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MD Research News

Issue 16

Monday February 21, 2011

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Drug treatment

Retina. 2011 Feb 11. [Epub ahead of print]

LONGER-TERM OUTCOMES OF A PROSPECTIVE STUDY OF INTRAVITREAL RANIBIZUMAB AS A TREATMENT FOR DECREASED VISUAL ACUITY SECONDARY TO CENTRAL RETINAL VEIN OCCLUSION.

Chang LK, Spaide RF, Klancnik JM, Sorenson J, Slakter JS, Freund KB, Yannuzzi LA, Tseng JJ, Klein R.

From the *Vitreous-Retina-Macula Consultants of New York; and †LuEsther T. Mertz Retinal Research Center, Manhattan Eye, Ear, and Throat Hospital, New York, New York.

PURPOSE: To evaluate long-term effectiveness and safety of intravitreal injection of ranibizumab as a potential treatment for decreased visual acuity secondary to central retinal vein occlusion.

METHODS: In this prospective interventional case series, patients with central retinal vein occlusion were administered intravitreal ranibizumab 0.5 mg at baseline and monthly for 2 additional doses. Thereafter, the patients were given additional ranibizumab if they had macular edema by optical coherence tomography, leakage during fluorescein angiography, or any intraretinal hemorrhage.

RESULTS: There were 35 eyes of 35 patients who at baseline had a mean visual acuity of 44.2 Early Treatment Diabetic Retinopathy Study letters and a mean central macular thickness of 638 μm. At 12 months, mean visual acuity of 32 eyes improved by 16.5 letters and macular thickness decreased to 164 μm ($P < 0.001$ vs. baseline for each). At 24 months, mean visual acuity of 24 eyes improved by 17.8 letters and macular thickness was 263 μm ($P < 0.001$ vs. baseline for each). Patients received an average of 10.2 injections during the first year and 6.6 injections during the second year. No cases of endophthalmitis, retinal detachment, or neovascularization were observed.

CONCLUSION: Intravitreal ranibizumab caused a significant improvement in visual acuity and central retinal thickness, which persisted for up to 2 years with minimal side effects.

PMID: 21317833 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2011 Feb 12. [Epub ahead of print]

Modelling the prevalence of age-related macular degeneration (2010-2020) in the UK: expected impact of anti-vascular endothelial growth factor (VEGF) therapy.

Minassian DC, Reidy A, Lightstone A, Desai P.

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Aims: To project the number of cases with age-related macular degeneration (AMD) and the numbers with attributable sight loss in the UK in 2010-2020, taking into account the expected beneficial effect of the new anti-vascular endothelial growth factor (VEGF) therapies.

Methods: A 'system dynamics' approach was used in constructing the model to simulate the dynamics of the disease in large populations. The model computed the pool of affected cases over the simulation period, taking into account the expected demographic changes. Other determinants taken into account included: prevalence; incidence; mortality; and the expected efficacy and coverage of anti-VEGF treatment.

Results: In the UK, 608 213 persons in 2010 are estimated to have AMD, and this is expected to increase to 755 867 by the end of the decade. Numbers with sight loss from AMD are expected to rise from 223 224 in 2010 to 291 982 by 2020. Cases with sight loss due to neovascular AMD are expected to increase from 145 697 to 189 890 by the end of the decade.

Conclusions: The model predicts that the beneficial effects of the treatment would be outweighed by the strong anticipated demographic 'ageing' effect. This reaffirms the importance of continuing efforts to develop more effective and more broadly applicable therapies for AMD.

PMID: 21317425 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2011 Feb 7. pii: C46D32F4-D094-4523-94BD-AA401BC01DAD. [Epub ahead of print]

Extensive submacular hemorrhage following intravitreal ranibizumab for small occult choroidal neovascular membrane.

Rouvas A, Petrou P, Vergados I, Theodossiadis G, Theodossiadis P.

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Purpose: Although intravitreal ranibizumab represents an established therapeutic approach for exudative age-related macular degeneration (AMD), the possible occurrence of adverse events remains under ongoing research. The purpose of this report is to present an incidence of an extensive submacular hemorrhage after intravitreal ranibizumab administration.

Methods: Interventional case report.

Results: A 72-year-old woman was referred to our retinal department for sudden visual loss in the right eye (RE). She had undergone an intravitreal ranibizumab injection 48 hours prior to her presentation. She had known AMD with a confirmed occult choroidal neovascularization (CNV) for which she had been subjected to a total of 24 intravitreal injections in the RE (with monthly intervals) over the last 2 years. Clinical examination revealed an extensive submacular hemorrhage in the RE.

Conclusions: To our knowledge, this is the first report of a submacular hemorrhage soon after ranibizumab administration in a patient with a small occult CNV. Although such a correlation cannot be established, the authors underline the possibility of such an adverse event in patients with small CNVs following a long therapeutic course involving high injection volume.

PMID: 21319137 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2011 Feb;129(2):200-5.

Patient-Reported Outcomes Among Sham vs No-Treatment Controls From Randomized Trials.

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OBJECTIVE: To compare 2-year changes from baseline scores on the National Eye Institute Visual Function Questionnaire (NEI-VFQ) between similar participants assigned to sham and no-treatment control arms in randomized clinical trials of treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration.

METHODS: We retrospectively matched sham controls from a randomized trial to no-treatment controls (no sham or placebo) from another trial on 7 baseline prognostic criteria. Two-year changes in overall and subscale scores were compared using data from those who had 2-year interviews and also using the last follow-up observation carried forward to impute missing 2-year interview scores.

RESULTS: A match to a no-treatment control on all 7 criteria was identified for 62 of 238 sham controls. Among the 42 matched pairs of controls interviewed at 2 years, no important difference in 2-year change in NEI-VFQ scores overall or by subscale was observed. Findings were similar for the 56 matched pairs of controls who could be analyzed for 2-year changes in scores using the method of last follow-up observation carried forward.

CONCLUSIONS: Findings from this retrospective matched-pairs analysis suggest that sham treatment to mask patient participants in clinical trials may be unnecessary when patient-reported outcomes are of interest and standard instruments are administered by interviewers masked to treatment assignment. This analysis, together with our earlier analysis of visual acuity outcomes, questions the necessity for sham (placebo) controls in randomized clinical trials in ophthalmology when other methods to minimize outcome assessment bias are incorporated into the design.

PMID: 21320967 [PubMed - in process]

Other treatment & diagnosis

Br J Ophthalmol. 2011 Feb 11. [Epub ahead of print]

Expanded polytetrafluoroethylene as a substrate for retinal pigment epithelial cell growth and transplantation in age-related macular degeneration.

Krishna Y, Sheridan C, Kent D, Kearns V, Grierson I, Williams R.

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Background: Retinal pigment epithelial (RPE) transplantation presents a potential treatment for age-related macular degeneration (AMD). A suitable transplant membrane that can support an intact functioning RPE monolayer is required. Expanded polytetrafluoroethylene (ePTFE) possesses the physical properties required for a transplanting device; however, cells do not attach and spread on ePTFE. This study investigated the ability of surface-modified ePTFE to optimise the growth and function of healthy RPE monolayers.

Methods: ePTFE discs were modified by ammonia gas plasma treatment. ARPE-19 cells were seeded on the membranes and maintained in media supplemented with retinoic acid and reduced serum. Cell number, morphology and proliferation were analysed. RPE monolayer function was investigated through formation of cell-cell junctions and phagocytosis of photoreceptor outer segments (POS).

Results: Ammonia gas plasma treatment resulted in enhanced cell growth and good monolayer formation

with evidence of cell-cell junctional proteins. Furthermore, RPE monolayers were able to phagocytose POS in a time-dependent manner. Conclusions ePTFE can be surface-modified to support an intact functional monolayer of healthy RPE cells with normal morphology and the ability to perform RPE-specific functions. Following further investigation ePTFE may be considered for use in transplantation.

PMID: 21317216 [PubMed - as supplied by publisher]

Jpn J Ophthalmol. 2011 Jan;55(1):35-38. Epub 2011 Feb 18.

Utility values in Japanese patients with exudative age-related macular degeneration.

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PURPOSE: To investigate the utility values associated with visual loss due to age-related macular degeneration (AMD) in Japanese patients.

METHODS: Utility values in 48 Japanese patients with bilateral exudative AMD were measured using the time trade-off and standard gamble methods.

RESULTS: The time trade-off method utility values correlated with the best-corrected visual acuity (BCVA) in the better-seeing eye. The estimated utility values according to the BCVA in the better-seeing eye were 0.534 (BCVA, 0.01-0.15), 0.574 (0.2-0.3), 0.613 (0.4-0.6), and 0.653 (0.7-1.0). The utility values obtained by the standard gamble method were not significantly correlated with BCVA in the betterseeing eye.

CONCLUSIONS: The present results concur with those of previous studies showing that AMD causes a substantial decrease in patient utility values. The utility values obtained in the current study provide important information for use in cost-utility analysis of interventions for Japanese AMD patients.

PMID: 21331690 [PubMed - as supplied by publisher]

Ophthalmologica. 2011 Feb 12;225(4):207-210. [Epub ahead of print]

Photodynamic Therapy for Variant Central Serous Chorioretinopathy: Efficacy and Side Effects.

Gupta B, Mohamed MD.

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Background: Retinal pigment epithelial detachment (PED) is a recognised associated finding in central serous chorioretinopathy (CSC). We report our experience in treating patients using photodynamic therapy (PDT) in a variant of chronic CSC that presents with only an isolated PED. We present long-term follow-up data and novel observations on the pattern of retinal pigment epithelium (RPE) changes seen after treatment.

Methods: Retrospective case series.

Results and Discussion: CSC with subfoveal PED can be associated with a poor visual prognosis especially when the PED becomes chronic. PDT has been used to treat typical CSC with good outcomes. Three eyes in 3 patients were successfully treated with PDT, using the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy protocol. However, marked RPE disturbance was observed after treatment directly overlying the areas of brisk choroidal hyperpermeability.

PMID: 21325872 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2011 Feb;151(2):384; author reply 384-5.

The effect of image quality on retinal nerve fiber layer measurement in Stratus OCT.

Qiu KL, Zhang MZ.

Comment on:

* Am J Ophthalmol. 2010 Oct;150(4):558-561.e1.

PMID: 21251500 [PubMed - indexed for MEDLINE]

Pathogenesis and epidemiology

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

Nicotine increases VEGF/PEDF ratio in retinal pigment epithelium: a possible mechanism for CNV in passive smokers with AMD.

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Purpose: Cigarette smoking is the strongest environmental risk factor for wet age-related macular degeneration (AMD). Inappropriate expression of pro-angiogenic vascular endothelial growth factor (VEGF) and anti-angiogenic pigment epithelium derived factor (PEDF) may cause choroidal neovascularization (CNV), key event of wet AMD resulting in vision loss. Nicotine (NT), a potent angiogenic agent abundant in second hand smoke, may play a major role in the pathogenesis of wet AMD. The purpose of this study was to evaluate the expression of nicotinic acetylcholine receptors (nAchR) in retinal pigment epithelium (RPE) and determine the effects of NT on RPE-derived VEGF and PEDF expression in the context of passive smoking.

Methods: Human RPE cells were treated with NT (10(-8)M) with or without nAchR non specific antagonist hexamethonium (HXM) (10(-5)M) for 72 hours. RPE sheets were microdissected from rats exposed to NT in drinking water (100 μg/mL) with or without HXM (40 mg/kg/day, intraperitoneal) for 72 hours. Cell death was determined by cell count and proliferation by Western blot for PCNA. nAchR expression was examined by real-time PCR and Western blot. ERK activation was evaluated by Western blot analysis. VEGF and PEDF expression was assessed by ELISA, Western blot and real-time PCR.

Results: Cultured RPE cells constitutively express nAchR α3, α10 and β1 subunits, β1 being most prevalent. nAchR α4, α5, α7 and β2 subunits were detected in RPE sheets from rats, among which α4 is the predominant subtype. NT which did not result in either cell death or proliferation, induced β1 nAchR, upregulated VEGF and downregulated PEDF expression through nAChR in ARPE-19 cells. Transcriptional activation of nAchR α4 subunit and nAChR-mediated upregulation of VEGF and PEDF were observed in RPE from rats exposed to NT.

Conclusion: NT increased VEGF-to-PEDF ratio in RPE through nAchR in vitro and in vivo which may play a key role in the progression to wet AMD in passive smokers.

PMID: 21330654 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2011 Feb;129(2):196-9.

Diabetes Mellitus and Early Age-related Macular Degeneration.

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OBJECTIVE: To examine the association of diabetes mellitus and early age-related macular degeneration (AMD) in Korean adults 50 years and older.

METHODS: This study included 3008 participants aged 50 to 87 years. Early AMD was assessed from retinal photographs based on a modified Wisconsin AMD grading system. Diabetes mellitus was defined as a fasting glucose level of 126 mg/dL or greater or the use of antidiabetic medications. Logistic regression was used to examine the association between diabetes mellitus and early AMD.

RESULTS: There were 88 subjects with early AMD and 315 subjects with diabetes mellitus. After adjusting for age, sex, current smoking, obesity, and hypertension, significant association was found between diabetes mellitus and early AMD. Subjects with diabetes mellitus were more likely to have early AMD (odds ratio, 1.87; 95% confidence interval, 1.07-3.28) than were those without diabetes mellitus.

CONCLUSION: There is a relationship between diabetes mellitus and early AMD in Korean adults 50 years and older. The underlying biological processes remain to be determined.

PMID: 21320966 [PubMed - in process]

Pre-clinical

Micron. 2011 Jan 25. [Epub ahead of print]

Quantitative chemical analysis of ocular melanosomes in stained and non-stained tissues.

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Abstract

Energy-filtered Analytical Electron Microscopy (AEM) was used to image the ultrastructure and determine quantitatively the chemical composition of rat melanosomes of the choroid and the Retinal Pigment Epithelium (RPE). For the first time, the effect of staining in elemental analysis of melanosomes was investigated. Detection limits and accuracies of the applied methods were determined. Compared to previous work applying only quantitative Energy Dispersive X-ray microanalysis (EDX) in the TEM (Eibl, O., et al., 2006. Micron 37, 262), here we present a combined quantitative EDX and Electron Energy Loss Spectroscopy (EELS) analysis, including N. This yields the fraction of eumelanin and pheomelanin in melanosomes by the S/N mole fraction ratio. Melanosomes of the sepia ink sac, used as eumelanin standard, showed an S/N mole fraction ratio of <0.004. Thus, they consist primarily of eumelanin as reported by degradation analysis. In contrast, melanosomes of the rats contained mixed melanin with significant amounts of pheomelanin (S/N 0.02) in the RPE and the choroid. Consistent with the previous publication, it was shown that oxygen mole fractions are especially large in melanosomes (7-10at.%) compared to other cell compartments, e.g. 2-4at.% oxygen in the cytoplasm. In the melanosomes of non-stained tissue, the oxygen mole fraction clearly correlated with the Ca mole fraction. EDX spectra used for quantitative analysis had about 15,000 net counts under the oxygen peak, which is necessary to obtain (i) a small statistical error for oxygen and (ii) optimum minimum detectable mole fractions for S, Ca and transition metals. The precise determination of the oxygen mole fraction in melanosomes is important for understanding metabolism. Therefore, a detailed analysis was carried out on the possible errors affecting quantification. While O, S, and N mole fractions yielded similar results in stained and non-stained ocular melanosomes of rats, transition metals can only be determined reliably in non-stained tissues. High-precision EDX analysis of melanosomes yielded minimum detectable mole fractions of less than 0.04at.% for Cu and Zn, these elements were present in melanosomes with mole fractions of about 0.3at.% and 0.1at.%, respectively. Zn is of great importance for metabo-

lism and for age related macular degeneration. Its mole fraction in melanosomes of rats is large enough to be detected and to be quantitatively analyzed by EDX spectroscopy. Ultrastructural information can now be correlated to the elemental composition. This is important to better understand the physical and chemical properties of melanosomal metabolism and turnover.

PMID: 21330141 [PubMed - as supplied by publisher]

Diet

Biochemistry. 2011 Feb 15. [Epub ahead of print]

Identification of StARD3 as a Lutein-binding Protein in the Macula of the Primate Retina.

Li B, Vachali P, Frederick JM, Bernstein PS.

Abstract

Lutein, zeaxanthin and their metabolites are the xanthophyll carotenoids that form the macular pigment of the human retina. Epidemiological evidence suggests that high levels of these carotenoids in the diet, serum and macula are associated with decreased risk of age-related macular degeneration (AMD), and the AREDS2 study is prospectively testing this hypothesis. Understanding the biochemical mechanisms underlying the selective uptakes of lutein and zeaxanthin into the human macula may provide important insights into the physiology of the human macula in health and disease. GSTP1 is the macular zeaxanthin-binding protein, but the identity of the human macular lutein-binding protein has remained elusive. Prior identification of the silkworm lutein-binding protein (CBP) as a member of the steroidogenic acute regulatory domain (StARD) protein family, and selective labeling of monkey photoreceptor inner segments by anti-CBP antibody provided an important clue toward identifying the primate retina lutein-binding protein. Homology of CBP to all 15 human StARD proteins was analyzed using database searches, western blotting and immunohistochemistry, and we here provide evidence to identify StARD3 (also known as MLN64) as a human retinal lutein-binding protein. Further, recombinant StARD3 selectively binds lutein with high affinity (KD = 0.45 micromolar) when assessed by surface plasmon resonance (SPR) binding assays. Our results demonstrate previously unrecognized, specific interactions of StARD3 with lutein and provide novel avenues to explore its roles in human macular physiology and disease.

PMID: 21322544 [PubMed - as supplied by publisher]