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Drug Treatment

Retina. 2011 Apr 14. [Epub ahead of print]

ONE-YEAR RESULTS OF A FLEXIBLE REGIMEN WITH RANIBIZUMAB THERAPY IN MACULAR DEGENERATION: Relationship with the Number of Injections.

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PURPOSE: To evaluate the efficacy and safety of a flexible regimen with intravitreal injections of ranibizumab in patients with naive choroidal neovascularization secondary to age-related macular degeneration and to determine whether the final outcome is related to the number of injections.

METHODS: Prospective, noncomparative, consecutive case series study. We included 90 eyes of 88 patients that were initially treated with 3 consecutive monthly intravitreal injections of ranibizumab, and thereafter, follow-up visits were progressively spread out to a maximum of 8 weeks apart in the absence of visual acuity loss and signs of lesion activity. The primary end points were changes in visual acuity (Early Treatment Diabetic Retinopathy Study letters), foveal thickness measured by spectral-domain optical coherence tomography, and lesion size (LS) measured by fluorescein angiography.

RESULTS: The median visual acuity improved from 53 letters at baseline to 60 letters at Month 1 ($P < 0.0001$), 63 letters at Month 3 ($P < 0.0001$), and 60 letters at Month 12 ($P < 0.0001$). A significant reduction was also observed in foveal thickness and LS ($P < 0.0001$). The mean number of injections was 4.4, and the mean number of visits was 8.0. Treatment consisted of 3 injections for 40% of patients, and 60% of patients received more than 3 injections. No significant association was observed between the visual acuity improvement and the number of injections. No relevant side effects were observed.

CONCLUSION: A flexible regimen with ranibizumab therapy is efficacious and safe in patients with neovascular age-related macular degeneration, reducing both the burden of injections and follow-up visits. The visual acuity improvement was independent of the number of injections.

PMID: 21499194 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2011 Apr 13. pii: E60EFC46-CB89-4567-8C73-7E73546B8ACC. doi: 10.5301/EJO.2011.7430. [Epub ahead of print]

Remission and dropout rate of anti-VEGF therapy for age-related macular degeneration.

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Purpose: Anti-vascular endothelial growth factor (VEGF) therapy is a first-line treatment for age-related macular degeneration (AMD) but frequent visits and injections can be a burden for patients. The purpose of this study is to estimate the remission rate and tolerability of anti-VEGF therapy for AMD in a clinical setting.

Methods: We investigated 90 eyes of 87 patients with AMD who underwent anti-VEGF therapy and were followed for more than 6 months. Ranibizumab and pegaptanib were used as anti-VEGF agents. Initial therapy was any of the following: a single injection, 3 consecutive monthly injections, or combination therapy with verteporfin. Additional injections were given as-needed during follow-up. An injection-free period greater than 6 months at the final observation was regarded as cessation; the reason for cessation was studied for each patient. Clinical characteristics were compared between patients with and without cessation.

Results: The mean follow-up period was 12.8 months. Mean logMAR before and 6 months after the treatment was 0.89 and 0.83, respectively. Cessation was noted in 32 eyes of 31 patients (35.6%). Remission was achieved in 13 (40.6%) of these eyes. The other cases either did not wish to undergo further treatment or dropped out. Poor baseline visual acuity (VA) was associated with cessation.

Conclusions: With current anti-VEGF therapy, remission was achieved in a limited number of AMD cases. The high frequency of voluntary cessation warrants consideration of an alternative treatment and/or supportive care for those with poor baseline VA.

PMID: 21500186 [PubMed - as supplied by publisher]

Biochem Biophys Res Commun. 2011 Apr 8. [Epub ahead of print]

Comparing protein VEGF inhibitors: In vitro biological studies.

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Abstract

VEGF inhibitors are widely used as a therapy for tumors and intravascular neovascular disorders, but limited and conflicting data regarding their relative biological potencies are available. The purpose of the study is to compare different protein VEGF inhibitors for their ability to inhibit VEGF-stimulated activities. We tested ranibizumab, the full-length variant of ranibizumab (Mab Y0317), bevacizumab, the VEGF-TrapR1R2 and Flt(1-3)-IgG in bioassays measuring VEGF-stimulated proliferation of bovine retinal microvascular endothelial cells or chemotaxis of human umbilical vein endothelial cells (HUVEC). The inhibitors were also compared for their ability to inhibit MAP kinase activation in HUVECs following VEGF addition. Ranibizumab, VEGF-TrapR1R2 and Flt(1-3)-IgG had very similar potencies in the bioassays tested. Bevacizumab was over 10-fold less potent than these molecules. Mab Y0317 was over 30-fold more potent than bevacizumab. The findings reported in this manuscript describe important intrinsic characteristics of several VEGF inhibitors that should be useful to interpret preclinical and clinical data.

PMID: 21501594 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmology. 2011 Apr 13. [Epub ahead of print]

A Systematic Comparison of Spectral-Domain Optical Coherence Tomography and Fundus Autofluorescence in Patients with Geographic Atrophy.

Sayegh RG, Simader C, Scheschy U, Montuoro A, Kiss C, Sacu S, Kreil DP, Prunte C, Schmidt-Erfurth U.

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PURPOSE: To evaluate spectral-domain optical coherence tomography (SD-OCT) in providing reliable and reproducible parameters for grading geographic atrophy (GA) compared with fundus autofluorescence (FAF) images acquired by confocal scanning laser ophthalmoscopy (cSLO).

DESIGN: Prospective observational study.

PARTICIPANTS: A total of 81 eyes of 42 patients with GA.

METHODS: Patients with atrophic age-related macular degeneration (AMD) were enrolled on the basis of total GA lesion size ranging from 0.5 to 7 disc areas and best-corrected visual acuity of at least 20/200. A novel combined cSLO-SD-OCT system (Spectralis HRA-OCT, Heidelberg Engineering, Heidelberg, Germany) was used to grade foveal involvement and to manually measure disease extent at the level of the outer neurosensory layers and retinal pigment epithelium (RPE) at the site of GA lesions. Two readers of the Vienna Reading Center graded all obtained volume stacks (20×20 degrees), and the results were correlated to FAF.

MAIN OUTCOME MEASURES: Choroidal signal enhancements and alterations of the RPE, external limiting membrane (ELM), and outer plexiform layer by SD-OCT. These parameters were compared with the lesion measured with severely decreased FAF.

RESULTS: Foveal involvement or sparing was definitely identified in 75 of 81 eyes based on SD-OCT by both graders (inter-grader agreement: $\kappa=0.6$, $P < 0.01$). In FAF, inter-grader agreement regarding foveal involvement was lower (48/81 eyes, inter-grader agreement: $\kappa=0.3$, $P < 0.01$). Severely decreased FAF was measured over a mean area of 8.97 mm² for grader 1 (G1) and 9.54 mm² for grader 2 (G2), consistent with the mean SD-OCT quantification of the sub-RPE choroidal signal enhancement (8.9 mm² [G1] -9.4 mm² [G2]) and ELM loss with 8.7 mm² (G1) -10.2 mm² (G2). In contrast, complete morphologic absence of the RPE layer by SD-OCT was significantly smaller than the GA size in FAF ($R(2)=0.400$). Inter-reader agreement was highest regarding complete choroidal signal enhancement (0.98) and ELM loss (0.98).

CONCLUSIONS: Absence of FAF in GA lesions is consistent with morphologic RPE loss or advanced RPE disruption and is associated with alterations of the outer retinal layers as identified by SD-OCT. Lesion size is precisely determinable by SD-OCT, and foveal involvement is more accurate by SD-OCT than by FAF.

PMID: 21496928 [PubMed - as supplied by publisher]

Retina. 2011 Apr 14. [Epub ahead of print]

TEN-YEAR FOLLOW-UP OF EYES TREATED WITH STEREOTACTIC FRACTIONATED EXTERNAL BEAM RADIATION FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To determine the long-term effects of stereotactic fractionated external beam radiation on eyes treated for neovascular age-related macular degeneration.

METHODS: A retrospective review of all eyes treated with stereotactic fractionated external beam radiation (20-40 Gy, 2-Gy fractions) between 1997 and 2000 was performed to identify eyes with ≥ 2 -year follow-up for analysis. A subset was imaged prospectively using a high-resolution Fourier-domain optical coherence tomography.

RESULTS: Among 94 eyes treated, 33 eyes (32 subjects) had ≥ 2 -year follow-up information (mean follow-up, 6.2 years; range, 2-10 years). Final visual acuity ranged from 20/50 to no light perception. Final macular findings included central geographic atrophy (49%), disciform scar (30%), and active choroidal neovascular membrane (9%). Fourier-domain optical coherence tomography images of three eyes with geographic atrophy revealed photoreceptor layer loss within areas of geographic atrophy with intact retinal morphology in areas of radiation exposure outside geographic atrophy. Radiation retinopathy was suspected in 18% and confirmed by fluorescein angiography in 15%, ranging from mild to neovascular glaucoma/phthisis bulbi (2 eyes). Mean time from stereotactic fractionated external beam radiation to development of radiation retinopathy was 5.4 years (range, 1-10 years).

CONCLUSION: A moderate rate of delayed radiation retinopathy was noted in eyes with neovascular age-related macular degeneration treated with stereotactic fractionated external beam radiation. Geographic atrophy was a common finding.

PMID: 21499195 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Apr 15. [Epub ahead of print]

Identification of Urinary Biomarkers for Age-related Macular Degeneration.

Guymer RH, Tao LW, Goh JK, Liew D, Ischenko O, Robman LD, Aung K, Cipriani T, Cain M, Richardson AJ, Baird PN, Langham R.

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Purpose: Age-related macular degeneration (AMD) can be considered as a chronic low-grade systemic inflammatory disease. This study was taken to test the associations of AMD with urinary pro-inflammatory cytokines, Transforming Growth Factor- $\beta 1$ (TGF- $\beta 1$), Macrophage Chemoattractant Protein-1 (MCP-1) and C3a-desArg, as potential non-invasive biomarkers for monitoring AMD.

Methods: A cross-sectional study of 103 AMD cases, comprising of early AMD (51), geographic atrophy (GA, 19) or choroidal neovascularisation (CNV, 33), and 54 unrelated controls, aged 73 ± 9 years, who attended the Royal Victorian Eye and Ear Hospital and private practice in Victoria, Australia. AMD status was determined from the bilateral retinal digital photographs and through angiography and optical coherence tomography images when confirmation of CNV was needed; Serum and urine cytokine levels were measured using immunoassay and the rs1061170 (Y402H) single nucleotide polymorphism of the complement factor H gene was determined.

Results: Multivariate logistic regression analyses demonstrated significant associations of urinary TGF- $\beta 1$ levels [OR+1.24 (1.02, 1.50), $p < 0.031$] and MCP-1 levels [OR+1.07 (1.02, 1.12), $p < 0.008$] with early AMD, and also MCP-1 levels with GA [OR+1.10 (1.03, 1.17), $p < 0.003$]. There was no correlation between urinary and serum cytokine levels. Individuals with one or more copies of the C allele (Y402H) were 2.5 times more likely to have urinary MCP-1 above median levels ($p < 0.040$).

Conclusions: This study demonstrates a novel finding of an association between the elevated urinary cytokines TGF- $\beta 1$ and MCP-1 levels and AMD. Further development of a urinary biomarker profile could provide a practical tool for detection of early AMD, progression monitoring, and assessment of treatment efficacy.

PMID: 21498607 [PubMed - as supplied by publisher]

Ophthalmologica. 2011 Apr 21;226(2):29-36. [Epub ahead of print]

Noninvasive Evaluation of Retinal Leakage Using Optical Coherence Tomography.

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Purpose: To demonstrate the association between changes in the blood-retinal barrier (BRB) identified by fluorescein leakage and those in the optical properties of the human retina determined by optical coherence tomography (OCT) and show how these changes can be quantified and their location identified within the retina. **Methods:** Two imaging techniques were applied: the retinal leakage analyzer, to map BRB function into intact or disrupted regions, and OCT, to measure refractive index changes along the light path within the human ocular fundus. **Results:** A total of 140 comparisons were made, 77 between areas of regions receiving the same classification (intact or disrupted BRB) and 63 between areas of regions receiving distinct classifications, from 4 pathological cases: 2 eyes with nonproliferative diabetic retinopathy and 2 eyes with wet age-related macular degeneration. In all cases, the distribution of OCT data between regions of intact and regions of disrupted BRB, identified by the retinal leakage analyzer, was quantified and was statistically significantly different ($p < 0.001$). In addition, it was found that the differences could be localized in the retina to specific structural sequences. **Conclusions:** Using a novel method to analyze OCT data, we showed that it may be possible to quantify differences in the extracellular compartment in eyes with retinal disease and alterations of the BRB. Based on quantitative techniques, our findings demonstrate the presence of indirect information on the BRB status within noninvasive OCT data.

PMID: 21508651 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2011 May;151(5):745-751.e1.

Indocyanine green angiography: a perspective on use in the clinical setting.

Yannuzzi LA.

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PURPOSE: To review the history of indocyanine green (ICG) angiography and to present a personal perspective on its use in the clinical setting today.

DESIGN: Perspective with literature review and opinions based on personal experience.

METHODS: To acquire views from international retinal physicians experienced with the technique on uses in their facilities and to compare them to the author's personal standards.

RESULTS: The author and contributing retinal physicians had surprisingly similar views for most, but not all, applications for ICG angiography use in the clinical setting.

CONCLUSIONS: ICG angiography is recommended for a few highly selective chorioretinal disorders, including certain forms of neovascularization in age-related macular degeneration, other neovascular maculopathies, chronic central serous chorioretinopathy, choroidal hemangiomas, and posterior uveitis.

PMID: 21501704 [PubMed - in process]

J Hum Hypertens. 2011 Apr 21. [Epub ahead of print]

How does hypertension affect your eyes?

Bhargava M, Ikram MK, Wong TY.

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Abstract

Hypertension has profound effects on various parts of the eye. Classically, elevated blood pressure results in a series of retinal microvascular changes called hypertensive retinopathy, comprising of generalized and focal retinal arteriolar narrowing, arteriovenous nicking, retinal hemorrhages, microaneurysms and, in severe cases, optic disc and macular edema. Studies have shown that mild hypertensive retinopathy signs are common and seen in nearly 10% of the general adult non-diabetic population. Hypertensive retinopathy signs are associated with other indicators of end-organ damage (for example, left ventricular hypertrophy, renal impairment) and may be a risk marker of future clinical events, such as stroke, congestive heart failure and cardiovascular mortality. Furthermore, hypertension is one of the major risk factors for development and progression of diabetic retinopathy, and control of blood pressure has been shown in large clinical trials to prevent visual loss from diabetic retinopathy. In addition, several retinal diseases such as retinal vascular occlusion (artery and vein occlusion), retinal arteriolar emboli, macroaneurysm, ischemic optic neuropathy and age-related macular degeneration may also be related to hypertension; however, there is as yet no evidence that treatment of hypertension prevents vision loss from these conditions. In management of patients with hypertension, physicians should be aware of the full spectrum of the relationship of blood pressure and the eye. Journal of Human Hypertension advance online publication, 21 April 2011; doi:10.1038/jhh.2011.37.

PMID: 21509040 [PubMed - as supplied by publisher]

Optometry. 2011 Apr 19. [Epub ahead of print]

Charles Bonnet syndrome.

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BACKGROUND: Charles Bonnet syndrome (CBS) involves nonthreatening hallucinations in patients who have no neurological and no psychological abnormalities but with significant visual impairment secondary to ocular disease, such as macular degeneration and diabetic retinopathy. Because of the fear of a mental illness being diagnosed, patients are often reluctant to discuss these hallucinations.

CASE REPORTS: Three cases are presented of patients who experienced CBS caused by decreased vision. Each patient had decreased vision and related visual hallucinations that were consistent with CBS. The first patient underwent magnetic resonance imaging and psychological evaluation, which confirmed our suspicion. The other 2 patients were not willing to undergo further testing, so our diagnosis is presumptive.

CONCLUSION: Management for these hallucinations includes treatment of the actual ocular disease as well as optimizing vision for the patient using appropriate low vision devices. As the population continues to age, more patients will be seen with reduced vision caused by a myriad of ocular diseases, increasing the likelihood that more patients may present with CBS in the future. It is therefore prudent to become familiar with the syndrome so primary care optometrists can properly identify CBS and help their patients deal with it.

PMID: 21511535 [PubMed - as supplied by publisher]

Epidemiology & pathogenesis

Invest Ophthalmol Vis Sci. 2011 Apr 15. [Epub ahead of print]

Reticular drusen associated with geographic atrophy in age-related macular degeneration.

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Purpose: To characterize reticular drusen(RDR) in patients with geographic atrophy(GA) secondary to age-related macular degeneration(AMD) in a prospective, multicenter, natural history study.

Methods: Confocal scanning laser ophthalmoscopy(cSLO) three-field fundus autofluorescence(FAF, exc.488, em.500-700nm), near-infrared reflectance(IR 820nm), and blue reflectance(BR 488nm) images as well as red-free(RF) and color fundus(CF) camera photographs were recorded in 458 GA patients. The digital images were evaluated by two independent readers with subsequent senior reader arbitration for prevalence and topographic distribution of RDR using a modified Early Treatment Diabetic Retinopathy Study grid.

Results: RDR were detected with at least one cSLO modality in 286 of 458(62%) patients in either eye (bilateral 207[45%]), while they were visible in fundus camera photographs in 66 of 371(18%) patients (bilateral 48[13%]). Prevalence of RDR by cSLO imaging was associated with increasing age($p=0.007$) and female gender($p=0.007$), but not with GA total lesion area($p=0.38$). Cohen kappa statistics showed good interobserver agreement for FAF(0.81) and IR(0.82) imaging modes, while moderate agreement was found for BR(0.48), RF(0.48) and CF(0.40). On three-field FAF images RDR were present most frequently superior to the fovea(99%).

Conclusions: RDR represent a common phenotypic hallmark in GA eyes. RDR are readily identified using cSLO imaging technology. These observations may explain the high prevalence determined herein, in contrast to previous reports based on fundus photographs. Incorporation of these novel imaging modalities in future natural history studies may facilitate efforts aimed at defining the role and predictive value of RDR in the progression of AMD.

PMID: 21498612 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Apr 15. [Epub ahead of print]

Disturbed matrix metalloproteinase (MMP) activity of Bruch's membrane in age-related macular degeneration (AMD).

Hussain AA, Lee Y, Zhang JJ, Marshall J.

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Purpose: To evaluate the potential role of the matrix metalloproteinase (MMP) system of Bruch's membrane in the pathology of age-related macular degeneration.

Methods: The free and bound pools of gelatinase activity in Bruch's-choroid preparations were isolated by phosphate buffered saline (PBS) and sodium dodecyl sulphate (SDS) extraction respectively. Individual MMP species were separated by gelatin-substrate zymography and levels quantified by densitometric techniques. Altogether, 13 control (age range 71-99 years) and 6 AMD (age range 71-95 years) donor eyes were utilised.

Results: All the gelatinase components normally present in control samples were also present in AMD tissue without any significant differences in their molecular weights. Total levels (bound plus free) of active

MMP2 and MMP9 were significantly reduced in AMD donors ($p < 0.05$). The decrease in active MMP2 could be attributed to a similar reduction in the level of free pro-MMP2, the precursor to the active form. Reduction in active MMP9 occurred despite a nearly 3.5-fold increase in free pro-MMP9. The high molecular weight gelatinases denoted by HMW1 & -2 and comprising homo- and hetero-polymers of pro MMPs 2 & 9 were also raised in AMD ($p < 0.05$). The sequestration of free pro-MMPs 2 and -9 by these high molecular weight complexes may further contribute to reduced rates for activation of MMPs.

Conclusion: The reduction in the levels of activated MMPs -2 and -9 may be responsible for impaired matrix degradation of Bruch's membrane leading to the pathology associated with age-related macular degeneration (AMD). The degradation pathway is therefore a viable therapeutic target for future intervention.

PMID: 21498613 [PubMed - as supplied by publisher]

J Biol Chem. 2011 Apr 15. [Epub ahead of print]

Isolevuglandins and mitochondrial enzymes in the retina: mass spectrometry detection of post-translational modification of Sterol-metabolizing CYP27A1.

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Abstract

We report the first peptide mapping and sequencing of an in vivo isolevuglandin-modified protein. Mitochondrial cytochrome P450 27A1 (CYP27A1) is a ubiquitous multifunctional sterol C27-hydroxylase that eliminates cholesterol and likely 7-ketocholesterol from the retina and many other tissues. We investigated the post-translational modification of this protein with isolevuglandins, arachidonate oxidation products. Treatment of purified recombinant CYP27A1 with authentic iso[4]levuglandin E(2) (iso[4]LGE(2)) in vitro diminished enzyme activity in a time and phospholipid-dependent manner. A multiple reaction monitoring (MRM) protocol was then developed to identify the sites and extent of iso[4]LGE(2) adduction. CYP27A1 exhibited only three Lys residues, Lys-134, Lys-358, and Lys-476, that readily interact with iso[4]LGE2 in vitro. Such selective modification enabled the generation of an internal standard, (15)N-labeled CYP27A1 modified with iso[4]LGE(2), for the subsequent analysis of a human retinal sample. Two MRM transitions arising from the peptide AVLK(358)(-C(20)H(26)O(3))ETLR in the retinal sample were observed which co-eluted with the corresponding two (15)N transitions from the supplemented standard. These data demonstrate that modified CYP27A1 is present in the retina. We suggest that such protein modification impairs sterol elimination and likely has other pathological sequelae. We also propose that the post-translational modifications identified in CYP27A1 exemplify a general mechanism whereby oxidative stress and inflammation deleteriously affect protein function, contributing, for example to cholesterol-rich lesions associated with age-related macular degeneration and cardiovascular disease. The proteomic protocols developed in the present investigation are generally applicable to characterization of lipid-derived oxidative protein modifications occurring in vivo, including proteins bound to membranes.

PMID: 21498512 [PubMed - as supplied by publisher]

Aging Clin Exp Res. 2011 Apr 14. [Epub ahead of print]

Association between oxidative stress and macromolecular damage in elderly patients with age-related macular degeneration.

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Background: The aim of the present study was to determine whether age and sex affect the imbalance between oxidant production and antioxidant levels in age-related macular degeneration (ARMD) patients.

Methods: Total superoxide dismutase (T-SOD), total glutathione peroxidase (T-GSHPx), and catalase (CAT) activities, as well as malondialdehyde (MDA), protein carbonyl (PC), 8-Hydroxy-2'-deoxyguanosine (8-OHdG) and total oxidation status (TOS) levels, were measured in the following groups subdivided by age and sex: 156 early-ARMD patients; 80 wet-late ARMD patients; 72 dry-late ARMD patients; and 207 healthy controls.

Results: Among all study participants, women aged 50 to 54 years displayed higher T-SOD and T-GSHPx activities and lower MDA, PC, TOS and 8-OHdG levels than age-matched males ($p < 0.05$), whereas older females were not significantly different from age-matched older males. Significantly increased oxidative damage was associated with ARMD patients > 60 years of age in both sexes compared to controls ($p < 0.01$ for 60-64 and 65-69 year old ARMD subgroups; $p < 0.001$ for 70-74 and 75-80 year old ARMD subgroups). Multiple regression analysis demonstrates that age significantly affects antioxidant status and oxidative damage in ARMD patients compared to controls (controls, $p < 0.05$; ARMD patients, $p < 0.001$). Moreover, a direct correlation with antioxidant enzyme activities and an inverse correlation with oxidative DNA, protein and lipid damage was observed in premenopausal women (controls, $p < 0.05$; ARMD patients, $p < 0.001$).

Conclusions: Ageing and postmenopausal status could be aggravating factors contributing to redox imbalance and oxidative damage in ARMD patients.

PMID: 21499024 [PubMed - as supplied by publisher]

Am J Epidemiol. 2011 Apr 15. [Epub ahead of print]

Variations in Apolipoprotein E Frequency With Age in a Pooled Analysis of a Large Group of Older People.

McKay GJ, Silvestri G, Chakravarthy U, Dasari S, Fritsche LG, Weber BH, Keilhauer CN, Klein ML, Francis PJ, Klaver CC, Vingerling JR, Ho L, De Jong PT, Dean M, Sawitzke J, Baird PN, Guymer RH, Stambolian D, Orlin A, Seddon JM, Peter I, Wright AF, Hayward C, Lotery AJ, Ennis S, Gorin MB, Weeks DE, Kuo CL, Hingorani AD, Sofat R, Cipriani V, Swaroop A, Othman M, Kanda A, Chen W, Abecasis GR, Yates JR, Webster AR, Moore AT, Seland JH, Rahu M, Soubrane G, Tomazzoli L, Topouzis F, Vioque J, Young IS, Fletcher AE, Patterson CC.

Abstract

Variation in the apolipoprotein E gene (APOE) has been reported to be associated with longevity in humans. The authors assessed the allelic distribution of APOE isoforms $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$ among 10,623 participants from 15 case-control and cohort studies of age-related macular degeneration (AMD) in populations of European ancestry (study dates ranged from 1990 to 2009). The authors included only the 10,623 control subjects from these studies who were classified as having no evidence of AMD, since variation within the APOE gene has previously been associated with AMD. In an analysis stratified by study center, gender, and smoking status, there was a decreasing frequency of the APOE $\epsilon 4$ isoform with increasing age (χ^2 for trend = 14.9 (1 df); $P = 0.0001$), with a concomitant increase in the $\epsilon 3$ isoform (χ^2 for trend = 11.3 (1 df); $P = 0.001$). The association with age was strongest in $\epsilon 4$ homozygotes; the frequency of $\epsilon 4$ homozygosity decreased from 2.7% for participants aged 60 years or less to 0.8% for those over age 85 years, while the proportion of participants with the $\epsilon 3/\epsilon 4$ genotype decreased from 26.8% to 17.5% across the same age range. Gender had no significant effect on the isoform frequencies. This study provides strong support for an association of the APOE gene with human longevity.

PMID: 21498624 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2011 Apr 20. [Epub ahead of print]

Serum carotenoids and risk of age-related macular degeneration in a Chinese population sample.

Zhou H, Zhao X, Johnson EJ, Lim A, Sun E, Yu J, Zhang Y, Liu X, Snellingsen T, Shang F, Liu N.

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

Purpose: It has been hypothesized that the macular carotenoids may protect against age-related macular degeneration (AMD). We evaluated the association between serum concentrations of carotenoids and the presence of AMD in a case-control sample of elderly Chinese subjects.

Methods: Two hundred sixty-three individuals aged between 50 and 88 years enrolled in the study. Subjects included 82 cases with exudative AMD, 92 cases with early AMD, and 89 control individuals. Serum carotenoids (lutein, zeaxanthin, lycopene, α - and β -carotenes, β -cryptoxanthin) and retinol were measured using reverse-phase high-performance liquid chromatography (HPLC).

Results: Serum levels of carotenoids and retinol were significantly lower in cases with exudative AMD than in controls. Median levels of lutein and zeaxanthin were 0.538 and 0.101 $\mu\text{mol/L}$, respectively, in control subjects, and 0.488 and 0.076 $\mu\text{mol/L}$, respectively, in cases with exudative AMD. After adjustment for age, gender, smoking status and body mass index (BMI), a significant inverse association was observed for exudative AMD with serum zeaxanthin (RRR=0.04, 95%CI: 0-0.35), lycopene (RRR=0.22, 95% CI: 0.1-0.48), and α -carotene (RRR=0.24, 95% CI: 0.12-0.51). Early AMD was inversely associated only with lycopene (RRR=0.49, 95% CI: 0.28-0.86) but positively associated with α -carotene (RRR=2.22, 95% CI: 1.37-3.58). No significant associations between serum lutein and cases with early or exudative AMD were observed.

Conclusion: Our data suggest that higher levels of serum carotenoids, in particular zeaxanthin and lycopene, may be associated with lower likelihood of having exudative AMD. Serum levels of carotenoids were relatively higher in this Chinese cohort as compared to previous reports of other ethnicities.

PMID: 21508112 [PubMed - as supplied by publisher]

Pre-clinical

Expert Opin Drug Metab Toxicol. 2011 Apr 18. [Epub ahead of print]

Corneal cell culture models: a tool to study corneal drug absorption.

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Abstract

In recent times, there has been an ever increasing demand for ocular drugs to treat sight threatening diseases such as glaucoma, age-related macular degeneration and diabetic retinopathy. As more drugs are developed, there is a great need to test in vitro permeability of these drugs to predict their efficacy and bioavailability in vivo. Corneal cell culture models are the only tool that can predict drug absorption across ocular layers accurately and rapidly. Cell culture studies are also valuable in reducing the number of animals needed for in vivo studies which can increase the cost of the drug developmental process. Currently, rabbit corneal cell culture models are used to predict human corneal absorption due to the difficulty in human corneal studies. More recently, a three dimensional human corneal equivalent has been developed using three different cell types to mimic the human cornea. In the future, human corneal cell

culture systems need to be developed to be used as a standardized model for drug permeation.

PMID: 21500964 [PubMed - as supplied by publisher]

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