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MD Research News

Issue 70

Monday March 5, 2012

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Drug treatment

Graefes Arch Clin Exp Ophthalmol. 2012 Mar 2. [Epub ahead of print]

EXTEND III: Efficacy and safety of ranibizumab in South Korean and Taiwanese patients with subfoveal CNV secondary to AMD.

Kwon OW, Lee FL, Chung H, Lai CC, Sheu SJ, Yoon YH; on behalf of the EXTEND III study group.

The Retina Center, Nune Eye Hospital, Seoul, Korea.

BACKGROUND:

The purpose of this study was to investigate the efficacy and safety of intravitreal ranibizumab 0.5 mg in South Korean and Taiwanese patients with subfoveal choroidal neovascularization (CNV) secondary to age -related macular degeneration (AMD).

METHODS:

This was a 12-month, open-label, single-arm, multi-center, phase III study. Ninety-five patients (Taiwanese: 51; South Korean: 44) were included in the study. Key outcome measures assessed included: mean change in best-corrected visual acuity (BCVA) from baseline to months 4 (primary endpoint) and 12 (secondary endpoint); other secondary endpoints comprising categorized mean change in BCVA from baseline at month 4 and month 12, mean change in BCVA from baseline at month 4 and month 12 per baseline characteristics; and incidence of ocular and non-ocular adverse events and serious adverse events (SAEs) at month 12.

RESULTS:

The mean BCVA change improved significantly ($p < 0.0001$) from baseline to both month 4 (+9.3 letters) and month 12 (+10.1 letters). At month 12, the proportion of patients who gained ≥5, 10, or 15 letters from baseline was 75.8%, 54.7%, and 32.6% respectively. Total and CNV lesion area significantly decreased from baseline ($p < 0.0001$). About 57% of patients showed complete absence of fluorescein leakage at month 12. Mean change from baseline visual acuity scores also increased significantly over time for all subgroups. At month 12, ocular SAEs occurred in 2.1% of patients (out of which one patient [1.1%] experienced endophthalmitis) and 16.8% of patients experienced non-ocular SAEs. There were no deaths reported during the study.

CONCLUSIONS:

Consistent with previous studies in Caucasian and Japanese populations, EXTEND III confirms that

monthly intravitreal injections of ranibizumab 0.5 mg administered over 12 months is effective and well-tolerated in South Korean and Taiwanese patients with subfoveal CNV secondary to AMD.

PMID: 22382503 [PubMed - as supplied by publisher]

Cir Cir. 2011 May;79(3):225-32.

[Laser-ranibizumab treatment for retinopathy of prematurity in umbral-preumbral disease. Three years of experience].

[Article in Spanish]

Orozco-Gómez LP, Hernández-Salazar L, Moguel-Ancheita S, Ramírez-Moreno MA, Morales-Cruz MV.

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Background: The "Early Treatment for Retinopathy of Prematurity Cooperative" reported a failure rate of 55.2% using laser in zone 1 for treatment of retinopathy of prematurity (ROP). We need to offer better alternatives for those patients. We undertook this study to evaluate the efficacy of combined laser-ranibizumab therapy for ROP with threshold-prethreshold and "plus disease" and to study development of the newborn.

Methods: This is a prospective, experimental, longitudinal and open study including newborns of either <32 weeks of gestation or with a birth weight <1500 g, with threshold-prethreshold retinopathy or "plus disease." The effect of treatment was analyzed and development of the newborn was determined.

Results: We studied 34 eyes of 17 patients. Age at birth was 29.9 ± 2.6 weeks. Birth weight was 1,120 ± 253 g. The statistics demonstrated an important relationship between severity of retinopathy and early birth age, along with a high probability of threshold-prethreshold disease at 29.4 weeks of age or 1204 g birth weight. The Bayley scale reported normal development in 23.5% of cases, global retardation in 23.5%, psychomotor retardation but normal mental behavior in 29.4%, and mental retardation but normal psychomotor development in 23.5%. We demonstrated regression of retinopathy in all cases. Persistence of vascular tortuosity was present in 17.6% of cases without vascular dilatation, and vitreous membrane development was demonstrated in 11.7% of patients.

Conclusions: Laser-ranibizumab treatment has allowed a better control of retinopathy for threshold-prethreshold and "plus disease" in this group of patients.

PMID: 22380989 [PubMed - in process]

Clin Ophthalmol. 2012;6:277-82. Epub 2012 Feb 20.

Effect of photodynamic therapy (PDT), posterior subtenon injection of triamcinolone acetonide with PDT, and intravitreal injection of ranibizumab with PDT for retinal angiomatous proliferation.

Nakano S, Honda S, Oh H, Kita M, Negi A.

Department of Surgery, Division of Ophthalmology, Kobe University Graduate School of Medicine, Kobe.

BACKGROUND:

The purpose of this work was to compare the efficacy of photodynamic therapy (PDT) with or without posterior subtenon injections of triamcinolone acetonide (STA) or intravitreal injections of ranibizumab (IVR) for retinal angiomatous proliferation (RAP).

METHODS:

Thirty-seven eyes from 33 consecutive patients with RAP were treated by PDT monotherapy (Group 1), PDT combined with STA (Group 2), or PDT combined with IVR (Group 3). The best-corrected visual acuity, greatest linear dimension, central retinal thickness, and number of treatments were compared among the three groups.

RESULTS:

The change in mean best-corrected visual acuity (logMAR) at month 3, 6, and 12 after the initial treatment was better in Group 2 (-0.13, -0.23, and -0.21, respectively) and Group 3 (-0.018, 0.0028, and -0.0067, respectively) than in Group 1 (0.13, 0.19, and 0.23, respectively); Group 1 versus Group 2 was statistically significant (P = 0.018). The mean central retinal thickness was reduced from baseline in all groups, but the reduction amplitude was significantly greater in Group 2 than in Group 1 and Group 3. The mean number of treatments was significantly lower in Group 2 (1.1 ± 0.4) and Group 3 (1.5 ± 0.5) than in Group 1 (2.9 ± 0.9) in the 12 months after the initial treatment.

CONCLUSION:

Treatment with STA + PDT may be an effective therapy for RAP lesions over 12 months of follow-up.

PMID: 22375096 [PubMed - in process] PMCID: PMC3287414

Clin Ophthalmol. 2012;6:225-30. Epub 2012 Feb 13.

Bilateral choroidal neovascularization associated with optic nerve head drusen treated by antivascular endothelial growth factor therapy.

Delas B, Almudí L, Carreras A, Asaad M.

Ophthalmology Service, Hospital de Terrassa, Barcelona, Spain.

OBJECTIVE:

To report a good clinical outcome in a patient with bilateral choroidal neovascularization (CNV) associated with optic nerve head drusen (ONHD) treated with intravitreal ranibizumab injection.

METHODS:

A 12-year-old girl was referred for loss of right eye vision detected in a routine check-up. Best-corrected visual acuity (BCVA) was hand movements in the right eye and 0.9 in the left eye. Funduscopy revealed the presence of superficial and buried bilateral ONHD, which was confirmed by ultrasonography and computed tomography, and the study was completed with perimetry. The presence of bilateral CNV, active in the right eye, was observed and subsequently confirmed using fluorescein angiography and optical coherence tomography.

RESULTS:

Treatment with two consecutive injections of intravitreal ranibizumab resulted in inactivation of the neovascular membrane with subretinal fluid reabsorption and improved right eye BCVA. After 12 months' follow-up, this was 20/60 and stable.

CONCLUSION:

Although there are no published studies of safety in children, antiangiogenic therapy for CNV secondary to ONHD may be useful and safe. A search of the literature produced only one previously reported case of ONHD-associated CNV treated with antivascular endothelial growth factor alone.

PMID: 22368440 [PubMed - in process] PMCID: PMC3284202 Free full text

Retina. 2012 Mar;32(3):434-57.

Pharmacokinetic rationale for dosing every 2 weeks versus 4 weeks with intravitreal ranibizumab, bevacizumab, and aflibercept (vascular endothelial growth factor trap-eye).

Stewart MW, Rosenfeld PJ, Penha FM, Wang F, Yehoshua Z, Bueno-Lopez E, Lopez PF.

From the *Mayo Clinic College of Medicine, Jacksonville, Florida; †Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida; ‡Department of Ophthalmology, Shanghai Jiaotong University, Shanghai First People's Hospital, Shanghai, China; §Center for Excellence in Eye Care, Baptist Hospital, Miami, Florida; and ¶Department of Ophthalmology, Herbert Wertheim College of Medicine, Florida International University, Miami, Florida.

PURPOSE:

Monthly dosing with inhibitors of vascular endothelial growth factor (VEGF) results in stable or improved visual acuity in most patients with neovascular age-related macular degeneration. However, a minority of patients show little if any response to therapy with persistent or worsening macular fluid. Pharmacokinetic modeling was performed to determine if more frequent dosing with anti-VEGF drugs could be theoretically beneficial.

METHODS:

A mathematical model comparing the time-dependent relative binding activities of ranibizumab, bevacizumab, and aflibercept (VEGF Trap-eye; VTE) was used to determine the theoretical peak and trough binding activities when the drugs were injected every 14 days and every 28 days. The intravitreal half-lives of ranibizumab, bevacizumab, and the VTE were estimated to be 3.2, 5.6, and 4.8 days, respectively. The relative molar binding activities of ranibizumab, bevacizumab, and the VTE used in the analyses were 1, 0.05 to 0.2, and 140, respectively. The expected peak and trough binding activities for ranibizumab, bevacizumab, and VTE were calculated. Dosing every 2 weeks was performed on selected patients who had a poor response to monthly therapy.

RESULTS:

Dosing of a drug every 2 weeks resulted in markedly improved trough binding activity, but had little impact on the peak binding activity when calculated through Day 28. The dosing of bevacizumab every 2 weeks resulted in trough binding levels that were superior to monthly dosing with ranibizumab at a dose of 0.5 mg and potentially superior to the levels achieved when ranibizumab was dosed monthly at a dose of 2.0 mg. The VTE displayed superior binding levels for both peak and trough levels even when compared with ranibizumab doses given every 2 weeks. Two case reports demonstrate the clinical usefulness of dosing with anti-VEGF therapy every 2 weeks in eyes with VEGF-dependent macular fluid appearing to be refractory to monthly dosing.

CONCLUSION:

The theoretical increase in trough binding levels when anti-VEGF drugs are dosed every 2 weeks most likely explains the clinical benefit observed in patients who received biweekly injections after their poor response to monthly therapy. The short-term use of biweekly dosing may be an attractive treatment option for those eyes that show a treatment response within 2 weeks of an injection, but rebound with increased macular fluid after a month. In the future, VTE should provide higher trough levels of anti-VEGF binding activity and eliminate the need for biweekly dosing in those eyes with VEGF-mediated exudation that appear unresponsive to monthly ranibizumab or bevacizumab.

PMID: 22374154 [PubMed - in process]

Retina. 2012 Mar;32(3):413-6.

Comparison of Age-Related Macular Degeneration Treatment Trials: What did we Learn?

Csaky KG.

Retina Foundation of the Southwest, Dallas, Texas.

PMID: 22374153 [PubMed - in process]

Eur J Pharm Biopharm. 2012 Feb 21. [Epub ahead of print]

siRNA LNCs - A novel platform of lipid nanocapsules for systemic siRNA administration.

David S, Resnier P, Guillot A, Pitard B, Benoit JP, Passirani C.

LUNAM Université, Ingénierie de la Vectorisation Particulaire, Angers, France; INSERM U646, Université d'Angers, Angers, France; INSERM, UMR915, Université de Nantes, Nantes, France.

Abstract

Several siRNA (small interfering RNA) therapeutics are undergoing clinical trials for cancer, respiratory diseases or macular degeneration, but most are administrated locally. In order to overcome the different barriers to attain an efficient siRNA action after systemic administration, nanocarriers able to carry and protect siRNA are awaited. With this aim, we developed a new platform of siRNA lipid nanocapsules (LNCs) using different cationic lipids, combining the properties of LNCs (siRNA protection and targeting) and lipoplexes (efficient siRNA delivery into the cell). The formulation was revealed to contain different compartments. A siRNA quantification method based on UV spectroscopy was developed to locate and quantify siRNA in each compartment. All in all, these novel siRNA LNCs presented sizes of about 55nm with a neutral surface charge and siRNA encapsulation efficiencies up to 65% representing appropriate characteristics for systemic administration.

PMID: 22381204 [PubMed - as supplied by publisher]

Trials. 2011 Dec 13;12 Suppl 1:A13. [Epub ahead of print]

Documentation of adverse events in non-commercial trials of intravitreal injection of anti-VEGF drugs to treat wet age-related macular degeneration (AMD).

Reeves BC, Underwood W, Cappel-Porter H, Baos S, Rogers CA, Arnott M, Harding SP, Chakravarthy U, Foss AE.

Clinical Trials and Evaluation Unit, University of Bristol, Bristol, BS2 8HW, UK.

PMID: 22376660 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Genome Med. 2012 Feb 24;4(2):16. [Epub ahead of print]

Systems-level analysis of age-related macular degeneration reveals global biomarkers and phenotype-specific functional networks.

Newman AM, Gallo NB, Hancox LS, Miller NJ, Radeke CM, Maloney MA, Cooper JB, Hageman GS,

Anderson DH, Johnson LV, Radeke MJ.

BACKGROUND:

Age-related macular degeneration (AMD) is a leading cause of blindness that affects the central region of the retinal pigmented epithelium (RPE), choroid, and neural retina. Initially characterized by an accumulation of sub-RPE deposits, AMD leads to progressive retinal degeneration, and in advanced cases, irreversible vision loss. Although genetic analysis, animal models, and cell culture systems have yielded important insights into AMD, the molecular pathways underlying AMD's onset and progression remain poorly delineated. We sought to better understand the molecular underpinnings of this devastating disease by performing the first comparative transcriptome analysis of AMD and normal human donor eyes.

METHODS:

RPE-choroid and retina tissue samples were obtained from a common cohort of 31 normal, 26 AMD and 11 potential pre-AMD human donor eyes. Transcriptome profiles were generated for macular and extramacular regions, and statistical and bioinformatic methods were employed to identify disease-associated gene signatures and functionally-enriched protein association networks. Selected genes of high significance were validated using an independent donor cohort.

RESULTS:

We identified over 50 annotated genes enriched in cell-mediated immune responses that are globally over-expressed in RPE-choroid AMD phenotypes. Using a machine learning model and a second donor cohort, we show that the top twenty global genes are predictive of AMD clinical diagnosis. We also discovered functionally-enriched gene sets in the RPE-choroid that delineate the advanced AMD phenotypes, neovascular AMD and geographic atrophy. Moreover, we identified a graded increase of transcript levels in the retina related to wound response, complement cascade, and neurogenesis that strongly correlates with decreased levels of phototransduction transcripts and increased AMD severity. Based on our findings, we assembled protein-protein interactomes that highlight functional networks likely to be involved in AMD pathogenesis.

CONCLUSIONS:

We discovered new global biomarkers and gene expression signatures of AMD. These results are consistent with a model whereby cell-based inflammatory responses represent a central feature of AMD etiology, and depending on genetics, environment, or stochastic factors, may give rise to the advanced AMD phenotypes characterized by angiogenesis and/or cell death. Genes regulating these immunological activities, along with numerous other genes identified here, represent promising new targets for AMD-directed therapeutics and diagnostics.

PMID: 22364233 [PubMed - as supplied by publisher]

BMC Med. 2012 Feb 27;10(1):21. [Epub ahead of print]

Transcriptome changes in age-related macular degeneration.

Whitmore SS, Mullins RF.

ABSTRACT:

Age-related macular degeneration (AMD) is a debilitating, common cause of visual impairment. While the last decade has seen great progress in understanding the pathophysiology of AMD, the molecular changes that occur in eyes with AMD are still poorly understood. In the current issue of Genome Medicine, Newman and colleagues present the first systematic transcriptional profile analysis of AMD affected tissues, providing a comprehensive set of expression data for different regions (macula vs. periphery), tissues

(retina vs. RPE/choroid), and disease state (control vs. early or advanced AMD). Their findings will serve as a foundation for additional systems-level research into the pathogenesis of this blinding disease. Please see related article: http://genomemedicine.com/content/4/2/16.

PMID: 22369667 [PubMed - as supplied by publisher]

Curr Eye Res. 2012 Feb 28. [Epub ahead of print]

Overexpression of Fibulin-5 in Retinal Pigment Epithelial Cells Inhibits Cell Proliferation and Migration and Downregulates VEGF, CXCR4, and TGFB1 Expression in Cocultured Choroidal Endothelial Cells.

Li F, Xu H, Zeng Y, Yin ZQ.

Southwest Hospital, Southwest Eye Hospital, Third Military Medical University , Chongqing , R.P.China.

Purpose of the study: Age-related macular degeneration (AMD) is the most common cause of irreversible vision loss. Fibulin-5 (FBLN5) plays a pleiotropic role in the pathogenesis of AMD. We examined whether the in vitro overexpression of FBLN5 in retinal pigment epithelial (RPE) cells alters the proliferation and migration of cocultured choroidal endothelial cells (CECs) and explored the possible mechanisms involved.

Materials and methods: A recombinant lentiviral vector carrying the Fbln5 gene was generated to transduce rat RPE cells. The expression of FBLN5 in transduced RPE cells was detected by quantitative real-time PCR and Western blot. The transduced RPE cells were then cocultured with rhesus macaque CECs in a Transwell coculture system. The impact of overexpression of FBLN5 in RPE cells on CEC proliferation and migration was assessed, as well as the impact on the mRNA expressions of vascular endothelial growth factor (VEGF), C-X-C chemokine receptor type 4 (CXCR4), and transforming growth factor β1 (TGFB1).

Results: Our results showed that a recombinant lentivirus carrying the Fbln5 gene, which could induce overexpression of FBLN5 in RPE cells, was successfully generated. Overexpression of FBLN5 in RPE cells inhibited cell proliferation and migration and downregulated the mRNA expressions of VEGF, CXCR4, and TGFB1 in cocultured CECs.

Conclusions: These findings suggest that FBLN5 may interfere with choroidal neovascularization by downregulating VEGF, CXCR4, and TGFB1 expression and inhibiting CEC proliferation and invasion, intensifying interest in FBLN5 as a target for therapeutic intervention in neovascular AMD.

PMID: 22369482 [PubMed - as supplied by publisher]

Comput Methods Biomech Biomed Engin. 2012 Feb 29. [Epub ahead of print]

Automatic detection of age-related macular degeneration pathologies in retinal fundus images.

Güven A.

Department of Biomedical Engineering , Erciyes University , 38039 , Kayseri , Turkey.

Abstract

Advanced techniques in image processing and analysis are being extensively studied to assist clinical diagnoses. Digital colour retinal fundus images are widely utilised to investigate various eye diseases. In this paper, we describe the detection of optic disc (OD), macula and age-related macular degeneration (ARMD) pathologies of the macular regions in colour fundus images. ARMD causes the loss of central vision in older adults. If the disease is detected early and treated promptly, much of the vision loss can be prevented. Eighty colour retinal fundus images were tested using our proposed algorithm. The Hough

transform was employed for OD determination. A fundus coordinate system was established based on the macula location. An ARMD pathology detection methodology using a subtraction process after contrast-limited adaptive histogram equalisation operations was proposed. The accuracies of the automated segmentations of the OD, macula and ARMD pathologies obtained were 100%, 100% and 95.49%, respectively. These results show that our algorithm is a useful tool for detecting ARMD in retinal fundus images. The application of our method may reduce the time needed by ophthalmologists to diagnose ARMD pathology while providing dependable detection precision. Integration of our technique into traditional software could be used in clinical implementations as an aid in disease diagnosis and as a tool for quantitative evaluation of treatment effectiveness.

PMID: 22372623 [PubMed - as supplied by publisher]

Seeing Perceiving. 2012 Feb 23. [Epub ahead of print]

Quantifying Eye Stability During a Fixation Task: A Review of Definitions and Methods.

Castet E, Crossland M.

Abstract

Several definitions, measurements, and implicit meanings of 'fixation stability' have been used in clinical vision research, leading to some confusion. One definition concerns eye movements observed within fixations (i.e., within periods separated by saccades) when observing a point target: drift, microsaccades and physiological tremor all lead to some degree of within-fixation instability. A second definition relates to eye position during multiple fixations (and saccades) when patients fixate a point target. Increased between -fixation variability, combined with within-fixation instability, is known to be associated with poorer visual function in people with retinal disease such as age-related macular degeneration. In this review article, methods of eye stability measurement and quantification are summarised. Two common measures are described in detail: the bivariate contour ellipse area (BCEA) and the within-isolines area. The first measure assumes normality of the underlying positions distribution whereas the second does not. Each of these measures can be applied to two fundamentally different kinds of eye position data collected during a period of target observation. In the first case, mean positions of eye fixations are used to obtain an estimate of between-fixation variability. In the second case, often used in clinical vision research, eye position samples recorded by the eyetracker are used to obtain an estimate that confounds within- and between-fixation variability.We show that these two methods can produce significantly different values of eye stability, especially when reported as BCEA values. Statistical techniques for describing eye stability when the distribution of eye positions is multimodal and not normally distributed are also reviewed.

PMID: 22370759 [PubMed - as supplied by publisher]

Pathogenesis

J Biol Chem. 2012 Feb 23. [Epub ahead of print]

Inhibiting alternative pathway complement activation by targeting the exosite of factor D.

Katschke KJ, Wu P, Ganesan R, Kelley RF, Mathieu MA, Hass PE, Murray J, Kirchhofer D, Wiesmann C, van Lookeren Campagne M.

Genentech Inc., United States;

Abstract

The alternative complement pathway, by virtue of its amplifying property, has been implicated in a number of inflammatory diseases and constitutes an attractive therapeutic target. An anti-factor D Fab fragment

(AFD) was generated to inhibit the alternative complement pathway in advanced dry age-related macular degeneration. AFD potently prevented factor D (FD)-mediated proteolytic activation of its macro-molecular substrate C3bB, but not proteolysis of a small synthetic substrate, indicating that AFD did not block access of substrate to the catalytic site. The crystal structures of AFD in complex with human and cynomolgus FD (at 2.4 Å and 2.3 Å, respectively) revealed the molecular details of the inhibitory mechanism. The structures showed that the AFD binding site included surface loops of FD that form part of the C3bB exosite. Thus, AFD inhibited FD proteolytic function by interfering with macromolecular substrate access rather than by inhibiting FD catalysis, providing the molecular basis of AFD-mediated inhibition of a rate-limiting step in the alternative complement pathway.

PMID: 22362762 [PubMed - as supplied by publisher]

Neurobiol Aging. 2012 Feb 28. [Epub ahead of print]

Cerebral microbleeds and age-related macular degeneration: the AGES-Reykjavik Study.

Qiu C, Cotch MF, Sigurdsson S, Eiriksdottir G, Jonasson F, Klein R, Klein BE, Harris TB, van Buchem MA, Gudnason V, Launer LJ.

Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, National Institutes of Health (NIH), Bethesda, MD, USA; Aging Research Center, Karolinska Institutet-Stockholm University, Stockholm, Sweden.

Abstract

We test the hypothesis that cerebral microbleeds (CMB) and age-related macular degeneration (AMD), both linked to amyloid-β deposition, are correlated. This study includes 4205 participants (mean age 76.2; 57.8% women) in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study (2002-2006). CMB were assessed from magnetic resonance images, and AMD was assessed using digital retinal images. Data were analyzed with multinomial logistic models controlling for major confounders. Evidence of CMB was detected in 476 persons (272 with strict lobar CMB and 204 with nonlobar CMB). AMD was detected in 1098 persons (869 with early AMD, 140 with exudative AMD, and 89 with pure geographic atrophy). Early and exudative AMD were not associated with CMB. The adjusted odds ratio of pure geographic atrophy was 1.62 (95% confidence interval 0.93-2.82, p = 0.089) for having any CMB, 1.43 (0.66-3.06, p = 0.363) for strict lobar CMB, and 1.85 (0.89-3.87, p = 0.100) for nonlobar CMB. This study provides no evidence that amyloid deposits in the brain and AMD are correlated. However, the suggestive association of geographic atrophy with CMB warrants further investigation.

PMID: 22382405 [PubMed - as supplied by publisher]

Epidemiology

Retina. 2012 Feb 23. [Epub ahead of print]

RECURRENT SUBMACULAR HEMORRHAGE IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

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PURPOSE:

To describe the incidence, risk factors for, and long-term visual outcomes of recurrent submacular hemorrhage in the context of age-related macular degeneration.

METHODS:

Medical records of patients with neovascular age-related macular degeneration with or without polypoidal choroidal vasculopathy showing submacular hemorrhage at their first visit to our institution were reviewed. The required minimum follow-up period was 24 months, and any newly developed submacular hemorrhage larger than 1 disk area after near-complete resolution of initial hemorrhage was defined as recurrence.

RESULTS:

A total of 47 eyes of 47 patients were eligible for inclusion. Twenty-four patients showed recurrent submacular hemorrhage during the follow-up period (Group I). Patients without recurrent submacular hemorrhage were included in Group II. The time to recurrent submacular hemorrhage in Group I patients was 21.4 ± 9.2 months. Polypoidal choroidal vasculopathy was present in 50% of Group I patients (n = 12) and 13% of Group II patients (n = 3) (P = 0.025). Intravitreal anti-vascular endothelial growth factor injection was performed during the follow-up period in 70.8% of Group I patients (n = 17) and 95.7% of Group II patients (n = 22) (P = 0.048). Visual acuity change during the follow-up period did not significantly differ between the two groups.

CONCLUSION:

In patients with neovascular age-related macular degeneration presenting with submacular hemorrhage at their first visit, the incidence of recurrent submacular hemorrhage was 51.1% in our retrospective long-term follow-up study. The presence of polypoidal choroidal vasculopathy was associated with an increased risk of recurrent submacular hemorrhage. Use of anti-vascular endothelial growth factor agents was correlated with a reduced risk of such hemorrhage. Visual acuity was stably maintained over 2 years regardless of hemorrhage recurrence.

PMID: 22366903 [PubMed - as supplied by publisher]

PLoS One. 2012;7(2):e32022. Epub 2012 Feb 21.

Presenting the uncertainties of odds ratios using empirical-bayes prediction intervals.

Lin WY, Lee WC.

Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan.

Abstract

Quantifying exposure-disease associations is a central issue in epidemiology. Researchers of a study often present an odds ratio (or a logarithm of odds ratio, logOR) estimate together with its confidence interval (CI), for each exposure they examined. Here the authors advocate using the empirical-Bayes-based 'prediction intervals' (PIs) to bound the uncertainty of logORs. The PI approach is applicable to a panel of factors believed to be exchangeable (no extra information, other than the data itself, is available to distinguish some logORs from the others). The authors demonstrate its use in a genetic epidemiological study on age-related macular degeneration (AMD). The proposed PIs can enjoy straightforward probabilistic interpretations-a 95% PI has a probability of 0.95 to encompass the true value, and the expected number of true values that are being encompassed is [Formula: see text] for a total of [Formula: see text] 95% PIs. The PI approach is theoretically more efficient (producing shorter intervals) than the traditional CI approach. In the AMD data, the average efficiency gain is 51.2%. The PI approach is advocated to present the uncertainties of many logORs in a study, for its straightforward probabilistic interpretations and higher efficiency while maintaining the nominal coverage probability.

PMID: 22363789 [PubMed - in process] PMCID: PMC3283699 Free full text

Genetics

Graefes Arch Clin Exp Ophthalmol. 2012 Feb 29. [Epub ahead of print]

An association between environmental factors and the IVS4+44C>A polymorphism of the DMT1 gene in age-related macular degeneration.

Wysokinski D, Zaras M, Dorecka M, Waszczyk M, Szaflik J, Blasiak J, Szaflik JP.

Department of Molecular Genetics, University of Lodz, Pomorska 141/143, 90-236, Lodz, Poland.

BACKGROUND:

Age-related macular degeneration (AMD) is an ocular disease affecting macula - the central part of the retina, resulting in the degeneration of photoreceptors and retinal epithelium and causing severe central vision impairment. The pathophysiology of the disease is not completely known, but a significant role is attributed to genetic factors. The contribution of oxidative stress in AMD as a trigger of the degenerative process is well-established. Iron ions may act as a source of reactive oxygen species; therefore, maintaining iron homeostasis is important for redox balance in the organism. Diversity in iron homeostasis genes may counterpart in unbalanced redox state, and thus be involved in AMD pathophysiology.

METHODS:

In this work, we searched for an association between some single nucleotide polymorphisms in the divalent metal transporter 1 (DMT1) gene intronic IVS4+44C>A (rs224589) and 3'-UTR c.2044T>C (rs2285230) and environmental factors and AMD. Genotyping was performed using the PCR-RFLP method. DNA was obtained from 436 AMD patients and 168 controls.

RESULTS:

We did not find any association between the genotypes of the two polymorphisms and AMD occurrence. However, we observed that AMD patients living in a rural environment and having the CC genotype of the IVS4+44C>A polymorphism had an increased risk of AMD, while individuals with the CA genotype or the A allele had a decreased risk of the disease. Moreover, in male AMD patients the C allele increased the risk of the disease, while the AA genotype decreased it.

CONCLUSIONS:

These results suggest that the VS4+44C>A polymorphism of the DMT1 gene may interact with place of living and gender to modulate the risk of AMD.

PMID: 22371024 [PubMed - as supplied by publisher]

Diet

Am J Ophthalmol. 2012 Feb 28. [Epub ahead of print]

The Short-term Effects of Antioxidant and Zinc Supplements on Oxidative Stress Biomarker Levels in Plasma: A Pilot Investigation.

Brantley MA Jr, Osborn MP, Sanders BJ, Rezaei KA, Lu P, Li C, Milne GL, Cai J, Sternberg P Jr.

Vanderbilt Eye Institute, Vanderbilt University Medical Center, Nashville, Tennessee.

PURPOSE:

To determine if short-term Age-Related Eye Disease Study (AREDS) antioxidant and zinc supplementation

affects biomarkers of oxidative stress, possibly serving as a predictor of their efficacy.

DESIGN:

Prospective interventional case series.

METHODS:

Nineteen subjects, 12 with intermediate or advanced age-related macular degeneration (AMD) (AREDS categories 3 or 4) and 7 non-AMD controls, were admitted to the Vanderbilt General Clinical Research Center and placed on a controlled diet for 7 days. Antioxidant and zinc supplements were stopped 2 weeks prior to study enrollment. Dietary supplementation with 500 mg vitamin C, 400 IU vitamin E, 15 mg β-carotene, 80 mg zinc oxide, and 2 mg cupric oxide per day was instituted on study day 2. Blood was drawn on study days 2 and 7, and plasma concentrations of cysteine (Cys), cystine (CySS), glutathione (GSH), isoprostane (IsoP), and isofuran (IsoF) were determined.

RESULTS:

Short-term AREDS supplementation significantly lowered mean plasma levels of CySS in participants on a regulated diet (P = .034). No significant differences were observed for Cys, GSH, IsoP, or IsoF. There were no significant differences between AMD patients and controls.

CONCLUSIONS:

This pilot interventional study shows that a 5-day course of antioxidant and zinc supplements can modify plasma levels of CySS, suggesting that this oxidative stress biomarker could help predict how likely an individual is to benefit from AREDS supplementation. Further, CySS may be useful for the evaluation of new AMD therapies, particularly those hypothesized to affect redox status.

PMID: 22381365 [PubMed - as supplied by publisher]

Lipids Health Dis. 2012 Feb 29;11(1):33. [Epub ahead of print]

The relation between serum lipids and lutein and zeaxanthin in the serum and retina: results from cross-sectional, case-control and case study designs.

Renzi LM, Hammond BR Jr, Dengler M, Roberts R.

BACKGROUND:

The xanthophyll carotenoids lutein (L) and zeaxanthin (Z) are found in and around the macula of the primate retina, where they are termed macular pigment (MP). Dietary L and Z are absorbed with fat in the gut and transported on lipoproteins to the retina. Both MP and serum lipoproteins have been related to risk for neurodegenerative diseases such as age-related macular degeneration (AMD). L and Z are carried on both HDL (related to reduced risk of AMD) and LDL (related to increased risk). The purpose of this set of studies was to analyze the relation between L and Z in the serum and retina with the circulating lipid profile.

METHODS:

In all experiments, lipoproteins were measured enzymatically from plasma, and MP optical density (MPOD) was measured using customized heterochromatic flicker photometry. Experiment 1: Relations between serum L and Z, MPOD and lipoprotein levels. 108 young, healthy subjects (M = 23.2, SD = 4.12 years) participated. Lipoprotein levels and MPOD were measured. In a subset of 66 participants, serum L and Z levels were also measured using high-performance liquid chromatography. Experiment 2: Relations between lipoprotein levels and MPOD in statin users. 20 subjects (M = 58.05, SD = 11.08 years) taking statin medication and 20 subjects (M = 57.95, SD = 11.03 years) not taking satin were recruited for participation. MPOD and lipoprotein levels were measured. Experiment 3: lowering lipoprotein levels to

impact MPOD. One individual (aged 41 years) with high MP density adhered first to an atorvastatin regimen, then, after a wash-out period, to a rosuvastatin regimen.

RESULTS:

Experiment 1: HDL were significantly ($p < 0.05$) related to MPOD ($r = 0.33$), to serum L ($r = 0.36$) and to serum Z ($r = 0.26$). MPOD was also significantly related to total cholesterol ($r = 0.19$). Experiment 2: MPOD was not lower in statin users when compared to matched non-statin users, but MPOD decreased significantly with increased duration of statin use ($r = 0.63$). Experiment 3: Administration of a statin regimen reduced MPOD with atorvastatin ($p < 0.05$) but not with rosuvastatin.

CONCLUSIONS:

Serum xanthophylls, retinal xanthophylls and lipoprotein concentrations are significantly related, and changing lipoprotein levels may impact levels of retinal xanthophylls.

PMID: 22375926 [PubMed - as supplied by publisher

Nutritional Supplements for Age-Related Macular Degeneration: A Systematic Review [Internet].

Editors

Kansagara D, Gleitsmann K, Gillingham M, Freeman M, Quiñones A.

Washington (DC): Department of Veterans Affairs (US); 2012 Jan.

VA Evidence-based Synthesis Program Reports.

Excerpt

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the developed world. In 2004, AMD affected 1.75 million persons in the United States, a number that is expected to rise to nearly 3 million by 2020 due to the aging of the population. The severity of macular degeneration ranges from Category 1 (least severe) to Category 4 (most severe), and “advanced AMD” is defined as having geographic atrophy involving the center of the macula or features of choroidal neovascularization. Observational studies suggest that people with dietary intakes higher in various carotenoids, antioxidants and omega-3 fatty acids have a lower risk of developing AMD. This has led to several supplementation trials designed to examine the ability of nutritional supplement with carotenoids, antioxidants, or omega-3 fatty acids to prevent the progression of AMD. Our report focuses on the evidence documenting the potential benefits and harms of certain dietary supplements in patients with AMD. We conducted a systematic review of published literature to address the following key questions: In patients with age-related macular degeneration, do nutritional supplements containing carotenoids, antioxidants, or omega-3 fatty acids alone or in combination prevent functional visual loss? In adult populations, what are the harms of carotenoid, antioxidant, and omega-3 fatty acid supplementation?

PMID: 22379659 [PubMed] Books & Documents

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