate BRB leakage. As Starling's rules apply, active transcellular transport of plasma proteins by the BRB endothelial cells causing increased interstitial osmotic pressure is probably the main factor in the formation of macular edema. The understanding of the complex cellular and molecular processes involved in BRB leakage has grown rapidly in recent years. Although appropriate animal models for human conditions like diabetic macular edema are lacking, these insights have provided tools for rational design of drugs aimed at restoring the BRB as well as for design of effective transport of drugs across the BRB, to treat the chronic retinal diseases such as DME that affect the quality of life of millions of patients.

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Epidemiology

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Prevalence of age-related macular degeneration in Nakuru, Kenya: a cross-sectional population-based study.

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BACKGROUND: Diseases of the posterior segment of the eye, including age-related macular degeneration (AMD), have recently been recognised as the leading or second leading cause of blindness in several African countries. However, prevalence of AMD alone has not been assessed. We hypothesized that AMD is an important cause of visual impairment among elderly people in Nakuru, Kenya, and therefore sought to assess the prevalence and predictors of AMD in a diverse adult Kenyan population.

METHODS AND FINDINGS: In a population-based cross-sectional survey in the Nakuru District of Kenya, 100 clusters of 50 people 50 y of age or older were selected by probability-proportional-to-size sampling between 26 January 2007 and 11 November 2008. Households within clusters were selected through compact segment sampling. All participants underwent a standardised interview and comprehensive eye examination, including dilated slit lamp examination by an ophthalmologist and digital retinal photography. Images were graded for the presence and severity of AMD lesions following a modified version of the International Classification and Grading System for Age-Related Maculopathy. Comparison was made between slit lamp biomicroscopy (SLB) and photographic grading. Of 4,381 participants, fundus photographs were gradable for 3,304 persons (75.4%), and SLB was completed for 4,312 (98%). Early and late AMD prevalence were 11.2% and 1.2%, respectively, among participants graded on images. Prevalence of AMD by SLB was 6.7% and 0.7% for early and late AMD, respectively. SLB underdiagnosed AMD relative to photographic grading by a factor of 1.7. After controlling for age, women had a higher prevalence of early AMD than men (odds ratio 1.5; 95% CI, 1.2-1.9). Overall prevalence rose significantly with each decade of age. We estimate that, in Kenya, 283,900 to 362,800 people 50 y and older have early AMD and 25,200 to 50,500 have late AMD, based on population estimates in 2007.

CONCLUSIONS: AMD is an important cause of visual impairment and blindness in Kenya. Greater availability of low vision services and ophthalmologist training in diagnosis and treatment of AMD would be appropriate next steps. Please see later in the article for the Editors' Summary.

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Genetics

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The albino mutation of tyrosinase alters ocular angiogenic responsiveness.

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Abstract: We have observed substantial differences in angiogenic responsiveness in mice and have mapped the genetic loci responsible for these differences. We have found that the albino mutation is one of the loci responsible for such differences. Using B6.A consomic strains, we determined that chromosome 7 bears a locus that inhibits VEGF-induced corneal neovascularization. F2 crosses between B6.A<Chromosome 7> consomic mice and C57BL/6J parents along with AXB and BXA recombinant inbred strains demonstrated highest linkage near the tyrosinase gene. This region was named AngVq4. Congenic animals confirmed this locus, but could not demonstrate that the classical tyrosinase albino (c) mutation was causative because of the existence of additional linked loci in the congenic region. However, in 1970, a second tyrosinase albino mutation (c-2J) arose in the C57BL/6J background at Jackson Labs. Testing this strain (C57BL/6J<c-2J>) demonstrated that the albino mutation is sufficient to completely explain the alteration in angiogenic response that we observed in congenic animals. Thus, we conclude that the classical tyrosinase mutation is responsible for AngVq4. In contrast to the cornea, where pigmented animals exhibit increased angiogenic responsiveness, iris neovascularization was inhibited in pigmented animals. These results may partially explain increased aggressiveness in amelanotic melanoma, as well as ethnic differences in diabetic retinopathy and macular degeneration.

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Influence of TIMP3/SYN3 polymorphisms on the phenotypic presentation of age-related macular degeneration.

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Abstract: Age-related macular degeneration (AMD) is a leading cause of irreversible central visual loss in the elderly. A recent genome-wide association studies (GWAS) reported that rs9621532 near the tissue inhibitor of metalloproteinase 3 (TIMP3)/synapsin III (SYN3) region of 22q12.3 is associated with AMD. In this study, we characterize its phenotypic influence on AMD using three independent study cohorts: case-control studies from the National Eye Institute Clinical Center (NEI, n=397) and the Age-Related Eye Disease Study (n=523) as well as a nested case-control study from Blue Mountains Eye Study (BMES, n=852). Comparisons between cases and controls show no association between rs9621532 and AMD in

the three sample sets. However, stratifying NEI cases uncovers a moderate protective role of rs9621532 in neovascular AMD (nAMD) and the association adhered to a dominant model (odds ratios=0.32; 95% CI: 0.11-0.89; P=0.02). The BMES data followed the same pattern of association with nAMD as that seen in the NEI sample but did not reach statistical significance. Polychotomous logistic regression showed a trend that rs9621532 correlates with less severe disease, for example, with the majority of carriers having intermediate AMD rather than nAMD/geographic atrophy AMD. Functionally, rs9621532 influences TIMP3 mRNA expression in cultured primary human fetal retinal pigment epithelium (hfRPE) cells. In hfRPE donors carrying the protective rs9625132 allele, we measured a reduction in TIMP3 mRNA by quantitative RT-PCR. Our data suggest that rs9621532 carriers have a lower risk of developing nAMD, potentially because of decreased transcription of TIMP3.European Journal of Human Genetics advance online publication, 20 February 2013; doi:10.1038/ejhg.2013.14.

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Diet

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Curcumin, a potential therapeutic candidate for retinal diseases.

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Abstract: Curcumin, the major extraction of turmeric, has been widely used in many countries for centuries both as a spice and as a medicine. In the last decade, researchers have found the beneficial effects of curcumin on multiple disorders are due to its antioxidative, anti-inflammatory, and antiproliferative properties, as well as its novel function as an inhibitor of histone aectyltransferases. In this review, we summarize the recent progress made on studying the beneficial effects of curcumin on multiple retinal diseases, including diabetic retinopathy, glaucoma, and age-related macular degeneration. Recent clinical trials on the effectiveness of phosphatidylcholine formulated curcumin in treating eye diseases have also shown promising results, making curcumin a potent therapeutic drug candidate for inflammatory and degenerative retinal and eye diseases.

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