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Drug treatment

Ophthalmology. 2011 Jun 17. [Epub ahead of print]

Sustained Benefits from Ranibizumab for Macular Edema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study.

Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, Adamis AP, Rubio RG, Murahashi WY.

Retinal Consultants of Houston, Houston, Texas.

PURPOSE: Assess 12-month efficacy and safety of intraocular injections of 0.3 mg or 0.5 mg ranibizumab in patients with macular edema after branch retinal vein occlusion (BRVO).

DESIGN: Prospective, randomized, sham injection-controlled, double-masked, multicenter trial.

PARTICIPANTS: A total of 397 patients with macular edema after BRVO.

METHODS: Eligible patients were randomized 1:1:1 to 6 monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections. After 6 months, all patients with study eye best-corrected visual acuity (BCVA) $\leq 20/40$ or central subfield thickness ≥ 250 μm were to receive ranibizumab. Patients could receive rescue laser treatment once during the treatment period and once during the observation period if criteria were met.

MAIN OUTCOME MEASURES: The main efficacy outcome reported is mean change from baseline BCVA letter score at month 12. Additional visual and anatomic parameters were assessed.

RESULTS: Mean (95% confidence interval) change from baseline BCVA letter score at month 12 was 16.4 (14.5-18.4) and 18.3 (15.8-20.9) in the 0.3 mg and 0.5 mg groups, respectively, and 12.1 (9.6-14.6) in the sham/0.5 mg group ($P < 0.01$, each ranibizumab group vs. sham/0.5 mg). The percentage of patients who gained ≥ 15 letters from baseline BCVA at month 12 was 56.0% and 60.3% in the 0.3 mg and 0.5 mg groups, respectively, and 43.9% in the sham/0.5 mg group. On average, there was a marked reduction in central foveal thickness (CFT) after the first as-needed injection of 0.5 mg ranibizumab in the sham/0.5 mg group, which was sustained through month 12. No new ocular or nonocular safety events were identified.

CONCLUSIONS: At month 12, treatment with ranibizumab as needed during months 6-11 maintained, on average, the benefits achieved by 6 monthly ranibizumab injections in patients with macular edema after BRVO, with low rates of ocular and nonocular safety events. In the sham/0.5 mg group, treatment with ranibizumab as needed for 6 months resulted in rapid reduction in CFT to a similar level as that in the 0.3 mg ranibizumab treatment group and an improvement in BCVA, but not to the extent of that in the 2 ranibizumab groups. Intraocular injections of ranibizumab provide an effective treatment for macular edema after BRVO.

PMID: 21684606 [PubMed - as supplied by publisher]

Retina. 2011 Jun 17. [Epub ahead of print]

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR MONOTHERAPY VERSUS COMBINATION TREATMENT WITH PHOTODYNAMIC THERAPY FOR SUBFOVEAL CHOROIDAL NEOVASCULARIZATION SECONDARY TO CAUSES OTHER THAN AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To compare the visual outcomes and retreatment rates of monotherapy with intravitreal bevacizumab versus combination with photodynamic therapy for choroidal neovascularization secondary to causes other than age-related macular degeneration.

METHODS: Seventeen patients received intravitreal bevacizumab, and 6 patients underwent intravitreal bevacizumab combined with verteporfin photodynamic therapy within 3 days. Additional bevacizumab was administered if there was persistent fluorescein leakage or subretinal fluid on optical coherence tomography.

RESULTS: The mean change in visual acuity was vision gain of 1.7 lines in the monotherapy group compared with 2.8 lines in the combination therapy group at 12-month follow-up ($P = 0.45$). At 12 months, 93% in the monotherapy group and 100% in the combination group lost <2 lines of vision ($P = 1.0$); 36% gained >3 lines of vision in the monotherapy compared with 60% in the combination therapy group ($P = 0.60$). The monotherapy group received a mean of 4.8 reinjections, while the combination group received 2.6 reinjections over 12 months ($P = 0.11$). Subgroup analysis of cases of choroidal neovascularization caused by pathologic myopia demonstrated a mean change in visual acuity of vision gain of +2.0 lines in the monotherapy group versus +2.3 lines in the combination therapy group ($P = 0.82$) and a mean of 7.2 reinjections versus 2 in monotherapy and combination group, respectively ($P = 0.0498$) at 12 months.

CONCLUSION: The majority of patients had stabilization or improvement in vision in both treatment groups. Combination therapy with bevacizumab plus photodynamic therapy showed lower retreatment rates in patients with myopia. Randomized clinical trials are necessary to confirm these findings.

PMID: 21691258 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2011 Jun 17. [Epub ahead of print]

Intravitreal Bevacizumab for Exudative Age-Related Macular Degeneration in Clinical Practice.

Jonas JB, Tao Y, Schlichtenbrede FC.

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Abstract Purpose: The purpose of this study was to evaluate whether baseline visual acuity and baseline anatomy of the macula influence visual outcome in patients receiving intravitreal bevacizumab as treatment of exudative age-related macular degeneration (AMD) in clinical practice.

Methods: This clinical case series study included 319 patients (406 eyes) who consecutively received intravitreal injections of bevacizumab for treatment of exudative AMD. The intervals between injections were 6 weeks and postinjection examinations were performed at 4 weeks after injection. Mean follow-up was 3.6 months.

Results: After 3 injections of bevacizumab, best-corrected visual acuity (BCVA) significantly ($P < 0.01$) improved in eyes with a baseline BCVA of less than 0.2 (group 1; 138 eyes; -0.10 ± 0.43 LogMAR) and in eyes

with a baseline BCVA ≥ 0.2 and < 0.4 (group 2; 117 eyes; -0.06 ± 0.24 LogMAR), but BCVA deteriorated in eyes with a baseline BCVA of ≥ 0.4 (group 3; 151 eyes; 0.09 ± 0.32 LogMAR). Correspondingly, regression analysis revealed that improvement in BCVA after 3 intravitreal bevacizumab injections was significantly ($P=0.001$) associated with a low baseline BCVA. After the first injection of bevacizumab, changes in optical coherent tomography measurements of the macula (height of subretinal fluid, macular tissue thickness) were statistically significant for group 1 ($P=0.03$, $P=0.03$, respectively) and group 2 ($P=0.01$, $P=0.02$, respectively), but not for group 3 ($P=0.85$, $P=0.22$, respectively).

Conclusions: In clinical practice, patients with exudative AMD and a baseline BCVA of < 0.2 have a better prognosis for an increase in BCVA after intravitreal bevacizumab injections than patients with a higher baseline BCVA.

PMID: 21682590 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Jun 21. [Epub ahead of print]

The Effect of Intravitreal Injection of Bevacizumab on Retinal Circulation in Patients with Neovascular Macular Degeneration.

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Purpose: Intravitreal (ITV) injection of anti-VEGF like bevacizumab are widely used to treat neovascular age-related macular degeneration (AMD). However VEGF is essential for biologic functions such as blood pressure regulation. Indeed, anti-VEGF intravenous administration is associated with hypertension. Therefore, the effect of ITV bevacizumab on retinal circulation was studied.

Methods: 23 patients with neovascular AMD treated with 3 repeat ITV injections of bevacizumab were recruited. Blood arteriolar diameter and flow measurements were performed with the Canon Laser Blood Flowmeter at baseline, one week after the first injection, just prior to the second injection and 5 weeks after the third injection. Scanning Laser Doppler Flowmetry was used to assess the effect of bevacizumab on tissue perfusion at the first and fourth visits.

Results: Arteriolar diameter significantly decreased from $122.5 \pm 14.5 \mu\text{m}$ to $118.9 \pm 14.0 \mu\text{m}$ ($p=0.03$) during the first week to reach a mean value $117.2 \pm 13.7 \mu\text{m}$ at the end of the study ($p<0.01$). Arterial blood flow did not change significantly. Neuroretinal rim (RIM) perfusion decreased from $181.1 \pm 84.1 \text{ a.u.}$ to $167.7 \pm 76.5 \text{ a.u.}$ which was borderline significant ($p=0.06$). No significant change was observed in the peripapillary retina.

Conclusion: Arteriolar diameter decreased significantly after the first injection and persisted until the end of the study suggesting a long term effect of bevacizumab on vascular tone. However, the blood flow change is not significant. A borderline significant decrease in RIM perfusion was observed and suggests that the RIM may be more sensitive than the peripapillary retina to the effects of bevacizumab.

PMID: 21693608 [PubMed - as supplied by publisher]

Ophthalmologe. 2011 Jun;108(6):575-584.

[Differences in the treatment of exudative age-related macular degeneration in Germany and Great Britain.] [Article in German]

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Abstract

The treatment of age-related macular degeneration with anti-VEGF medications has resulted not only in significant improvements in eye treatment but also in rising costs of ophthalmological therapy. This new treatment has been rapidly introduced into daily practice in Germany with its social security healthcare system and also in Great Britain with its National Health Service. In both countries the most prevalent treatment scheme currently includes three baseline injections of ranibizumab followed by additional injections depending on persisting disease activity.

PMID: 21695609 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2011 Jun 20. [Epub ahead of print]

[New treatments for diabetic retinopathy.] [Article in French]

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Abstract

Even if several studies have clearly demonstrated that a good control of glycemia and arterial pressure allow reducing the incidence and the progression of diabetic retinopathy, there is currently no drug treatment to prevent the incidence or progression of diabetic retinopathy. However, significant progress has been made in treating the complications of diabetic retinopathy, including diabetic macular edema. Ranibizumab is effective in improving visual acuity in diabetic macular edema, but at the cost of repeated injections and monthly follow-ups. It has obtained a marketing authorization (MA) in this indication. Injections of intravitreal triamcinolone acetonide are also effective in reducing macular edema and in improving visual acuity but at the cost of significant side effects and without MA for intraocular use. The latter must be proposed after failure and/or injection of anti-VEGF or laser therapy.

PMID: 21696846 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Jun 17. [Epub ahead of print]

PET/CT imaging of I-124 radiolabeled bevacizumab and ranibizumab after intravitreal injection in a rabbit model.

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Purpose: To determine whether bevacizumab and ranibizumab remain confined within the vitreous cavity after intravitreal injection and to determine the pharmacokinetic properties of these agents within the vitreous cavity.

Methods: Radiolabeling with I-124 was completed using a modified Iodogen METHOD: After testing for radiochemical purity, three anesthetized Dutch-belted rabbits underwent intravitreal injection with I-124-bevacizumab and three with I-124 ranibizumab. All rabbits were imaged with a Micro PET-CT scanner on days 0, 2, 5, 7, 14, 21, 28 and 35.

Results: The intravitreally placed radiolabeled agents were found to be contained within the vitreous cavity for the duration of the study with no extravasation into the central nervous system or elsewhere. I-124 bevacizumab was detectable until day 28 while I-124 ranibizumab was detectable until day 21. The kinetic model appears to represent a 2-compartment model and the average retention times for bevacizumab and ranibizumab after correction for radioactive decay were found to be 4.2 days and 2.8 days respectively. This is in agreement with previously reported results using immunoassay methodology.

Conclusions: There was no significant escape of bevacizumab and ranibizumab from the vitreous cavity after intravitreal injection. After correction for radioactive decay both agents remain detectable until 28 and 21 days respectively with retention properties that validate those methods reported in previous studies.

PMID: 21685343 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2011 Jun 17. [Epub ahead of print]

Relationship between Outer Retinal Thickness Substructures and Visual Acuity in Eyes with Dry Age Related Macular Degeneration.

Pappuru RR, Ouyang Y, Nittala MG, Hemmati HD, Keane PA, Walsh AC, Sadda SR.

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Purpose: To explore the correlation between outer retinal substructures and visual acuity in dry age related macular degeneration (AMD).

Methods: Analysis of spectral domain optical coherence tomography (Topcon 3D OCT 1000) datasets from 100 eyes of 100 consecutive patients with dry AMD was performed using 3D OCTOR software. The internal limiting membrane, outer nuclear layer (ONL), external limiting membrane (ELM), inner segment-outer segment (IS-OS) junction, outer photoreceptor border, inner and outer retinal pigment epithelium (RPE) borders, and Bruch's membrane, were manually segmented by Doheny Image Reading Center (DIRC) graders. Areas, thicknesses and volumes of RPE, IS, OS, ONL, and the total retina in the foveal central subfield were correlated with the logarithm of minimal angle of resolution (logMAR) visual acuity using univariable and multivariable regression analysis.

Results: The visual acuity in this group ranged from logMAR 0 to 1.3 with a mean of 0.23. Areas, thicknesses, and volumes of ONL, IS and OS, thicknesses of total retinal and RPE, and intensities of IS, OS, and RPE, showed statistically significant association ($P < 0.05$) with logMAR best corrected visual acuity. The highest correlations were observed for the ONL (thickness: $r = -0.49$, volume: -0.47 , area: -0.50) and photoreceptor IS (thickness: -0.59 , area: -0.63 , volume: -0.53). The model with the highest correlation in this study included thicknesses of ONL, IS, OS and RPE, as well as area of ONL, IS, OS, RPE, and intensity of RPE.

Conclusions: Although integrity of outer retinal substructures in the foveal central subfield correlates with visual acuity in the eyes of patients with dry AMD, the correlation is only moderate and does not fully explain the variability in acuity in these cases.

PMID: 21685337 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2011 Jun 15. doi: 10.5301/ejo.5000014. [Epub ahead of print]

Bilateral symmetric autosomal dominant sector chorioretinopathy with late maculopathy: a review

based on a case with 48 years follow-up.

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Purpose: To describe the long-term course of bilateral symmetric autosomal dominant sector chorioretinopathy in a 79-year-old man who was diagnosed at age 31.

Methods: Ophthalmic examinations including fundus photography, fluorescein and indocyanine angiography, adaptometry, and ocular electrophysiology were performed at intervals from 1962 to 2010.

Results and Conclusions: The patient experienced no visual symptoms during his entire working life, but acquired an exudative maculopathy in his left eye at age 67. Two years later, a central subretinal neovascular membrane affected the right eye. The latter responded only temporarily to photodynamic therapy (Visudyne), and from age 71 he had best-corrected visual acuities <0.1 in both eyes, with eccentric fixation. We are not aware of any report on late macular involvement in this disorder. Whether the maculopathy should be considered a late manifestation of the sector chorioretinopathy or a coincidental occurrence of age-related macular degeneration remains unsettled.

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Invest Ophthalmol Vis Sci. 2011 Jun 21. [Epub ahead of print]

Spectral-Domain Optical Coherence Tomography as an Indicator of Fluorescein Angiography Leakage from Choroidal Neovascularization.

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Purpose: To evaluate spectral-domain optical coherence tomography (SD-OCT) findings that predict angiographic leakage in choroidal neovascularization (CNV).

Methods: SD-OCT and fluorescein angiography (FA) images of 93 eyes of 93 patients were retrospectively analyzed. All patients were previously treated with anti-vascular endothelial growth factor agents for CNV from age-related macular degeneration. FA images were analyzed to assess the presence of leakage. SD-OCT images were analyzed to identify the overall presence of fluid, as well as specific patterns of fluid presentation including intraretinal cystic spaces (ICS), retinal pigment epithelium detachment (PED), and neurosensory detachment (NSD). The presence of ultrastructural features such as intraretinal hyperreflective flecks, and the inherent reflectivity and boundary definition of the subretinal material was evaluated. The association, as well as the sensitivity, specificity, and positive and negative predictive values of SD-OCT findings compared to FA leakage were calculated.

Results: A statistically significant association between SD-OCT findings and FA leakage was found for eyes that displayed fluid, NSD, intraretinal flecks, and low reflectivity or undefined boundaries from subretinal material, and not for PED or ICS. Sensitivity and specificity for SD-OCT findings were, respectively: 94% and 27% for fluid; 68% and 88% for NSD; 81% and 83% for intraretinal flecks; 63% and 92% for undefined boundaries of subretinal material; and 94% and 87% for low reflectivity from subretinal material.

Conclusions: The evidence of fluid on SD-OCT is sensitive but non-specific in identifying FA leaky CNV. The assessment of neurosensory detachment as well as other ultrastructural elements may increase the specificity of analysis.

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Invest Ophthalmol Vis Sci. 2011 Jun 21. [Epub ahead of print]

Image Registration and Multimodal Imaging of Reticular Pseudodrusen.

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Purpose: To characterize reticular pseudodrusen (RPD) by utilizing a point-to-point comparison of the reticular pattern on infrared reflectance (IR), autofluorescence (AF), and red-free (RF) images registered with en face sections of the choroid from spectral domain optical coherence tomography (SD-OCT) scans.

Methods: A cross-sectional, retrospective study of all patients with the diagnosis of age-related macular degeneration (AMD), who presented to the Doheny Retina Institute from 12/2007 to 11/2009 was conducted to identify patients with RPD. IR, AF, and RF images were obtained using confocal scanning laser ophthalmoscopy and were manually registered to OCT choroidal sections to study the location of RPD. The main outcome measured was point-to-point localization of RPD across multiple imaging modalities.

Results: Of the 153 patient with AMD, 51 had RPD. In all 51 patients (97 eyes), RPD appeared as areas of hypo-autofluorescence and hypo-reflectance on AF and IR imaging, respectively, and as hyporeflective interlacing networks on RF. Reticular lesions on AF, IR, and RF consistently co-localized with stromal regions between large choroidal vessels on registered en face choroidal sections. In contrast, outer retinal changes and sub-retinal deposits tended to localize immediately adjacent to the RPD.

Conclusions: Point-to-point correlation of registered images in IR, AF, and RF consistently localizes the reticular pattern to the inter-vascular choroidal stroma on en face OCT sections. In contrast, sub-retinal deposits and disturbances of the inner-outer segment on OCT did not co-localize with the RPD, and may represent secondary mechanical or biological disturbances in the overlying retinal pigment epithelium and outer retina.

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Invest Ophthalmol Vis Sci. 2011 Jun 21. [Epub ahead of print]

Early Perfusion of a Free RPE-Choroid Graft in Patients with Exudative Macular Degeneration Can Be Imaged with Spectral Domain OCT.

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Purpose: To study early flow and revascularization in a free, autologous, retinal pigment epithelium (RPE)-choroid graft.

Methods: This prospective cohort study employed spectral domain optical coherence tomography (SD-OCT) after RPE-choroid graft surgery in 12 patients. This SD-OCT was combined with fluorescein angiography (FA) and indocyanine green angiography (ICGA) in 5 patients.

Results: SD-OCT revealed that vessel diameter, number of vessels, and graft thickness increased in 10 of 12 patients, starting between three and ten days after surgery. A subsequent decrease in thickness was found in all ten patients, beginning as early as eight days after surgery. Initially, the graft vessels were optically clearer than the underlying choroidal recipient vessels. Between 8 days and 30 days after surgery, the optically clear vessels became gray, similar to the recipient choroid. FA and ICGA revealed perfusion in 4 of 5 patients between postoperative days 6 and 15. Between postoperative days 12 and 60, the entire choroidal structure of the graft was visible on ICGA.

Conclusions: These data suggest that enlargement of vessel diameter, increase in the number of choroidal vessels, and graft thickening visualized by SD-OCT correspond with the ingrowth of afferent vessels, as demonstrated by ICGA. The subsequent establishment of efferent vessels results in flow, imaged as a change in color of the graft's vessels from optically clear to gray, graft thinning on SD-OCT, and complete revascularization on ICGA. Spectral domain OCT, a non-invasive examination, can be used to demonstrate early graft perfusion in patients.

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Drugs Today (Barc). 2011 Jun;47(6):441-55.

Nanotechnology in ocular delivery: Current and future directions.

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Abstract

Our knowledge in the field of ocular drug delivery is rapidly expanding. An increase in the understanding of ocular drug absorption and disposition vis-à-vis developments in nanotechnology has led to the emergence of many of the nanotechnology-based ocular drug delivery systems including nanoparticles, microemulsions, liposomes, solid lipid nanoparticles, light-sensitive nanocarrier systems, etc. The need to develop effective treatments for posterior eye segment diseases is more important than surface delivery. Treatment of blinding diseases of the eye, such as proliferative retinopathy or macular degeneration, requires effective and safe delivery of drugs to posterior eye segment tissues, and recent advances in nanotechnology have demonstrated successful outcomes. Nanoscientists should focus their efforts on nano-ophthalmology. This review describes the current status and progress made so far, and the course that needs to be pursued in the future.

PMID: 21695286 [PubMed - in process]

Epidemiology & pathogenesis

Proc Natl Acad Sci U S A. 2011 Jun 20. [Epub ahead of print]

Anti-amyloid therapy protects against retinal pigmented epithelium damage and vision loss in a model of age-related macular degeneration.

Ding JD, Johnson LV, Herrmann R, Farsiu S, Smith SG, Groelle M, Mace BE, Sullivan P, Jamison JA, Kelly U, Harrabi O, Bollini SS, Dilley J, Kobayashi D, Kuang B, Li W, Pons J, Lin JC, Rickman CB.

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Abstract

Age-related macular degeneration (AMD) is a leading cause of visual dysfunction worldwide. Amyloid β (A β) peptides, A β 1-40 (A β 40) and A β 1-42 (A β 42), have been implicated previously in the AMD disease process. Consistent with a pathogenic role for A β , we show here that a mouse model of AMD that invokes multiple factors that are known to modify AMD risk (aged human apolipoprotein E 4 targeted replacement mice on a high-fat, cholesterol-enriched diet) presents with A β -containing deposits basal to the retinal pigmented epithelium (RPE), histopathologic changes in the RPE, and a deficit in scotopic electroretinographic response, which is reflective of impaired visual function. Strikingly, these electroretinographic deficits are abrogated in a dose-dependent manner by systemic administration of an antibody targeting the C termini of

A β 40 and A β 42. Concomitant reduction in the levels of A β and activated complement components in sub-RPE deposits and structural preservation of the RPE are associated with anti-A β 40/42 antibody immunotherapy and visual protection. These observations are consistent with the reduction in amyloid plaques and improvement of cognitive function in mouse models of Alzheimer's disease treated with anti-A β antibodies. They also implicate A β in the pathogenesis of AMD and identify A β as a viable therapeutic target for its treatment.

PMID: 21690377 [PubMed - as supplied by publisher]

Exp Eye Res. 2011 Jun 12. [Epub ahead of print]

Retinal pigment epithelial expression of complement regulator CD46 is altered early in the course of geographic atrophy.

Vogt SD, Curcio CA, Wang L, Li CM, McGwin G Jr, Medeiros NE, Philp NJ, Kimble JA, Read RW.

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Abstract

In geographic atrophy (GA), the non-neovascular end stage of age-related macular degeneration (AMD), the macular retinal pigment epithelium (RPE) progressively degenerates. Membrane cofactor protein (MCP, CD46) is the only membrane-bound regulator of complement expressed on the human RPE basolateral surface. Based on evidence of the role of complement in AMD, we hypothesized that altered CD46 expression on the RPE would be associated with GA development and/or progression. Here we report the timeline of CD46 protein expression changes across the GA transition zone, relative to control eyes, and relative to events in other chorioretinal layers. Eleven donor eyes (mean age 87.0 ± 4.1 yr) with GA and 5 control eyes (mean age 84.0 ± 8.9 yr) without GA were evaluated. Macular cryosections were stained with PASH for basal deposits, von Kossa for calcium, and for CD46 immunoreactivity. Internal controls for protein expression were provided by an independent basolateral protein, monocarboxylate transporter 3 (MCT3) and an apical protein, ezrin. Within zones defined by 8 different semi-quantitative grades of RPE morphology, we determined the location and intensity of immunoreactivity, outer segment length, and Bruch's membrane calcification. Differences between GA and control eyes and between milder and more severe RPE stages in GA eyes were assessed statistically. Increasing grades of RPE degeneration were associated with progressive loss of polarity and loss of intensity of staining of CD46, beginning with the stages that are considered normal aging (grades 0-1). Those GA stages with affected CD46 immunoreactivity exhibited basal laminar deposit, still-normal photoreceptors, and concomitant changes in control protein expression. Activated or anteriorly migrated RPE (grades 2-3) exhibited greatly diminished CD46. Changes in RPE CD46 expression occur early in GA, before there is evidence of morphological RPE change. At later stages of degeneration, CD46 alterations occur within a context of altered RPE polarity. These changes precede degeneration of the overlying retina and suggest that therapeutic interventions be targeted to the RPE.

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Pharmacol Res. 2011 Jun 7. [Epub ahead of print]

Celastrol regulates innate immunity response via NF- κ B and Hsp70 in human retinal pigment epithelial cells.

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Abstract

Elevated nuclear factor kappa B (NF- κ B) activity and interleukin-6 (IL-6) secretion participates in the pathology of several age and inflammatory-related diseases, including age-related macular degeneration (AMD), in which retinal pigment epithelial cells are the key target. Recent findings reveal that heat shock protein 70 (Hsp70) may affect regulation of NF- κ B. In the current study, effects of Hsp70 expression on NF- κ B RelA/p65 activity were evaluated in human retinal pigment epithelial cells (ARPE-19) by using celastrol, a novel anti-inflammatory compound. Anti-inflammatory properties of celastrol were determined by measuring expression levels of IL-6 and endogenous NF- κ B levels during lipopolysaccharide (LPS) exposure by using enzyme-linked immunosorbent assays (ELISA). Cell viability was measured by MTT and LDH assay, and Hsp70 expression levels were analyzed by Western blotting. ARPE-19 cells were transfected with hsp70 small interfering RNA (siRNA) in order to attenuate Hsp70 expression and activity of NF- κ B RelA/p65 was measured using NF- κ B consensus bound ELISA. Simultaneous exposures to LPS and celastrol reduced IL-6 expression levels as well as activity of phosphorylated NF- κ B at serine 536 (Ser536) in ARPE-19 cells when compared to LPS exposure alone. In addition, inhibition of NF- κ B RelA/p65 activity by celastrol was attenuated when Hsp70 response was silenced by siRNA. Favorable anti-inflammatory concentrations of celastrol showed no signs of cytotoxic response. Our findings reveal that celastrol is a novel plant compound which suppresses innate immunity response in human retinal pigment epithelial cells via NF- κ B and Hsp70 regulation, and that Hsp70 is a critical regulator of NF- κ B.

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Ophthalmology. 2011 Jun 17. [Epub ahead of print]

Risk Factors Associated with Incident Cataracts and Cataract Surgery in the Age-Related Eye Disease Study (AREDS) AREDS Report Number 32.

Chang JR, Koo E, Agrón E, Hallak J, Clemons T, Azar D, Sperduto RD, Ferris FL 3rd, Chew EY; Age-Related Eye Disease Study Group.

Neurobiology, Neurodegeneration and Repair Laboratory, National Eye Institute/National Institutes of Health, Bethesda, Maryland.

OBJECTIVE: To investigate potential risk factors associated with incident nuclear, cortical, and posterior subcapsular (PSC) cataracts and cataract surgery in participants in the Age-Related Eye Disease Study (AREDS).

DESIGN: Clinic-based prospective cohort study.

PARTICIPANTS: Persons (n = 4425) 55 to 80 years of age enrolled in a controlled clinical trial of antioxidant vitamins and minerals, AREDS, for age-related macular degeneration and cataract.

METHODS: Lens photographs were graded centrally for nuclear, cortical, and PSC opacities using the AREDS system for classifying cataracts. Type-specific incident cataracts were defined as an increase in cataract grade from none or mild at baseline to a grade of moderate at follow-up, also with a grade of at least moderate at the final visit, or cataract surgery. Cox regression analyses were used to assess baseline risk factors associated with type-specific opacities and cataract surgery.

MAIN OUTCOME MEASURES: Moderate cataract was defined as a grade of 4.0 or more for nuclear opacity, 10% or more involvement within the full visible lens for cortical opacity, and 5% or more involvement of the central 5-mm circle of the lens for PSC opacity. These were graded on baseline and annual lens photographs.

RESULTS: A clinic-based cohort of 4425 persons 55 to 80 years of age at baseline was followed up for an average of 9.8 $\pm$ 2.4 years. The following associations were found: increasing age with increased risk of all types of cataract and cataract surgery; males with increased risk of PSC and decreased risk of cortical

cataracts; nonwhite persons with increased risk of cortical cataract; hyperopia with decreased risk of PSC, nuclear cataract, and cataract surgery; Centrum (Wyeth Consumer Healthcare, Madison, NJ) use with decreased risk of nuclear cataract; diabetes with increased risk of cortical, PSC cataract, and cataract surgery; higher educational level with decreased risk of cortical cataract; and smoking with increased risk of cortical cataract and cataract surgery. Estrogen replacement therapy in female participants increased the risk of cataract surgery.

CONCLUSIONS: These findings largely are consistent with the results of previous studies, providing further evidence for possible modifiable risk factors for age-related cataract.

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Racial Differences in Age-Related Macular Degeneration Rates in the United States: A Longitudinal Analysis of a Managed Care Network.

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PURPOSE: To compare the incidence, prevalence, and hazard of nonexudative and exudative age-related macular degeneration (AMD) among different races throughout the United States.

DESIGN: Retrospective longitudinal cohort study.

METHODS: Billing records of all encounters for 2 259 061 beneficiaries aged ≥ 40 enrolled in a large, national US managed care network from 2001 through 2007 were reviewed and the incidence and prevalence of nonexudative and exudative AMD were determined and stratified by race. Cox regression analyses determined the hazard of nonexudative and exudative AMD for each race, with adjustment for confounders.

RESULTS: During the study, 113 234 individuals (5.0%) were diagnosed with nonexudative and 17 181 (0.76%) with exudative AMD. After adjustment for confounders, blacks had a significantly reduced hazard of nonexudative (hazard ratio [HR] = 0.75, 95% confidence interval [CI]: 0.71-0.79) and exudative AMD (HR = 0.70, 95% CI: 0.59-0.83) at age 60 and a reduced hazard of nonexudative (HR = 0.56, 95% CI: 0.52-0.60) and exudative AMD (HR = 0.45, 95% CI: 0.37-0.54) at age 80 relative to whites. Similar comparisons for Latinos demonstrated an 18% reduced hazard for nonexudative AMD at age 80 (HR = 0.82, 95% CI: 0.76-0.88) relative to whites. Asian Americans showed a 28% increased hazard for nonexudative AMD at age 60 (HR = 1.28, 95% CI: 1.20-1.36) but a 46% decreased hazard for exudative AMD at age 80 (HR = 0.54, 95% CI: 0.40-0.73).

CONCLUSIONS: Racial minorities, including Latinos and Asian Americans, do not appear to have similar risks of developing nonexudative and exudative AMD as whites. Additional studies using other sources should be conducted to determine the generalizability of this study's findings to other groups.

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Genetics

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Identifying Subtypes of Patients with Neovascular Age-Related Macular Degeneration by Genotypic and Cardiovascular Risk Characteristics.

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BACKGROUND: One of the challenges in the interpretation of studies showing associations between environmental and genotypic data with disease outcomes such as neovascular age-related macular degeneration (AMD) is understanding the phenotypic heterogeneity within a patient population with regard to any risk factor associated with the condition. This is critical when considering the potential therapeutic response of patients to any drug developed to treat the condition. In the present study, we identify patient subtypes or clusters which could represent several different targets for treatment development, based on genetic pathways in AMD and cardiovascular pathology.

METHODS: We identified a sample of patients with neovascular AMD, that in previous studies had been shown to be at elevated risk for the disease through environmental factors such as cigarette smoking and genetic variants including the complement factor H gene (CFH) on chromosome 1q25 and variants in the ARMS2/HTRA serine peptidase 1 (HTRA1) gene(s) on chromosome 10q26. We conducted a multivariate segmentation analysis of 253 of these patients utilizing available epidemiologic and genetic data.

RESULTS: In a multivariate model, cigarette smoking failed to differentiate subtypes of patients. However, four meaningfully distinct clusters of patients were identified that were most strongly differentiated by their cardiovascular health status (histories of hypercholesterolemia and hypertension), and the alleles of ARMS2/HTRA1 rs1049331.

CONCLUSIONS: These results have significant personalized medicine implications for drug developers attempting to determine the effective size of the treatable neovascular AMD population. Patient subtypes or clusters may represent different targets for therapeutic development based on genetic pathways in AMD and cardiovascular pathology, and treatments developed that may elevate CV risk, may be ill advised for certain of the clusters identified.

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Crystallographic determination of the disease-associated T1184R variant of complement regulator factor H.

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Abstract

The soluble 155 kDa glycoprotein factor H (FH) protects host tissue from damage by the human complement system. It accelerates decay of the alternative-pathway C3 convertase, C3bBb, and is a cofactor for factor I-mediated cleavage of the opsonin C3b. Numerous mutations and single-nucleotide polymorphisms (SNPs) occur in the gene encoding FH and the resulting missense mutations and truncation products result in altered functionality that predisposes to the development of the serious renal condition atypical haemolytic uraemic syndrome (aHUS). Other polymorphisms are linked to membranoproliferative glomerulonephritis and macular degeneration. The two C-terminal modules of FH (FH19-20) harbour numerous aHUS-associated mutations that disrupt the ability of factor H to protect host cells from complement-mediated damage. In this work, the crystal structure of an aHUS-associated T1184R variant of FH19-20 at a resolution of 1.52 Å is described. It is shown that this mutation has negligible structural effects but causes a significant change in the electrostatic surface of these two domains. Mechanisms are discussed by which this mutation may alter FH-ligand interactions, particularly with regard to the extension of a region of this molecule within module 20 that has been associated with the binding of glycosaminoglycans (GAGs) or sialic acid residues.

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Effect of miR-23 on oxidant-induced injury in human retinal pigment epithelium cells.

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Purpose: MicroRNAs (miRNAs) negatively regulate a wide variety of genes through degradation or post-translational inhibition of their target genes. The purpose of this study is to investigate the role of miR-23a in modulating RPE cell survival and gene expression in response to oxidative damage.

Methods: The expression level of miR-23a was measured in macular retinal pigment epithelial (RPE) cells from aged-related macular degeneration (AMD) patients and normal aged donors by using qRT-PCR. Cultured human ARPE-19 cells were transfected with miR-23a mimic or inhibitor. Cell viability was assessed by the MTT assay. Apoptosis was determined by incubating cells with hydrogen peroxide (H₂O₂) or t-butylhydroperoxide (tBH). Caspase-3 activity and DNA fragmentation were measured using enzyme-linked immunosorbent assays. The protein relevant to apoptosis, such as Fas expression level, was analyzed using Western blot.

Results: MiR-23a expression was remarkably downregulated in macular RPE cells from AMD patients. H₂O₂-induced ARPE-19 cell death and apoptosis was increased by miR-23a inhibitor and decreased by miR-23a mimic. Computational analysis found a putative target site of miR-23a in the 3'UTR of Fas mRNA, which was verified by luciferase reporter assay. Forced overexpression of miR-23a decreased H₂O₂ or tBH-induced Fas upregulation, and this effect was blocked by downregulation of miR-23a.

Conclusion: The protection of RPE cells against oxidative damage is afforded by miR-23a through regulation of Fas, which may be a novel therapeutic target in retina degenerative diseases.

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Diet

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A Lutein-Enriched Diet Prevents Cholesterol Accumulation and Decreases Oxidized LDL and Inflammatory Cytokines in the Aorta of Guinea Pigs.

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Abstract

Lutein has been shown to be protective against age-related macular degeneration; however, the antiinflammatory and antioxidant effects of this carotenoid in aortas are less known. Guinea pigs were fed a hypercholesterolemic diet (0.25 g cholesterol/100 g) and randomly allocated to a control group (n = 9) or a lutein group (n = 10) (0.1 g/100 g lutein) and fed the experimental diets for 12 wk. Plasma LDL cholesterol and TG did not differ between groups; however, the lutein group had lower concentrations of medium size LDL (P < 0.05). As expected, guinea pigs from the lutein group had higher concentrations of plasma and liver lutein than those from the control group (P < 0.0001). Aortic cholesterol and malondialdehyde concentrations were lower in the lutein group (9.6 ± 2.8 mmol/g and 1.69 ± 1.35 nmol/mg protein) compared to the control group (15.5 ± 2.3 mmol/g and 2.98 ± 1.45 nmol/mg protein) (P < 0.05). Hematoxylin and eosin staining indicated that aortas from the control group presented focal intimal thickening, whereas either less thickness or no visible thickness was present in aortas from the lutein group. Oxidized LDL (oxLDL) was lower both in plasma and aorta in the lutein group compared to the control group (P < 0.001). Aortic cytokines

were also lower in the lutein group ($P < 0.05$). Plasma lutein and oxLDL ($r = -0.79$; $P < 0.0001$) and plasma lutein and aortic oxLDL ($r = -0.64$; $P < 0.0001$) were negatively correlated. These data suggest that lutein exerts potent antioxidant and antiinflammatory effects in aortic tissue that may protect against development of atherosclerosis in guinea pigs.

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