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MD Research News

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

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Drug treatment

J Drugs Dermatol. 2013 Sep 1;12(9):1052-5.

Cutaneous lupus erythematosus in a patient undergoing intravitreal bevacizumab injections: case report and review of the literature.

Cleaver N, Ramirez J, Gildenberg S.

INTRODUCTION: Bevacizumab is a recombinant humanized antibody against vascular endothelial growth factor (VEGF). It is approved by the Food and Drug Administration (FDA) for metastatic colorectal cancer, advanced non-small cell lung cancer, metastatic renal cell cancer and glioblastoma. Bevacizumab has also been used off label in ophthalmology for age-related macular degeneration, diabetic retinopathy, retinal vein occlusions, retinopathy of prematurity, and other chorioretinal vascular disorders. Numerous case reports have described various cutaneous reactions in response to bevacizumab therapy including acneiform eruptions and exfoliative dermatitis.

CASE PRESENTATION: We report a case of a 63 year-old Caucasian female who presented with subacute cutaneous lupus erythematosus six weeks after initiating two intravitreal injections of bevacizumab for central serous choroidopathy.

CONCLUSION: We report the first documented case of a cutaneous lupus erythematosus eruption following bevacizumab administration as a monotherapy.

PMID: 24002156 [PubMed - in process]

Ophthalmology. 2013 Sep;120(9):e68-9. doi: 10.1016/j.ophtha.2013.06.031.

Long-term Safety of Ranibizumab in Neovascular Age-related Macular Degeneration.

Matonti F, Courjaret JC, Hoffart L, Amouyal F, Denis D.

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PMID: 24001549 [PubMed - in process]

Other treatment & diagnosis

Ophthalmology. 2013 Aug 28. pii: S0161-6420(13)00612-X. doi: 10.1016/j.ophtha.2013.07.013. [Epub ahead of print]

Quantitative Classification of Eyes with and without Intermediate Age-related Macular Degeneration Using Optical Coherence Tomography.

Farsiu S, Chiu SJ, O'Connell RV, Folgar FA, Yuan E, Izatt JA, Toth CA; Age-Related Eye Disease Study 2 Ancillary Spectral Domain Optical Coherence Tomography Study Group.

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OBJECTIVE: To define quantitative indicators for the presence of intermediate age-related macular degeneration (AMD) via spectral-domain optical coherence tomography (SD-OCT) imaging of older adults.

DESIGN: Evaluation of diagnostic test and technology.

PARTICIPANTS AND CONTROLS: One eye from 115 elderly subjects without AMD and 269 subjects with intermediate AMD from the Age-Related Eye Disease Study 2 (AREDS2) Ancillary SD-OCT Study.

METHODS: We semiautomatically delineated the retinal pigment epithelium (RPE) and RPE drusen complex (RPEDC, the axial distance from the apex of the drusen and RPE layer to Bruch's membrane) and total retina (TR, the axial distance between the inner limiting and Bruch's membranes) boundaries. We registered and averaged the thickness maps from control subjects to generate a map of "normal" non-AMD thickness. We considered RPEDC thicknesses larger or smaller than 3 standard deviations from the mean as abnormal, indicating drusen or geographic atrophy (GA), respectively. We measured TR volumes, RPEDC volumes, and abnormal RPEDC thickening and thinning volumes for each subject. By using different combinations of these 4 disease indicators, we designed 5 automated classifiers for the presence of AMD on the basis of the generalized linear model regression framework. We trained and evaluated the performance of these classifiers using the leave-one-out method.

MAIN OUTCOME MEASURES: The range and topographic distribution of the RPEDC and TR thicknesses in a 5-mm diameter cylinder centered at the fovea.

RESULTS: The most efficient method for separating AMD and control eyes required all 4 disease indicators. The area under the curve (AUC) of the receiver operating characteristic (ROC) for this classifier was >0.99. Overall neurosensory retinal thickening in eyes with AMD versus control eyes in our study contrasts with previous smaller studies.

CONCLUSIONS: We identified and validated efficient biometrics to distinguish AMD from normal eyes by analyzing the topographic distribution of normal and abnormal RPEDC thicknesses across a large atlas of eyes. We created an online atlas to share the 38 400 SD-OCT images in this study, their corresponding segmentations, and quantitative measurements.

PMID: 23993787 [PubMed - as supplied by publisher]

Ugeskr Laeger. 2013 Sep 2;175(36):2035-2038.

[New perspectives for the treatment of age-related macular degeneration.][Article in Danish]

Rafique I, Munch IC.

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Abstract: Currently, age-related macular degeneration (AMD) is untreatable, except for its neovascular complications. We review the primary pathogenesis of AMD and the pipeline of experimental interventions currently under way in clinical trials. They focus on four mechanisms: suppression of inflammation, visual cycle modification, prevention of oxidative damage and neuroprotection. Regulatory approval is years away, but the development may be accelerated by re-purposing of medications designed for systemic diseases.

PMID: 23992911 [PubMed - as supplied by publisher]

J Med Econ. 2013 Sep 4. [Epub ahead of print]

A Systematic Literature Review of Utility Weights in Wet Age-Related Macular Degeneration.

Pearson I, Rycroft C, Irving A, Ainsworth C, Wittrup-Jensen K.

RTI Health Solutions, Manchester, UK.

Abstract Objective: The objective of the study was to conduct a systematic review of utility weight estimates relevant to economic models for wet age-related macular degeneration (wAMD). Methods: A systematic literature search of PubMed, Embase, the Cochrane Library, and EconLit was performed (January 1995-December 2010) and then updated (October 2010-May 2012; February 2012-July 2013) identifying articles reporting utilities in patients with wAMD and visual impairment. Extracted studies were also assessed for compliance with the NICE reference case.

Results: Of 2,415 articles identified from the searches, 212 articles were reviewed in full, and 17 selected for data extraction. Most studies used time trade-off (TTO) techniques to estimate utilities; other methods included standard gamble, EuroQoL Health Questionnaire 5 Dimensions (EQ-5D); Short-Form 6D Health Status Questionnaire (SF-6D); and Health Utilities Index Mark III (HUI3). Correlation between utility estimates and visual acuity (VA) differed between the instruments. Time trade-off methods were more sensitive to VA changes than standard gamble methods. HUI3 estimates were most highly correlated with VA changes, followed by TTO; no trend was observed between VA and EQ-5D or SF-6D utility weights. Six of the 17 studies complied with the NICE reference case.

Conclusions: Several instruments have been used to elicit utilities from patients with wAMD. Because TTO methods were more sensitive to VA changes than standard gamble and HUI3 estimates were most highly correlated with VA changes, TTO and HUI3 may be suitable methods for economic evaluations in these patients. The EQ-5D and SF-6D were poor indicators of the impact of VA on HRQL.

PMID: 24004384 [PubMed - as supplied by publisher]

Adv Healthc Mater. 2013 Jul;2(7):1056-62.

Eyes on 3D-current 3D biomimetic disease concept models and potential applications in age-related macular degeneration.

Feigl B, Hutmacher D.

Abstract: Three-dimensional cellular models that mimic disease are being increasingly investigated and have opened an exciting new research area into understanding pathomechanisms. The advantage of 3D in vitro disease models is that they allow systematic and in depth studies of physiological and pathophysiological processes with less costs and ethical concerns that have arisen with animal models. The purpose of the 30 approach is to allow crosstalk between cells and microenvironment, and with cues from the microenvironment,cells can assemble their niche similar to in vivo conditions. The use of 3D models for mimicking disease processes such as cancer, osteoarthritis etc., Is only emerging and allows

multidisciplinary teams consisting of tissue engineers, biologist biomaterial scientists and clinicians to work closely together. While in vitro systems require rigorous testing before they can be considered as replicates of the in vivo model, major steps have been made,suggesting that they will become powerful tools for studying physiological and pathophysiological processes. This paper aims to summarize some of the existing 3D models and proposes a novel 3D model of the eye structures that are involved in the most common cause of blindness in the Western World,namely age-related macular degeneration (AMD).

PMID: 24000403 [PubMed - in process]

Mo Med. 2014 Jul-Aug;110(4):344-8.

Eye on statins: A comprehensive review.

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Abstract: Over the last 25 years, statins have demonstrated their safety from an ophthalmologic standpoint. Studies relating statin to cataract formation are insufficient to alter the usual and customary prescription of statins. If there is an association between statins and cataracts, it is weak and clinically insignificant. Prospective studies have not demonstrated a benefit of adding statin therapy in patients with age-related macular degeneration (ARMD), but these studies have not been adequately powered to detect moderate differences. A subset of patients with persistently elevated lipids despite taking statins may be at higher risk of developing wet ARMD. The use of statins for the prevention and/ or treatment of glaucoma patients warrants further prospective study. There is a possibility that statins may unmask or exacerbate myasthenia gravis.

PMID: 24003655 [PubMed - in process]

Pathogenesis

Adv Gerontol. 2013;26(1):122-9.

[Potential of melatonin for prevention of age-related macular degeneration: experimental study].

[Article in Russian]

[No authors listed]

Abstract: Decline with age of the content of melatonin is considered as one of the leading mechanisms of aging and development of associated diseases, including age-related macular degeneration (AMD)--the disease, which becomes the most common cause of blindness and acuity of vision deterioration in elderly. The prospects of the use of melatonin in the prevention of AMD is being actively discussed, but as a rule on the basis of the results of the experiments on cells in retinal pigment epithelium (RPE). We showed previously that the senescence-accelerated OXYS rat is an adequate animal model of AMD, already used for identifying the relevant therapeutic targets. Here we have investigated the effect of Melatonin (Melaksen, 0,004 mg per kg--a dose equivalent to the recommended one for people) on the development of retinopathy similar to AMD in OXYS rats. Ophthalmoscopic examinations show that Melatonin supplementation decreased the incidence and severity of retinopathy and improved some (but not all) histological abnormalities associated with retinopathy. Thus, melatonin prevented the structural and functional changes in RPE cells, reduced the severity of microcirculatory disorders. Importantly, Melatonin prevented destruction of neurosensory cells, associative and gangliolar neurons in the retina. Taken together, our data suggest the therapeutic potential of Melatonin for treatment and prevention of AMD.

PMID: 24003738 [PubMed - in process]

Vestn Ross Akad Med Nauk. 2013;(4):63-7.

[Investigation of possible approaches to angiogenesis regulation in vitro with the help of recombinant fragments of angiogenesis inhibitors such as endostatin, tumstatin and PEDF].

[Article in Russian]

[No authors listed]

Abstract: Neovascular diseases of visual organ such as age-related macular degeneration, retinopathy of prematurity, diabetic retinopathy, thrombosis of central retina vein and its branches, neovascular glaucoma, choroid and retina tumors have the leading positions in the list of ophtalmopatologies that result in blindness and incapacity. The variety of angiostatic medications of applied ophtalmology is scant. The aim of work was to study the possibile approaches to angiogenesis regulation in vitro with the help of recombinant fragments of natural inhibitors of angiogenesis such as endostatin, tumstatin and PEDF (pigment epithelial derived factor), and also theirability to be the base of potentially feasible and pharmacologically active substances. It is determined that endostatin, tumstatin and PEDF, as well as the comparison medication Bevacizumab in vitro have pro-or antiangiogenic influence. The direction of the biological effect depends on the cultivation conditions, peptide concentration in the cultural fluid and stage of angiogenesis.

PMID: 24003724 [PubMed - in process]

J Zhejiang Univ Sci B. 2013 Sept.;14(9):763-773.

Structures and biogenetic analysis of lipofuscin bis-retinoids.

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Abstract: Age-related macular degeneration (AMD) is still an incurable blinding eye disease because of complex pathogenic mechanisms and unusual diseased regions. With the use of chemical biology tools, great progress has been achieved in improving the understanding of AMD pathogenesis. The severity of AMD is, at least in part, linked to the non-degradable lipofuscin bis-retinoids in retinal pigment epithelial (RPE). This material is thought to result from the lifelong accumulation of lysosomal residual bodies containing the end products derived from the daily phagocytosis of rod outer segments by RPE cells. Here, we present previously recognized bis-retinoids with focus on structures and biosynthetic pathways. In addition to a brief discussion on the mutual conversion relationships of bis-retinoids, future perspectives and the medical relevance of such studies on these lipofuscin constituents are also highlighted.

PMID: 24009196 [PubMed - as supplied by publisher]

Epidemiology

J Environ Sci Health A Tox Hazard Subst Environ Eng. 2013;48(14):1757-63. doi: 10.1080/10934529.2013.823323.

Nitrate-nitrogen levels in rural drinking water: Is there an association with age-related macular degeneration?

Klein BE, McElroy JA, Klein R, Howard KP, Lee KE.

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Health , Madison , Wisconsin , USA.

Abstract: We examined the association of nitrate-nitrogen exposure from rural private drinking water and incidence of age-related macular degeneration (AMD). All participants in the Beaver Dam Eye Study (53916 improvement plan code) completed a questionnaire and had an ocular examination including standardized, graded fundus photographs at five examinations. Only information from rural residents in that study are included in this report. Data from an environmental monitoring study with probabilistic-based agro -chemical sampling, including nitrate-nitrogen, of rural private drinking water were available. Incidence of early AMD was associated with elevated nitrate-nitrogen levels in rural private drinking water supply (10.0% for low, 19.2% for medium, and 26.1% for high nitrate-nitrogen level in the right eye). The odds ratios (ORs) were 1.77 (95% confidence interval [CI]: 1.12-2.78) for medium and 2.88 (95% CI: 1.59-5.23) for high nitrate-nitrogen level. Incidence of late AMD was increased for those with medium or high levels of nitrate-nitrogen compared to low levels (2.3% for low and 5.1% for the medium or high nitrate-nitrogen level, for the right eye). The OR for medium or high nitrate-nitrogen groups was 2.80 (95% CI: 1.07-7.31) compared to the low nitrate-nitrogen group.

PMID: 24007430 [PubMed - in process]

Genetics

Asia Pac J Ophthalmol (Phila). 2013 Jul;2(4):269-274.

Genetic and Epigenetic Regulation in Age-related Macular Degeneration.

Wei L, Chen P, Lee JH, Nussenblatt RB.

Laboratory of Immunology, National Eye Institute, Bethesda, MD 20892, USA ; National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD 20892, USA ; Zhongshan Ophthalmic Center, Guangzhou, China.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the older population worldwide. While strong genetic risk factors have been associated with AMD etiology, environmental influences through epigenetic regulation are also likely to play a role. Recent advances in epigenetic studies have resulted in the development of numerous epigenetic drugs for the treatment of cancer and inflammation. Here, we review the current literature on the genetic and epigenetic mechanisms of AMD and suggest that understanding the cooperation of epigenetic and genetic mechanisms will greatly advance the clinical management of AMD.

PMID: 23997991 [PubMed] PMCID: PMC3755470 [Available on 2014/7/1]

Diet

PLoS One. 2013 Aug 29;8(8):e73387. doi: 10.1371/journal.pone.0073387.

The effect of lutein supplementation on blood plasma levels of complement factor d, c5a and c3d.

Tian Y, Kijlstra A, van der Veen RL, Makridaki M, Murray IJ, Berendschot TT.

University Eye Clinic, Maastricht, Maastricht, The Netherlands.

Abstract: Lutein is selectively taken up by the primate retina and plays an important role as a filter for harmful blue light and as an antioxidant. Recent studies have shown that lutein has systemic anti-inflammatory properties. Dietary lutein has been associated with reduced circulating levels of inflammatory biomarkers such as CRP and sICAM. Whether lutein also affects activation of the complement system has

not yet been addressed and was the purpose of the study described here. Seventy-two subjects with signs of early macular degeneration were randomly assigned to receive either a 10 mg lutein supplement or a placebo during one year. EDTA blood samples were collected at 0, 4, 8 and 12 months. Complement factor D (CFD), a rate limiting component of the alternative pathway of complement activation and the complement activation products C5a and C3d were determined in the plasma samples by ELISA. A significant 0.11 µg/ml monthly decrease in plasma CFD concentration was observed in the lutein group ($p<0.001$), resulting in a 51% decrease from 2.3 µg/ml at baseline to 1.0 µg/ml at 12 months. The C5a concentration showed a significant 0.063ng/ml monthly decrease in the lutein group ($p<0.001$) resulting in a 36% decrease from 2.2ng/ml at baseline to 1.6ng/ml at 12 months. The C3d concentration showed a significant 0.19µg/ml monthly decrease in the lutein group ($p=0.004$) that gave rise to a 9% decrease from 15.4µg/ml at baseline to 14.4µg/ml at 12 months. In the placebo group we found a significant 0.04 µg/ml monthly decrease in plasma CFD concentration, whereas no changes were observed for C5a and C3d. Lutein supplementation markedly decreases circulating levels of the complement factors CFD, C5a and C3d levels, which might allow a simple method to control this inflammatory pathway of the innate immune system.

PMID: 24009749 [PubMed - in process] PMCID: PMC3756963