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MD Research News

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Drug treatment

Clin Ophthalmol. 2013;7:1487-90. doi: 10.2147/OPTH.S46317. Epub 2013 Jul 22.

Initial non-responders to ranibizumab in the treatment of age-related macular degeneration (AMD).

Otsuji T, Nagai Y, Sho K, Tsumura A, Koike N, Tsuda M, Nishimura T, Takahashi K.

Department of Ophthalmology, Kansai Medical University, Takii Hospital, Osaka, Japan.

BACKGROUND: Patients with exudative age-related macular degeneration (AMD) who did not respond to ranibizumab at the induction phase were assessed and referred to as initial non-responders.

METHODS: We retrospectively reviewed the medical records of 215 patients (218 eyes) with exudative AMD. For the initial treatments, patients received three intravitreal injections of ranibizumab (IVR) every 4 weeks. Minimum follow-up period was 12 months. We defined patients with no improvement of best corrected logMAR visual acuity (BCVA), and with no decrease of central retinal thickness (CRT) at the end of the initial treatment, as initial non-responders. Patients who had previous treatment history prior to this investigation were included, but patients who had photodynamic therapy (PDT) with IVR were excluded.

RESULTS: Twenty-two eyes (10.1%) were identified as initial non-responders. The mean BCVA of initial non-responders before IVR and after induction phase were 0.39 and 0.36, respectively. There was no significant difference between these values, however the mean BCVA decreased significantly to 0.55 at 12 months after the beginning of the induction phase (P = 0.021). The mean greatest linear dimension (GLD) of the lesion before IVR of initial non-responders was 4,121 μm. We found 16 eyes with typical AMD, and six eyes with polypoidal choroidal vasculopathy. One eye had predominantly classic choroidal neovascularization (CNV), and others had occult CNV of typical AMD. As additional treatments, twelve eyes received PDT, and in three of the eyes exudation remained after PDT.

CONCLUSION: Initial non-responders were more prevalent in patients with occult CNV than in patients with other CNV types. Some of the initial non-responders did not respond to PDT. This study suggested possible involvement of other factors, in addition to vascular endothelial growth factor, in the occurrence of CNV in initial non-responder patients.

PMID: 23901256 [PubMed] PMCID: PMC3726592

Am J Ophthalmol. 2013 Jul 24. pii: S0002-9394(13)00374-7. doi: 10.1016/j.ajo.2013.05.037. [Epub ahead of print]

One Year Follow-up of Functional Recovery in Neovascular AMD During Monthly Anti-VEGF

Treatment.

Munk MR, Kiss C, Huf W, Sulzbacher F, Roberts P, Mittermüller TJ, Sacu S, Simader C, Schmidt-Erfurth U.

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

PURPOSE: To identify neurosensory recovery, testing different functional variables during monthly intravitreal standard anti-vascular endothelial growth factor (VEGF) therapy in neovascular age-related macular degeneration (AMD).

DESIGN: Prospective interventional cohort study.

METHODS: Sixty-four treatment-naïve neovascular AMD patients with subfoveal lesions were treated and examined monthly for distance visual acuity, reading acuity, maximum reading speed, and contrast sensitivity and with microperimetry evaluating the percentage of absolute and relative scotoma and mean central retinal sensitivity weighted by area. Improvements in reading acuity, distance acuity, reading speed, contrast sensitivity, mean central retinal sensitivity, and scotoma area in dependence of age, lesion type, lesion size, and mean central retinal sensitivity were evaluated by a random-slope and random-intercept model. Recovery pattern of parameters was compared by correlating the individual slopes of each variable.

RESULTS: Initially, a rapid short-term effect of anti-VEGF treatment was documented throughout all functional variables. Progressive functional gain over 1 year was observed for distance visual acuity ($P = .011$), contrast sensitivity ($P \leq .0001$), and mean central retinal sensitivity ($P \leq .0001$), but not for reading acuity ($P = .31$) and maximum reading speed ($P = .94$). Decrease of absolute scotoma area missed statistical significance over time ($P = .053$) and also fixation stability did not improve ($P = .08$). However, lesion size influenced the course of absolute scotoma area ($P = .0015$), while lesion type had no effect on any visual function variable evaluated. The individual slopes of reading acuity and distance visual acuity showed a moderate correlation; however, all other variables showed only a weak or no significant correlation among each other.

CONCLUSION: Visual recovery in anti-VEGF therapy is reflected in a characteristic pattern of functional changes over time, whereas distance visual acuity does not seem to comprehensively reflect overall visual function gain.

PMID: 23891335 [PubMed - as supplied by publisher]

J Pak Med Assoc. 2013 Jun;63(6):707-10.

A one-year follow-up study of ocular and systemic complications of intravitreal injection of bevacizumab (Avastin).

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OBJECTIVES: To report systemic and ocular complications within a year of intravitreal injection of bevacizumab (Avastin) in ocular neovascularisation.

METHODS: The quasi-experimental (randomized without control) study was carried out at the Eye Department of Abbasi Shaheed Hospital, Karachi, from July 2008 to June 2010. It comprised 150 patients selected from the outpatient department with ocular neovascularisation through non-probability purposive sampling. After detailed history and examination, the patients were counseled for intravitreal injection Avastin (bevacjzumab) which was injected into the vitreous cavity in sterile environment in the operation theatre using fully aseptic technique. The injection site was compressed for several seconds to avoid reflux when the needle was removed. Paracentesis was done following the injection as soon as possible. Patients

were discharged on moxifloxcin eye drops and steroid antibiotic combination ointment at night time. They were followed up the very next day, after 2 weeks, 6 weeks, 3 months, 6 months and 1 year. Injection was repeated after 6 weeks if required and further repetition was done again after 6 weeks according to the need of the patient.

RESULTS: Of the 150 patients, 93 (62%) were males and 57 (38%) were females. Most commonly presenting age group was between 50-60 years (n=51; 34%) followed by 41-50 years (n=41; 27.4%). Most common indication for intravitreal injection Avastin (bevacizumab) was proliferative diabetic retinopathy in 134 (89.33%) patients, followed by age-related macular degeneration (wet type) in 5 (3.3%) patients. Most frequently presenting ocular complication was subconjunctival haemorrhage seen in 35 (23%) patients, followed by regurgitation of drug from the site of injection in 8 (5.3%) patients, transient rise of intraocular pressure in 7 (4.7%) patients, mild uveitiS in 4 (2.7%) patients, lens injury in 3 (2%) patients, conjunctival chemosis and iatrogenic vitreous haemorrhage in 1 (0.7%) patients. Among the systemic complications were acute rise of blood pressure in 4 (2.7%) patients, and mild irritation and allergic reaction on skin in 1 (0.7%) patient.

CONCLUSION: Avastin is generally a safe drug for treatment of ocular neovascularization. The complications reported were more associated with the technique of the procedure and not the drug itself and were easily manageable. Drug-related complications were limited, transient and easily managed with treatment.

PMID: 23901669 [PubMed - in process]

Eye (Lond). 2013 Aug 2. doi: 10.1038/eye.2013.159. [Epub ahead of print]

Influence of seasonal sunlight intensity and iris color on the anti-VEGF therapy for neovascular age -related macular degeneration.

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Purpose: To investigate the influence of seasonal light intensity and patients' iris color on the visual recovery after anti-vascular endothelial growth factor (VEGF) therapy with ranibizumab or bevacizumab for neovascular age-related macular degeneration (AMD).

Methods: The visual acuity of 555 eyes (529 patients) with neovascular AMD was evaluated after intravitreal injections of either ranibizumab or bevacizumab in respect to global radiation intensity and iris color.

Results: The functional results during anti-VEGF therapy revealed a seasonal oscillation with a negative correlation between visual recovery and global radiation intensity (R2=-0.756, P=0.004). Although the influence of the sunlight intensity on the visual recovery was significant after the first injection, this effect vanished within the continuous course of treatment. Regarding the improvement of functional recovery depending on iris color, dark-colored eyes (16.0%) gained 8.5±10.0 letters after the first injection and 9.9±12.8 letters after the second injection, compared with 3.4±8.6 letters and 4.4±11.0 letters in light-colored eyes (84.0%), respectively (P=0.005 and P=0.019).

Conclusions: Our results indicate that seasonal sunlight intensity and iris color might influence the visual recovery of neovascular AMD patients undergoing anti-VEGF therapy. Our findings may be used as suggestions to refine individual anti-VEGF therapy regimens, especially in patients with light-colored eyes.Eye advance online publication, 2 August 2013; oi:10.1038/eye.2013.159.

PMID: 23907626 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmology. 2013 Jul 25. pii: S0161-6420(13)00528-9. doi: 10.1016/j.ophtha.2013.06.024. [Epub ahead of print]

Appearance of Regressing Drusen on Optical Coherence Tomography in Age-related Macular Degeneration.

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OBJECTIVE: To describe and interpret a multilaminar sub-retinal pigment epithelium (RPE) intense hyper-reflectivity observed in vivo in eyes clinically diagnosed with regressing drusen.

DESIGN: Observational case series.

PARTICIPANTS: Twenty-three consecutive patients clinically diagnosed with regressing calcific drusen due to nonneovascular age-related macular degeneration (AMD).

METHODS: Patients were submitted to confocal scanning laser ophthalmoscopy (cSLO) fundus imaging and "eye-tracked" spectral-domain optical coherence tomography (SD-OCT).

MAIN OUTCOME MEASURES: Localization and possible origin and composition of the multilaminar sub-RPE hyperreflectivity.

RESULTS: Thirty eyes of 23 consecutive patients (8 male and 15 female; mean age, 82.7±10.1 years) showing on SD-OCT an intense multilaminar sub-RPE hyperreflectivity, which matched with regressing calcific drusen as visualized by cSLO infrared (IR) and MultiColor (Heidelberg Engineering, Heidelberg, Germany) images, were included in this study. The multilaminar hyperreflectivity was found to localize to beneath the RPE and above the outer Bruch's membrane (oBM) layer. A mean of 1.2 multilaminar sub-RPE hyperreflectivities per SD-OCT scan were identified by 2 readers. The SD-OCT analysis allowed the 2 readers to describe 3 different types of sub-RPE hyperreflectivity. "Type 1" laminar/multilaminar hyperreflectivity (found in 24 scans of 12 eyes) was characterized by an intense signal originating from what we interpreted as the inner Bruch's membrane (iBM) layer. "Type 2" multilaminar hyperreflectivity (found in 130 scans of 27 eyes) was characterized by an intense signal originating from the oBM layer. "Type 3" multilaminar fragmented hyperreflectivity (found in 22 scans of 11 eyes) was characterized by an intense signal originating from what we interpreted as both the iBM and the oBM, showing different degrees of fragmentation.

CONCLUSIONS: We describe a novel SD-OCT finding appearing as multilaminar sub-RPE intense hyper-reflectivity observed in vivo in eyes with regressing drusen. This multilaminar sub-RPE hyperreflectivity could be interpreted as layers of lipid mineralization (membranous debris also called "lipoprotein-derived debris" developing calcification), internal and external to the basement membrane, with different degrees of fragmentation.

PMID: 23891523 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2013 Aug;27(4):268-75. doi: 10.3341/kjo.2013.27.4.268. Epub 2013 Jun 28.

Foveal Thickness between Stratus and Spectralis Optical Coherence Tomography in Retinal Diseases.

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PURPOSE: To compare the foveal thickness (FT) parameters measured by Stratus optical coherence tomography (OCT) and Spectralis OCT in various retinal diseases and to construct conversion formulas between the two types of OCT devices.

METHODS: We examined 366 consecutive patients (475 eyes) with retinal diseases and 13 normal controls (13 eyes). The patients were categorized into eight retinal disease groups. The mean amount and distribution of foveal thickness differences (FTD) measured by Stratus and Spectralis OCT were determined, and conversion formulas were constructed for Stratus OCT FT from Spectralis OCT FT for each retinal disease group.

RESULTS: Among retinal diseases, the mean FTD was significantly larger in exudative age-related macular degeneration (AMD) patients (mean ± SD, 94.0 ± 55.0 μm) compared to normal subjects (66.2 ± 11.7 μm; $p < 0.0001$). The proportion of eyes with a mean FTD outside 1.96 standard deviations of normal subject FTD was greatest in the exudative AMD (50.0%) group and smallest in the macular hole (18.2%) group. The predicted FTs obtained through the conversion formulas showed lower variance than the actual FTD values, especially in the exudative AMD group. The prediction line for exudative AMD deviated most from that of normal subjects.

CONCLUSIONS: FTD shows diverse values and variances among various retinal diseases, especially in exudative AMD, which indicates that Stratus OCT FT cannot be predicted from Spectralis OCT FT by FTD value alone. We constructed statistically significant conversion formulas, which provided more reliable methods to predict Stratus OCT-measured FT from Spectralis OCT measurements for different retinal disease groups.

PMID: 23908573 [PubMed - in process]

Am J Ophthalmol. 2013 Jul 24. pii: S0002-9394(13)00371-1. doi: 10.1016/j.ajo.2013.05.034. [Epub ahead of print]

Geographic Chorioretinal Atrophy in Pseudoxanthoma Elasticum.

Schoenberger SD, Agarwal A.

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PURPOSE: To describe a series of patients with geographic atrophy independent of choroidal neovascularization (CNV) in pseudoxanthoma elasticum and to report progression over time.

DESIGN: Retrospective observational case series.

METHODS: Records of all Vanderbilt Eye Institute patients with pseudoxanthoma elasticum and at least 1 set of color fundus photographs were reviewed (41 eyes of 21 patients). Fluorescein angiography, fundus autofluorescence, and optical coherence tomography images were reviewed, when available. In patients with geographic atrophy and at least 1 year of follow-up, atrophy was measured using fundus photographs. Main outcome measures included incidence of geographic atrophy, progression over time, and macular features associated with development or progression of geographic atrophy.

RESULTS: Eight eyes (20%) of 5 patients had geographic atrophy independent of CNV. Progression was documented in 6 eyes of 4 patients followed for at least 1 year (mean 3.5 years). Mean initial and final area was 2.9 and 9.5 mm2, respectively, and growth rate was 1.7 mm2 per year. Of the 6 eyes, 3 had a final visual acuity of 20/20 and the other 3 ranged from 20/150 to 20/400. All 8 eyes had pattern dystrophy, and 5 had linear pigment deposits that appeared to predict development or growth of atrophy.

CONCLUSIONS: Isolated geographic atrophy independent of CNV can develop in pseudoxanthoma elasticum, causing significant vision loss. Linear pigmented pattern dystrophy appears to predate geographic atrophy. Progression is similar to age-related macular degeneration. Recognition of this feature is important, especially if therapies to slow or reverse geographic atrophy become available.

PMID: 23891334 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2013 Jul 26. doi: 10.1111/aos.12192. [Epub ahead of print]

The entoptic view of the retinal vessels.

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Abstract: The first time the retinal vessels were seen in man in vivo was reported in 1819 by Purkinje as an entoptic view. This was understood to show the shadow of the vessels, an interpretation objected to in 1834 by Brewster. Müller in 1855 (Über die entoptische wahrnehmung der netzhautgefässe, insbesondere als beweismittel für die lichtperception durch die nach hinten gelegenen netzhautelemente, Stahel, Würzburg) used the phenomenon to deduce the location of the photoreceptive layer of the retina, and his conclusion is accepted as true today. Because the phenomenon has some characteristics of an afterimage, it touches on the question of what is subjective and what is objective physical reality. It was recently used clinically to measure potential visual acuity and in the diagnoses of diabetic retinopathy and macular degeneration.

PMID: 23890291 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2013 Jul 26. doi: 10.1111/aos.12185. [Epub ahead of print]

Stem cell-based treatment in geographic atrophy: promises and pitfalls.

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Abstract: Geographic atrophy is a common and untreatable form of advanced age-related macular degeneration. The degeneration primarily affects the retinal pigment epithelium and photoreceptors of the retina and their restoration by cell transplantation seems attractive. Recently, a patient with geographic atrophy was the first human to receive cells derived from human embryonic stem cells. In this short review, the rationale, potential and obstacles for stem cell-derived therapy in geographic atrophy are discussed.

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Acta Ophthalmol. 2013 Jul 26. doi: 10.1111/aos.12178. [Epub ahead of print]

There is no relation between the occurrence of proliferative vitreoretinopathy and the location of the donor site after transplantation of a free autologous retinal pigment epithelium-choroid graft.

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Purpose: A free autologous retinal pigment epithelium (RPE)-choroid graft can be harvested during transplantation surgery from a 6 or 12 o'clock site in the midperiphery. This study evaluated whether

proliferative vitreoretinopathy (PVR) occurs more frequently in patients with an inferior donor site retinotomy, which is not closed by the tamponade and is in contact with the hydrophilic, pro-inflammatory and fibrotic environment, than in patients with a superior donor site retinotomy.

Methods: Retrospective analysis of a prospective cohort of 246 patients with exudative age-related macular degeneration treated with an RPE-choroid graft transplantation and a lighter-than-water, 5000 centistoke silicone oil endotamponade. The location of the donor site, the presence or absence of PVR development and the location of PVR were noted. The two-tailed Fisher's exact test was used for statistical analysis.

Results: Thirty-nine of 246 (15.9%) patients developed PVR, of whom 35 had a superior donor site and four an inferior donor site. Of the 209 patients without PVR, 155 had a superior donor site and 25 had an inferior one. For 27 patients, no donor site location was explicitly documented in the patient files. We found no difference between the groups with a superior or inferior donor site and the occurrence of PVR ($p = 0.8$).

Conclusion: Shifting the inflammatory aqueous milieu away from the graft donor site does not prevent the occurrence of PVR.

PMID: 23890210 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Jul 26;54(7):5087-96. doi: 10.1167/iovs.12-11239.

Subretinal implantation of retinal pigment epithelial cells derived from human embryonic stem cells: improved survival when implanted as a monolayer.

Diniz B, Thomas P, Thomas B, Ribeiro R, Hu Y, Brant R, Ahuja A, Zhu D, Liu L, Koss M, Maia M, Chader G, Hinton DR, Humayun MS.

Doheny Eye Institute, Los Angeles, California.

PURPOSE: To evaluate cell survival and tumorigenicity of human embryonic stem cell-derived retinal pigment epithelium (hESC-RPE) transplantation in immunocompromised nude rats. Cells were transplanted as a cell suspension (CS) or as a polarized monolayer plated on a parylene membrane (PM).

METHODS: Sixty-nine rats (38 male, 31 female) were surgically implanted with CS (n = 33) or PM (n = 36). Cohort subsets were killed at 1, 6, and 12 months after surgery. Both ocular tissues and systemic organs (brain, liver, kidneys, spleen, heart, and lungs) were fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned. Every fifth section was stained with hematoxylin and eosin and analyzed histologically. Adjacent sections were processed for immunohistochemical analysis (as needed) using the following antibodies: anti-RPE65 (RPE-specific marker), anti-TRA-1-85 (human cell marker), anti-Ki67 (proliferation marker), anti-CD68 (macrophage), and anti-cytokeratin (epithelial marker).

RESULTS: The implanted cells were immunopositive for the RPE65 and TRA-1-85. Cell survival ($P = 0.006$) and the presence of a monolayer ($P < 0.001$) of hESC-RPE were significantly higher in eyes that received the PM. Gross morphological and histological analysis of the eye and the systemic organs after the surgery revealed no evidence of tumor or ectopic tissue formation in either group.

CONCLUSIONS: hESC-RPE can survive for at least 12 months in an immunocompromised animal model. Polarized monolayers of hESC-RPE show improved survival compared to cell suspensions. The lack of teratoma or any ectopic tissue formation in the implanted rats bodes well for similar results with respect to safety in human subjects.

PMID: 23833067 [PubMed - in process] PMCID: PMC3726243 [Available on 2014/1/1]

Pathogenesis

Exp Eye Res. 2013 Jul 25. pii: S0014-4835(13)00216-9. doi: 10.1016/j.exer.2013.07.018. [Epub ahead of print]

VEGF but not PlGF disturbs the barrier of retinal endothelial cells.

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Abstract: Elevated permeability of retinal endothelial cells (REC), as observed in diabetic retinopathy (DR), is induced by extended exposure to ≥25 ng/ml vascular endothelial growth factor A165 (VEGF165) for up to 3 d and this effect is more pronounced when equimolar amounts of basic fibroblast growth factor (bFGF) and insulin-like growth factor (IGF-1) are present. Down-regulation of the tight-junction protein claudin-1 and its loss from the plasma membrane is associated with induced higher permeability, whereas other tight-junction proteins (e.g. claudin-3, claudin-5, ZO-1) show only subtle changes in our experimental setting. Using immortalized bovine REC (iBREC) as a well-established model, we investigated effects of other members of the VEGF family, i.e. VEGF121, placental growth factor (PlGF-1 and PlGF-2) and viral VEGF-E which activate different sets of VEGF receptors, on barrier function after extended treatment: iBREC were incubated with 1-100 ng/ml of the growth factors for up to 2 days before barrier function was assessed by measuring transendothelial resistance (TER). Presence of TJ-proteins was determined by western blot analyses and immunofluorescence staining. Similar experiments were performed to evaluate whether the primary actions of PlGF-1, PlGF-2 or VEGF121 are modulated by bFGF or IGF-1 when all growth factors (each at 25 ng/ml, but 10 ng/ml IGF-1) act simultaneously at equimolar concentrations. We also studied the potential normalization of the barrier disturbed with combinations of growth factors by addition of the VEGF-specific Fab fragment ranibizumab or the recombinant protein aflibercept which binds VEGF and PlGF. Whereas 1 ng/ml VEGF-E were sufficient to impair the iBREC barrier, a higher concentration of 100 ng/ml VEGF121 was needed to reduce TER and expression of claudin-1 over 2 days. By PlGF-1 or PlGF-2, the barrier was not affected even at the highest concentration tested (100 ng/ml) and these factors also did not modulate the effect of VEGF165. The weak barrier derangement caused by VEGF121 was slightly enhanced by bFGF and IGF-1. After induction of the barrier breakdown with various combinations of all growth factors included in the study, normal TER and claudin-1 expression was re-established by ranibizumab. Both VEGF inhibitors ranibizumab and aflibercept similarly reinstated lost claudin-1, even when applied at a small fraction of the clinically relevant concentrations. These results show that VEGF-A, but not PlGF impairs the barrier function of iBREC and that the longer isoform VEGF165 is more potent than VEGF121. To induce barrier dysfunction in iBREC, activation of VEGF receptor 2 - probably in concert with neuropilin-1 - seems to be sufficient because VEGF-E and VEGF165, but not PlGF-1/-2 reduced TER or claudin-1 expression.

PMID: 23891860 [PubMed - as supplied by publisher]

Exp Eye Res. 2013 Jul 26. pii: S0014-4835(13)00215-7. doi: 10.1016/j.exer.2013.07.017. [Epub ahead of print]

The role of SIRT1 in ocular aging.

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Abstract: The sirtuins are a highly conserved family of nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylases that helps regulate the lifespan of diverse organisms. The human genome

encodes seven different sirtuins (SIRT1-7), which share a common catalytic core domain but possess distinct N- and C-terminal extensions. Dysfunction of some sirtuins have been associated with age-related diseases, such as cancer, type II diabetes, obesity-associated metabolic diseases, neurodegeneration, and cardiac aging, as well as the response to environmental stress. SIRT1 is one of the targets of resveratrol, a polyphenolic SIRT1 activator that has been shown to increase the lifespan and to protect various organs against aging. A number of animal studies have been conducted to examine the role of sirtuins in ocular aging. Here we review current knowledge about SIRT1 and ocular aging. The available data indicate that SIRT1 is localized in the nucleus and cytoplasm of cells forming all normal ocular structures, including the cornea, lens, iris, ciliary body, and retina. Upregulation of SIRT1 has been shown to have an important protective effect against various ocular diseases, such as cataract, retinal degeneration, optic neuritis, and uveitis, in animal models. These results suggest that SIRT1 may provide protection against diseases related to oxidative stress-induced ocular damage, including cataract, age-related macular degeneration, and optic nerve degeneration in glaucoma patients.

PMID: 23892278 [PubMed - as supplied by publisher]

Epidemiology

J Atheroscler Thromb. 2013 Aug 1. [Epub ahead of print]

Cardio-Ankle Vascular Index Elevation in Patients with Exudative Age-Related Macular Degeneration.

Taniguchi H, Shiba T, Takahashi M, Kanai H, Hori Y, Shirai K, Maeno T.

Department of Ophthalmology, Toho University Sakura Medical Center.

Aim: To clarify whether the cardio-ankle vascular index (CAVI) independently contributes to the development of exudative age-related macular degeneration (AMD) compared with carotid arteriosclerosis parameters and other risk factors.

Methods: Eighty-eight consecutive patients with exudative AMD were enrolled. A control group (40 age-matched men, 65 years of age or older) was also evaluated, and the parameters were compared between the two groups. A logistic regression analysis was used to determine independent factors for the diagnosis of AMD. In addition, simple linear and multiple regression analyses were used to determine the relationships between the CAVI and other parameters.

Results: The carotid intima-media thickness and plaque scores in the AMD group did not differ significantly from those observed in the control group. The CAVI in the AMD group was significantly (p=0.01) higher than that observed in the control group. A logistic regression analysis showed that the CAVI (odds ratio [OR], 1.91; 95% confidence interval [CI], 1.26-7.20; p= 0.007) and the use of lipid-lowering drugs (OR, 0.29; 95% CI, 0.10-0.86; p= 0.03) independently contributed to the diagnosis of AMD. Age, the high-sensitivity C-reactive protein level and the incidence of exudative AMD each independently contributed to the CAVI.

Conclusions: The CAVI is more significantly associated with exudative AMD than carotid atherosclerosis parameters. The overall arterial stiffness is correlated with the pathogenesis of exudative AMD. The CAVI is a useful marker of exudative AMD in elderly patients with arteriosclerosis risk factors.

PMID: 23903297 [PubMed - as supplied by publisher]

Genetics

Zhonghua Yan Ke Za Zhi. 2013 Apr;49(4):350-6.

[Association of single nucleotide polymorphism in complement factor I gene with age-related macular degeneration]. [Article in Chinese]

Wu PB, Gu H, Yang XF, Liu NP.

Beijing Ophthalmology & Visual Sciences Key Laboratory, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China.

OBJECTIVE: To investigate the association of three single nucleotide polymorphism (SNP) in the upstream of the complement factor I (CFI) gene with age-related macular degeneration (AMD) in a Chinese population.

METHODS: Case-control study. Patients with early or late stages of AMD and healthy control subjects were recruited. Genomic DNA was extracted from the peripheral venous blood. Genotyping for SNP rs10033900: T > C, rs13117504: C > G and rs2285714: C > T in the upstream of the CFI gene was determined by using a method of polymerase chain reaction (PCR) followed by restriction enzyme digestion and direct sequencing. Statistical analysis was performed using the R statistical analysis package.

RESULTS: A total of three hundreds and seventy nine participants were enrolled in the study, including 119 patients with exudative AMD, 120 patients with early AMD and 140 control individuals without AMD. Frequency of the minor allele C of rs10033900 in exudative AMD, early AMD and control groups were 17.4% (40/230), 22.5% (54/240) and 29.3% (82/280), respectively. Significant association of rs10033900 was detected with exudative AMD ($\chi(2) = 9.82$, P = 0.002, OR = 0.57, 95%CI: 0.36 - 0.88), but not with early AMD ($\chi(2) = 3.08$, P = 0.079). Frequency of the minor allele G of rs13117504 in exudative AMD, early AMD and control groups were 38.6% (91/236), 54.2% (130/240) and 51.8% (145/280), respectively. Significant association of rs13117504 was detected with exudative AMD ($\chi(2) = 9.03$, P = 0.003, OR = 0.56, 95%CI: 0.39 - 0.82), but not with early AMD ($\chi(2) = 0.29$, P = 0.59). No association was detected between rs2285714 and exudative AMD ($\chi(2) = 0.72$, P = 0.31) or between rs2285714 and early AMD ($\chi(2) = 2.30$, P = 0.13).

CONCLUSION: The minor allele of rs10033900 and rs13117504 in the CFI gene may have a protective role against the risk of exudative AMD.

PMID: 23900096 [PubMed - in process]

Diet

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Candidate gene study of macular response to supplemental lutein and zeaxanthin.

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Abstract: Supplementation with carotenoids is proposed to protect against age-related macular degeneration. There is, however, considerable variability in retinal macular pigment response, which may be due to underlying genetic variation. The purpose of this study was to determine whether genetic factors, which have been previously associated with cross-sectional macular pigment levels in the retina or serum lutein, also influence response to supplementation. To this end we conducted an association study in 310 subjects from the TwinsUK cohort between variants in 8 candidate genes and serum lutein and retinal

macular pigment optical density (MPOD) levels before and after supplementation. Four variants were associated with MPOD response to supplementation ($p < 0.05$): rs11057841 (SCARB1), rs4926339 (RPE65), rs1929841 (ABCA1) and rs174534 (FADS1). We also confirmed previous associations between rs6564851 near BMCO1 ($p < 0.001$) and rs11057841 within SCARB1 ($p = 0.01$) and baseline measures of serum lutein; while the latter was also associated with MPOD response, none of the BMCO1 variants were. Finally, there was evidence for association between variants near RPE65 and ELOVL2 and changes in lutein concentration after supplementation. This study is the first to show association between genetic variants and response to carotenoids supplementation. Our findings suggest an important link between MP response and the biological processes of carotenoids transport and fatty acid metabolism.

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Astaxanthin protects ARPE-19 cells from oxidative stress via upregulation of Nrf2-regulated phase II enzymes through activation of PI3K/Akt.

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PURPOSE: Oxidative stress on retinal pigment epithelial (RPE) cells is thought to play a crucial role in the development and progression of age-related macular degeneration. Astaxanthin (AST) is a carotenoid that shows significant antioxidant properties. This study was designed to investigate the protective effect of AST on ARPE-19 cells against oxidative stress and the possible underlying mechanism.

METHODS: ARPE-19 cells exposed to different doses of H2O2 were incubated with various concentrations of AST and cell viability subsequently detected with the (4-[3-[4-iodophenyl]-2-4(4-nitrophenyl)-2H-5-tetrazolio-1,3-benzene disulfonate]; WST-1) assay. The apoptosis rate and intracellular levels of reactive oxygen species (ROS) were measured with flow cytometry. NAD(P)H quinine oxidoreductase 1 (NQO1), hemeoxygenase-1 (HO-1), glutamate-cysteine ligase modifier subunit (GCLM), and glutamate-cysteine ligase catalytic subunit (GCLC) expression were examined with real-time PCR and western blotting. The nuclear localization of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein and the expression levels of cleaved caspase-3 and protein kinase B proteins were evaluated with western blotting.

RESULTS: AST clearly reduced H2O2-induced cell viability loss, cell apoptosis, and intracellular generation of ROS. Furthermore, treatment with AST activated the Nrf2-ARE pathway by inducing Nrf2 nuclear localization. Consequently, Phase II enzymes NQO1, HO-1, GCLM, and GCLC mRNA and proteins were increased. AST inhibited expression of H2O2-induced cleaved caspase-3 protein. Activation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway was involved in the protective effect of AST on the ARPE-19 cells.

CONCLUSIONS: AST protected ARPE-19 cells against H2O2-induced oxidative stress via Nrf2-mediated upregulation of the expression of Phase II enzymes involving the PI3K/Akt pathway.

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Retinal structure in vitamin A deficiency as explored with multimodal imaging.

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PURPOSE: To define the retinal structural abnormalities in a patient with vitamin A deficiency.

METHODS: The patient had a complete ophthalmic examination, electroretinography (ERG), short-wave fundus autofluorescence (SW-AF) and spectral domain optical coherence tomography (SD-OCT) imaging. Serum vitamin A levels were measured.

RESULTS: A 63-year-old man with alcoholic cirrhosis, sclerosing cholangitis and chronic pancreatitis experienced blurred vision and nyctalopia for over a year. There was no family history of eye disorders or consanguinity. His best-corrected visual acuity was 20/20 in each eye; color vision as determined with Ishihara color plates was normal in each eye. Anterior segment examination was unremarkable. He was pseudophakic in both eyes. Standard ERGs showed non-detectable rod function, a cone-mediated dark-adapted response to the standard flash and borderline reduced cone function. Serum vitamin A levels were below 0.06 mg/L (normal 0.3-1.2 mg/L). Fundus examination revealed numerous round yellow-white lesions along the superior arcade and nasal to the optic nerve in both eyes. These lesions were hypoautofluorescent on SW-AF. SD-OCT cross sections demonstrated that they were focal disruptions distal to the ellipsoid band of the photoreceptors with hyperreflective images bulging up the ellipsoid and region. The retinal pigment epithelium and the inner retina appeared intact. Limited and gradual vitamin A supplementation for over a month (20 000 IU/day) led to a dramatic improvement in retinal function and to the resolution of the symptoms. The retinal lesions remained unchanged.

CONCLUSIONS: Imaging of this patient with nyctalopia and severe rod dysfunction suggests that the retinal white lesions known to occur in vitamin A deficiency localize to the photoreceptor layer, particularly the outer segment. On OCT, they are reminiscent of lesions observed in genetic diseases with retinoid cycle dysfunction and of drusenoid subretinal deposits, an abnormality commonly associated with age-related macular degeneration.

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