Macular Disease Foundation AUSTRALIA
Our focus is your vision

MD Research News

Issue 219

Monday 16 February, 2015

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

If you have not already subscribed, please email Rob Cummins at **research@mdfoundation.com.au** with 'Subscribe to MD Research News' in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your 'unsubscribe' request.

Drug treatment

Ophthalmologica. 2015 Jan 30. [Epub ahead of print]

Intravitreal Ranibizumab for Predominantly Hemorrhagic Choroidal Neovascularization in Age-Related Macular Degeneration.

Lazzeri S, Figus M, Sartini MS, et al

Purpose: To evaluate the effects of intravitreal ranibizumab monotherapy on predominantly hemorrhagic choroidal neovascularization with foveal involvement associated with age-related macular degeneration.

Materials and Methods: Twenty-two consecutive eyes with hemorrhagic neovascularization were treated with 3 monthly intravitreal ranibizumab injections. Additional injections were administered according to retreatment criteria during 12 months of follow-up.

Results: A mean of 6.64 ± 1.36 injections was administered. Overall, the mean visual acuity increased from 10.90 ± 6.02 to 12.81 ± 8.34 ETDRS letters ($p > 0.05$) at 12 months. The 'early treatment group' gained a mean of 2.83 ± 2.24 ETDRS letters ($p < 0.05$), while the 'late treatment group' gained a mean of 0.30 ± 1.25 ETDRS letters ($p > 0.05$) with significant differences between the groups ($p < 0.05$). A progressive resolution of macular bleeding was registered in 20 patients (mean time: 5.3 ± 1.6 months).

Conclusions: Ranibizumab injections can be considered a beneficial approach for the management of predominantly hemorrhagic choroidal neovascularization with foveal involvement associated with age-related macular degeneration. Furthermore, the time interval between hemorrhage and the first injection seems to be an important predicting factor of final visual acuity.

PMID: 25662794 [PubMed - as supplied by publisher]

Ophthalmologe. 2015 Feb 12. [Epub ahead of print]

[Retrospective investigation of anti-VEGF treatment reality and effectiveness in patients with neovascular age-related macular degeneration (AMD) in Germany : Treatment reality of ranibizumab for neovascular AMD in Germany.][Article in German]

Ziemssen F, Eter N, Fauser S, et al

BACKGROUND:Neovascular (wet) age-related macular degeneration (wAMD) is a progressive and degenerative retinal disease. This study reports the real-life use in Germany of the standard anti-vascular endothelial growth factor (VEGF) therapy for wAMD as an intravitreal operative drug application.

PATIENTS AND METHODS:Within the framework of an international retrospective study the medical records of patients with wAMD who were first treated with ranibizumab between 1 January and 31 August

2009 were evaluated. Data were collected until the end of treatment and/or monitoring or until 31 August 2011. The primary objective was to evaluate changes in visual acuity after the start of anti-VEGF therapy. Secondary outcomes included determining real-life anti-VEGF treatment regimens and disease-monitoring practices.

RESULTS:Out of 2227 patients who received ≥ 1 anti-VEGF injection with a baseline visual acuity assessment and ≥ 1 post-baseline visual acuity assessment for the treated eye, 420 were included in the German cohort. Visual acuity improved until about day 90 but these gains in visual acuity were not maintained. The mean changes in visual acuity scores from baseline to years 1 and 2 were 1.1 ± 15.7 and -0.8 ± 17.2 letters, respectively. Patients received a mean of 4.3 ± 1.9 and 1.3 ± 2.2 injections in years 1 and 2, respectively. The majority of visits (98.6 %) were conducted irregularly and outside the time frame recommended at the time of the study, with an average of 47.7 ± 36.7 days between visits. More frequent visits and injections were associated with greater improvements in visual acuity.

CONCLUSION:Treatment intensity was not sufficient to maintain the initial improvement in visual acuity by ranibizumab treatment. Real-life results for visual acuity and injection frequency in the German cohort were worse at that time than in other countries. Regular follow-up visits as well as timely retreatment in the presence of signs of disease activity are required to achieve optimal results in wAMD when applying a pro re nata-based strategy.

PMID: 25668709 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2015 Feb;50(1):37-43.

Parafoveal contributions to retinal function during ranibizumab therapy for age-related macular degeneration.

Eisenbarth W, Feucht N, Enders C, et al.

OBJECTIVE: The standard measure for the assessment of functional vision in the central retina is best corrected visual acuity (VA). Our aim was to investigate whether it is an advantage to include tests for functional changes in the near retinal periphery to monitor treatment effects in patients receiving multiple injections of anti-vascular endothelial growth factor (anti-VEGF) agents for advanced exudative age-related macular degeneration (AMD).

DESIGN: Prospective pilot study.

PARTICIPANTS: Our cohort consisted of 24 patients with exudative AMD (mean age ± SD: 77.46 ± 7.82 years) treated at an ophthalmology clinic.

METHODS: We compared data from standard functional measurements, VA-near, and contrast sensitivity (CS), with results from the macular mapping test (MMT) at 10% and 100% contrast. Measurements of retinal thickness by optical coherence tomography (OCT) were used to document the morphologic efficacy of the anti-VEGF agent. Tests were performed at baseline and 4 weeks after 3 monthly ranibizumab injections.

RESULTS: All 4 functional tests yielded successes (equal or better visual performance after treatment) in 79.2% to 83.3% of cases. Including test locations in the near periphery yielded the highest success rate in the MMT at 10% contrast. Values for VA-near and CS also improved in a majority of cases. OCT measurements of retinal thickness indicated that the agent was effective in the fovea and near periphery.

CONCLUSIONS: Our findings indicate that using the MMT adds information about functional changes in the near periphery of the retina and allows more sensitive assessment of treatment effects or disease progression without the high expense of other techniques.

PMID: 25677281 [PubMed - in process]

Open Ophthalmol J. 2014 Dec 31;8:101-4.

Incidence of Retinal Pigment Epithelial Tears and Associated Risk Factors After Treatment of Age-Related Macular Degeneration with Intravitreal Anti-VEGF Injections.

Empeslidis T, Vardarinos A, Konidaris V, et al

PURPOSE: To study the incidence and risk factors for retinal pigment epithelium tears following intravitreal anti-vascular endothelial growth factor (VEGF) injections.

METHODS: Retrospective longitudinal study. 4027 intravitreal anti-VEGF injections in 628 patients (676 eyes) for choroidal neovascularisation associated with age related macular degeneration in a period of 18 months were studied.

RESULTS: Seventeen patients (mean age 83.95±5.84) developed retinal pigment epithelium tears. The incidence rate was 0.4%. Fibrovascular pigment epithelium detachment (PED) was previously observed in all cases. In 88 % (15/17) of AMD patients that had a RPE tear, PED height was found to be less than 400 microns at presentation. In 5 of 7 patients with RPE tear grade <4, continuing of anti-VEGF treatment resulted to improvement of visual acuity.

CONCLUSION: Critical risk factors for RPE tears are presence of PED as well as advanced age. Visual improvement appears to depend more on the extent and location of the RPE tear and less on the PED height.

PMID: 25674188 [PubMed]

Ophthalmology. 2015 Feb 7. [Epub ahead of print]

Visual Impairment and Blindness Avoided with Ranibizumab in Hispanic and Non-Hispanic Whites with Diabetic Macular Edema in the United States.

Varma R, Bressler NM, Doan QV, et al

OBJECTIVE: To estimate visual impairment (VI) and blindness avoided with intravitreal ranibizumab 0.3 mg treatment for central-involved diabetic macular edema (DME) among Hispanic and non-Hispanic white individuals in the United States.

DESIGN: Population-based model simulating visual acuity (VA) outcomes over 2 years after diagnosis and treatment of DME.

PARTICIPANTS: Visual acuity changes with and without ranibizumab were based on data from the RISE, RIDE, and DRCR Network trials.

METHODS: For the better-seeing eye, VA outcomes included VI, defined as worse than 20/40 in the better-seeing eye, and blindness, defined as VA of 20/200 or worse in the better-seeing eye. Incidence of 1 or both eyes with central-involved DME in 2010 were estimated based on the 2010 United States population, prevalence of diabetes mellitus, and 1-year central-involved DME incidence rate. Sixty-one percent of incident individuals had bilateral DME and 39% had unilateral DME, but DME could develop in the fellow eye.

MAIN OUTCOMES MEASURES: Cases of VI and blindness avoided with ranibizumab treatment.

RESULTS: Among approximately 102 million Hispanic and non-Hispanic white individuals in the United States 45 years of age and older in 2010, an estimated 37 274 had central-involved DME and VI eligible for ranibizumab treatment. Compared with no ranibizumab treatment, the model predicted that ranibizumab 0.3 mg every 4 weeks would reduce the number of individuals with VI from 11 438 (95% simulation interval [SI], 7249-16 077) to 6304 (95% SI, 3921-8981), a 45% (95% SI, 36%-53%) reduction at 2 years. Ranibizumab would reduce the number of incident eyes with VA worse than 20/40 from 16 910 (95% SI, 10 729-23 577)

to 9361 (95% SI, 5839-13 245), a 45% (95% SI, 38%-51%) reduction. Ranibizumab was estimated to reduce the number of individuals with legal blindness by 75% (95% SI, 58%-88%) and the number of incident eyes with VA of 20/200 or worse by 76% (95% SI, 63%-87%).

CONCLUSIONS: This model suggests that ranibizumab 0.3 mg every 4 weeks substantially reduces prevalence of VI and legal blindness 2 years after initiating treatment among Hispanic and non-Hispanic white individuals in the United States with central-involved DME that has caused vision loss.

PMID: 25670501 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Feb 12. [Epub ahead of print]

Ziv-aflibercept in macular disease.

Mansour AM, Al-Ghadban SI, Yunis MH, El-Sabban ME.

BACKGROUND/AIMS: Aflibercept is an approved therapy for neovascular age-related macular degeneration (AMD) and diabetic macular oedema (DME). In vitro and in vivo studies did not detect toxicity to the retinal pigment epithelium cells using the approved cancer protein, ziv-aflibercept. Our purpose is to determine if ziv-aflibercept can be used in AMD and DME without ocular toxicity, to test the stability of ziv-aflibercept, and to do a cost analysis.

METHODS: Prospectively, consecutive patients with AMD or DME and poor vision underwent one intravitreal injection of 0.05 mL of fresh filtered ziv-aflibercept (1.25 mg). Monitoring of best-corrected visual acuity, intraocular inflammation, cataract progression, and retinal structure by spectral domain optical coherence tomography was done at 1 day and 1 week after injection. Ziv-aflibercept activity over 4 weeks was measured by capturing vascular endothelial growth factor by ELISA.

RESULTS: There were no signs of retinal toxicity, intraocular inflammation or change in lens status in four eyes with AMD and two eyes with DME. Visual acuity improved (p=0.05) and central foveal thickness decreased in all patients (p=0.05). Ziv-aflibercept had no loss of anti-VEGF activity when kept at 4°C in polycarbonate syringes over 4 weeks. Similar to bevacizumab, compounded ziv-aflibercept would yield a tremendous saving compared with aflibercept or ranibizumab.

CONCLUSIONS: Off-label use of ziv-aflibercept improves visual acuity without ocular toxicity and may offer a cheaper alternative to the same molecule aflibercept.

PMID: 25677668 [PubMed - as supplied by publisher]

Cochrane Database Syst Rev. 2015 Feb 11;2:CD006927. [Epub ahead of print]

Statins for age-related macular degeneration.

Gehlbach P, Li T, Hatef E.

BACKGROUND: Age-related macular degeneration (AMD) is a progressive late onset disorder of the macula affecting central vision. Age-related macular degeneration is the leading cause of blindness in people over 65 years in industrialized countries. Recent epidemiologic, genetic, and pathological evidence has shown AMD shares a number of risk factors with atherosclerosis, leading to the hypothesis that statins may exert protective effects in AMD.

OBJECTIVES: The objective of this review was to examine the effectiveness of statins compared with other treatments, no treatment, or placebo in delaying the onset and progression of AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 6), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations,

Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2014), EMBASE (January 1980 to June 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to June 2014), PubMed (January 1946 to June 2014), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 5 June 2014.

SELECTION CRITERIA: We included randomized controlled trials (RCTs) that compared statins with other treatments, no treatment, or placebo in participants who were either susceptible to or diagnosed as having early stages of AMD.

DATA COLLECTION AND ANALYSIS: We used standard methodological procedures expected by The Cochrane Collaboration. Two authors independently evaluated the search results against the selection criteria, abstracted data, and assessed risk of bias. We did not perform meta-analysis due to heterogeneity in the interventions and outcomes among the included studies.

MAIN RESULTS: Two RCTs with 144 total participants met the selection criteria. Both trials compared simvastatin versus placebo in older people (> 50 or 60 years) with high risk of developing AMD (drusen present on examination). The larger trial with 114 participants was conducted in Australia and used a higher dose (40 mg daily) of simvastatin for three years. Participants and study personnel in this trial were adequately masked; however, data were missing for 30% of participants at three years follow-up. The smaller trial of 30 participants was conducted in Italy and used a lower dose (20 mg) of simvastatin for three months. This trial reported insufficient details to assess the risk of bias.Neither trial reported data for change in visual acuity. Analysis of 30 participants in the smaller trial did not show a statistically significant difference between the simvastatin and placebo groups in visual acuity values at three months of treatment (decimal visual acuity 0.21 ± 0.56 in simvastatin group and 0.19 ± 0.40 in placebo group) or 45 days after the completion of treatment (decimal visual acuity 0.20 ± 0.50 in simvastatin group and 0.19 ± 0.48 in placebo group). The lack of a difference in visual acuity was not explained by lens or retina status, which remained unchanged during and after the treatment period for both groups.Preliminary analyses of 42 participants who had completed 12 months follow-up in the larger trial did not show a statistically significant difference between simvastatin and the placebo groups for visual acuity, drusen score, or visual function (effect estimates and confidence intervals were not available). Complete data for these outcomes at three years follow-up were not reported. At three years, the effect of simvastatin in slowing progression of AMD compared with placebo was uncertain (odds ratio 0.51, 95% confidence interval 0.23 to 1.09).One trial did not report adverse outcomes. The second trial reported no difference between groups in terms of adverse events such as death, muscle aches, and acute hepatitis.

AUTHORS' CONCLUSIONS: Evidence from currently available RCTs is insufficient to conclude that statins have a role in preventing or delaying the onset or progression of AMD.

PMID: 25675254 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2015 Feb 12. [Epub ahead of print]

Fundus Autofluorescence Characteristics of Nascent Geographic Atrophy in Age-Related Macular Degeneration.

Wu Z, Luu CD, Ayton LN, Goh JK, Lucci LM, Hubbard WC, Hageman J, Hageman G, Guymer RH.

Purpose: To examine the fundus autofluorescence (FAF) characteristics of nascent geographic atrophy (nGA), pathological features preceding the development of drusen-associated atrophy in eyes with age-related macular degeneration (AMD) that can be visualized using high-resolution optical coherence tomography (OCT).

Methods: Spectral-domain OCT (SD-OCT) and FAF imaging were performed longitudinally in 221 eyes with intermediate AMD (having at least drusen >125 µm), and 7 areas that developed drusen-associated atrophy in 5 eyes were examined and categorized with respect to FAF characteristics. These categories were then used to characterize 49 areas of nGA or drusen-associated atrophy on SD-OCT identified in a cross-sectional study with 230 participants with bilateral intermediate AMD.

Results: Sequential imaging revealed that FAF characteristics in the atrophic areas could be grouped into three categories: predominantly hyperautofluorescent (hyperAF), both hyper- and hypoautofluorescence (mixed AF) or predominantly hypoautofluorescent (hypoAF). In the cross-sectional study, the FAF characteristics were significantly dependent on the type of atrophic area (P = 0.002), where areas of nGA appeared most commonly as being mixed AF (63%) while areas of drusen-associated atrophy most commonly as hypoAF (86%).

Conclusions: FAF imaging revealed that areas of nGA were most commonly characterized by both hyper- and hypoautofluorescent changes, which differs from areas of drusen-associated atrophy that most often appeared hypoautofluorescent. These findings provide important insights into the FAF characteristics of areas undergoing atrophic changes in eyes still considered to be in the early stages of AMD by current methods, and thus assist in the characterization of disease severity in these early stages.

PMID: 25678689 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Feb 10. [Epub ahead of print]

In Vivo Quantification of Retinal Changes Associated with Drusen in Age-Related Macular Degeneration.

Rogala J, Zangerl B, Assaad N, et al.

Purpose: Drusen alter retinal architecture in early age-related macular degeneration (AMD). However abnormalities may also exist in drusen-free areas of the AMD retina. This study examines retinal thickness above drusen relative to drusen-free areas in the same patient and a normal population.

Methods: Patients with early to intermediate AMD (n=122) or no disease (n=30) were examined at the Centre for Eye Health. Spectral domain optical coherence tomography (SD-OCT) scans through single, isolated druse (n=125) or confluent drusen (n=54) were obtained. The thickness of individual retinal layers was measured above the druse and in a drusen-free area, 150µm from the drusen edge.

Results: Intra-eye comparisons found total retinal thickness above drusen was 16±0.6% less than drusen-free areas. Thinning was mostly in the retinal pigment epithelium/photoreceptor layer (32±1% reduction) and the outer nuclear layer (22±1% reduction). Confluent drusen showed similar thinning of the outer retina as well as inner retina loss (5%). Thinning was strongly correlated to drusen height but only modestly correlated to drusen width. When compared to the normal population, retinal thickness above drusen and drusen-free areas were both significantly reduced.

Conclusions: We confirm outer retina thinning above drusen in early/intermediate AMD compared to drusen -free areas in the same retina or a normal population. Interestingly, drusen-free areas in AMD patients were not the same as control patients suggesting 'normal' areas of the AMD retina are abnormal. The strong correlation between retinal thinning and drusen height, rather than width suggests current grading systems for AMD may need refinement.

PMID: 25670493 [PubMed - as supplied by publisher]

Pathogenesis

Exp Eye Res. 2015 Feb 4;132C:208-215. [Epub ahead of print]

Quercetin alleviates 4-hydroxynonenal-induced cytotoxicity and inflammation in ARPE-19 cells.

Hytti M, Piippo N, Salminen A, et al.

Abstract: Retinal pigment epithelium (RPE) plays the principal role in age-related macular degeneration (AMD), a progressive eye disease with no cure and limited therapeutical options. In the pathogenesis of AMD, degeneration of RPE cells by multiple factors including increased oxidative stress and chronic inflammation precedes the irreversible loss of photoreceptors and central vision. Here, we report that the plant-derived polyphenol, quercetin, increases viability and decreases inflammation in stressed human ARPE-19 cells after exposure to the lipid peroxidation end product 4-hydroxynonenal (HNE). Several previous studies have been conducted using the direct oxidant H2O2 but we preferred HNE since natural characteristics predispose RPE cells to the type of oxidative damage evoked by lipid peroxidation. Quercetin improved cell membrane integrity and mitochondrial function as assessed in LDH and MTT tests. Decreased production of proinflammatory mediators IL-6, IL-8, and MCP-1 were indicated at the RNA level by qPCR and at the protein level by the ELISA technique. In addition, we probed the signaling behind the effects and observed that p38 and ERK MAPK pathways, and CREB signaling are regulated by quercetin in ARPE-19 cells. In conclusion, our present data suggests that HNE is highly toxic to serum-starved ARPE-19 cells but quercetin is able to reverse these adverse effects even when administered after an oxidative insult.

PMID: 25662315 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Jan 20;56(2):1002-13.

Canonical/β-Catenin Wnt Pathway Activation Improves Retinal Pigmented Epithelium Derivation From Human Embryonic Stem Cells.

Leach LL, Buchholz DE, Nadar VP,et al

PURPOSE: The purpose of this study was to better understand the role canonical/β-catenin Wnt signaling plays in the differentiation of human embryonic stem cells (hESCs) into retinal pigmented epithelium (RPE), with the goal of improving methods for derivation.

METHODS: Fluorescent reporters were generated to monitor RPE differentiating from hESCs by using a previously described 14-day derivation protocol. Reporters were used to test the effects of the canonical/β-catenin Wnt pathway agonist CHIR99021 on differentiating RPE. Cells derived from differentiation studies were characterized by lineage-specific transcription factor expression, morphology, pigmentation, and function. The RPE derivation efficiency was determined from percentage positive PMEL17 expression.

RESULTS: Fluorescent reporters mimicked expression of endogenous genes during 14-day differentiation to RPE. Analysis of Wnt pathway gene expression showed that the pathway components are expressed in differentiating RPE cells. Addition of CHIR99021 improved RPE derivation based on morphology, expression of RPE-specific lineage markers, and genes involved in melanogenesis. Additionally, expression of the neural retina marker CHX10 was suppressed during differentiation with CHIR99021. Addition of soluble WNT3A, but not WNT5A, had the same result. The CHIR99021-modified protocol yielded cell populations that were 97.77% ± 0.1% positive for the RPE marker PMEL17 at day 14. After cells were expanded to passage 3, they were shown to express RPE markers, carry out phagocytosis of rod outer segments, and secrete pigment epithelium-derived factor apically and vascular endothelial growth factor basally.

CONCLUSIONS: Our findings demonstrated the importance of canonical/β-catenin Wnt signaling in RPE differentiation and showed that manipulating the pathway significantly improves RPE derivation from hESC.

PMID: 25604686 [PubMed - in process]

PLoS One. 2015 Feb 13;10(2):e0117777.

Intracameral Interleukin 1β, 6, 8, 10, 12p, Tumor Necrosis Factor α and Vascular Endothelial Growth Factor and Axial Length in Patients with Cataract.

Zhu D, Yang DY, Guo YY, Zheng YF, Li JL, Wang B, Tao Y, Jonas JB.

OBJECTIVE: To assess associations between the aqueous humour concentration of interleukin IL-1β, IL-6, IL-8, IL-10 and IL-12p, tumor necrosis factor α (TNF-α) and vascular endothelial growth factor (VEGF) and axial length in eyes with cataract.

METHODS: The hospital-based investigation included patients who underwent cataract surgery between March 2014 and April 2014. Using aqueous humour collected at the start of cataract surgery, the interleukins IL-1β, IL-6, IL-8, IL-10 and IL-12p, TNF-α and VEGF were examined using a cytometric bead array. Axial length was determined by partial coherence laser interferometry (IOL Master).

RESULTS: The study included 33 patients with cataract (33 eyes) with a mean age of 69.2±10.8 years (range:50-87 years) and a mean axial length of 24.7±1.9 mm (range:22.6-31.5 mm). Lower aqueous concentration of VEGF was significantly associated with longer axial length (VEGF concentration (pg/mL) = -5.12 x Axial Length (mm) + 163; correlation coefficient r = -0.41; P<0.001) and more myopic refractive error (VEGF concentration (pg/mL) = 1.27xspherical equivalent (diopters)+44.8; r = 0.383; P = 0.002). The aqueous concentrations of all other substances were not significantly (all P>0.10) associated with axial length or refractive error.

CONCLUSIONS: Higher intravitreal concentrations of VEGF were measured in eyes with a longer axial length, while the intraocular concentrations of IL-1β, IL-6, IL-8, IL-10, IL-12p and TNF-α were not correlated with axial length. The lower concentration of VEGF in axially elongated eyes may be one of the reasons for the lower prevalence of age-related macular degeneration and diabetic retinopathy in myopic eyes.

PMID: 25679504 [PubMed - as supplied by publisher]

PLoS One. 2015 Feb 12;10(2):e0117911.

TNF-α Mediates PKCδ/JNK1/2/c-Jun-Dependent Monocyte Adhesion via ICAM-1 Induction in Human Retinal Pigment Epithelial Cells.

Lee IT, Liu SW, Chi PL, Lin CC, Hsiao L, Yang CM.

Abstract: Retinal inflammatory diseases induced by cytokines, such as tumor necrosis factor-α (TNF-α) are associated with an up-regulation of intercellular adhesion molecule-1 (ICAM-1) in the retinal pigment epithelial cells (RPECs). Retinal pigment epithelium (RPE) is a monolayer of epithelial cells that forms the outer blood-retinal barrier in the posterior segment of the eye, and is also implicated in the pathology of, such as neovascularization in age-related macular degeneration (AMD). However, the detailed mechanisms of TNF-α-induced ICAM-1 expression are largely unclear in human RPECs. We demonstrated that in RPECs, TNF-α could induce ICAM-1 protein and mRNA expression and promoter activity, and monocyte adhesion. TNF-α-mediated responses were attenuated by pretreatment with the inhibitor of PKCs (Ro318220), PKCδ (Rottlerin), MEK1/2 (U0126), JNK1/2 (SP600125), or AP-1 (Tanshinone IIA) and transfection with siRNA of TNFR1, TRAF2, JNK2, p42, or c-Jun. We showed that TNF-α could stimulate the TNFR1 and TRAF2 complex formation. TNF-α-stimulated JNK1/2 was also reduced by Rottlerin or SP600125. However, Rottlerin had no effect on TNF-α-induced p42/p44 MAPK phosphorylation. We observed that TNF-α induced c-Jun phosphorylation which was inhibited by Rottlerin or SP600125. On the other hand, TNF-α-stimulated ICAM-1 promoter activity was prominently lost in RPECs transfected with the point-mutated AP-1 ICAM-1 promoter plasmid. These results suggest that TNF-α-induced ICAM-1 expression and monocyte adhesion is mediated through a TNFR1/TRAF2/PKCδ/JNK1/2/c-Jun pathway in RPECs. These findings concerning TNF-α-induced ICAM-1 expression in RPECs imply that TNF-α might play an important role in ocular inflammation and diseases.

PMID: 25675437 [PubMed - as supplied by publisher]

Epidemiology

Invest Ophthalmol Vis Sci. 2015 Feb 10. [Epub ahead of print]

Diabetes, Cardiovascular Morbidity and Risk of Age-Related Macular Degeneration in a Primary Care Population.

Vassilev Z, Ruigómez A, Soriano-Gabarró M, et al

Purpose: Age-Related Macular Degeneration (AMD) is the most common cause of legal blindness in Western patients over 65 years of age. We aimed to establish the incidence of AMD, and the association of diabetes, cardiovascular and eye diseases with the risk of AMD, in a large cohort of primary care patients in the United Kingdom (UK).

Methods: Using data from The Health Improvement Network database in the UK, all individuals with a first recorded diagnosis of AMD from 2004-2010 were identified (N=10,516) and frequency-matched to 19,389 AMD-free individuals by age, gender and calendar year of AMD occurrence. Logistic regression was used to examine co-morbidities and risk factors for AMD.

Results: The incidence of AMD was 18.08 (95% confidence interval [CI]: 17.74-18.43) per 10,000 person-years. A positive association with AMD was observed for smoking, a high frequency of primary care visits, and referrals. Diabetes and use of anti-diabetic drugs were both associated with an increased risk of AMD. Prevalence of cardiovascular diseases among AMD patients was slightly higher than in controls, with a small increased risk of AMD among patients with myocardial infarction, heart failure or hyperlipidemia. Positive associations were observed between prior eye diseases and risk of AMD, in particular for chorioretinal disorders.

Conclusions: The incidence of AMD in the UK is in line with previously reported incidence rates from population-based studies. The study suggests an association between diabetes, prior eye diseases, cardiovascular co-morbidities and AMD risk, and a link between AMD and higher healthcare utilization.

PMID: 25670489 [PubMed - as supplied by publisher]

Ophthalmologica. 2015 Feb 7. [Epub ahead of print]

Prevalence of Age-Related Macular Degeneration in Portugal: The Coimbra Eye Study - Report 1.

Cachulo MD, Lobo C, Figueira J, et al

Purpose: To evaluate the age- and gender-specific prevalence of early and late age-related macular degeneration (AMD) in a Portuguese population-based sample.

Methods: All patients aged ≥55 years of a Portuguese primary health-care unit were recruited for a cross-sectional population-based study. Responders underwent complete ophthalmological examination and digital fundus imaging. Early and late AMD was defined according to the International Age-Related Macular Epidemiological Study Group Classification, and the adopted staging for AMD was the same as that used in the Rotterdam study. The age- and gender-adjusted prevalence of early and late forms of AMD was calculated.

Results: Of the 4,370 eligible subjects, 3,000 underwent study procedures (68.6% response rate) and 2,975 were included in the analysis; they had a mean age of 68.9 ± 8.6 years. The overall prevalence of early and late AMD was 15.53% (95% CI 14.25-16.88) and 0.67% (95% CI 0.41-1.04), respectively. Neovascular AMD (NV-AMD) and geographic atrophy (GA) accounted for 0.44% (95% CI 0.23-0.75) and 0.27% (95% CI 0.12-0.53) of individuals, respectively. The highest prevalence of advanced AMD was among those aged ≥75 years (1.13% for NV-AMD; 0.63% for GA).

Conclusions: To our knowledge, this is the first AMD epidemiological study in a Portuguese population. The

early forms of the disease had a similar prevalence to that of other large-scale population-based cohorts, but late AMD was less frequent than previously reported. © 2015 S. Karger AG, Basel.

PMID: 25677077 [PubMed - as supplied by publisher]

Open Ophthalmol J. 2014 Dec 31;8:95-100.

Population-based age group specific annual incidence rates of symptomatic age-related macular degeneration.

Saari JM.

PURPOSE: To study the population-based annual incidence rates of exudative, dry and all cases of symptomatic age-related macular degeneration (AMD) in different age and sex groups.

METHODS: This is a one year, prospective, population-based study on all consecutive new patients with AMD in the hospital district of Central Finland. The diagnosis was confirmed in all patients with slit lamp biomicroscopy, optical coherence tomography (OCT) using a Spectralis HRA + OCT device, and the Heidelberg Eye Explorer 1.6.2.0 program. Fluorescein angiograms were taken when needed.

RESULTS: The population-based annual incidence rates of all cases of symptomatic AMD increased from 0.03% (95% CI, 0.01-0.05%) in the age group 50-59 years to 0.82% (95% CI, 0.55-1.09%) in the age group 85-89 years and were 0.2% (95% CI, 0.17-0.24%) in exudative, 0.11% (95% CI, 0.09-0.14%) in dry, and 0.32% (95% CI, 0.28-0.36%) in all cases of AMD in the age group 60 years and older. During the next 20 years in Central Finland the population-based annual incidence rates can be estimated to increase to 0.27% (95% CI, 0.24-0.30%) in exudative, to 0.13% (95% CI, 0.11-0.15%) in dry, and to 0.41% (95% CI, 0.37-0.45%) in all cases of AMD in the age group 60 years and older. The population-based annual incidence of AMD did not show statistically significant differences between males and females (p>0.1).

CONCLUSION: The population-based age-group specific annual incidence rates of symptomatic AMD of this study may help to plan health care provision for patients of AMD.

PMID: 25674187 [PubMed]

Genetics

Prog Retin Eye Res. 2015 Feb 7. [Epub ahead of print]

Vision from next generation sequencing: Multi-dimensional genome-wide analysis for producing gene regulatory networks underlying retinal development, aging and disease.

Yang HJ, Ratnapriya R, Cogliati T, et al

Abstract: Genomics and genetics have invaded all aspects of biology and medicine, opening uncharted territory for scientific exploration. The definition of "gene" itself has become ambiguous, and the central dogma is continuously being revised and expanded. Computational biology and computational medicine are no longer intellectual domains of the chosen few. Next generation sequencing (NGS) technology, together with novel methods of pattern recognition and network analyses, has revolutionized the way we think about fundamental biological mechanisms and cellular pathways. In this review, we discuss NGS-based genome-wide approaches that can provide deeper insights into retinal development, aging and disease pathogenesis. We first focus on gene regulatory networks (GRNs) that govern the differentiation of retinal photoreceptors and modulate adaptive response during aging. Then, we discuss NGS technology in the context of retinal disease and develop a vision for therapies based on network biology. We should emphasize that basic strategies for network construction and analyses can be transported to any tissue or cell type. We believe that specific and uniform guidelines are required for generation of genome,

transcriptome and epigenome data to facilitate comparative analysis and integration of multi-dimensional data sets, and for constructing networks underlying complex biological processes. As cellular homeostasis and organismal survival are dependent on gene-gene and gene-environment interactions, we believe that network-based biology will provide the foundation for deciphering disease mechanisms and discovering novel drug targets for retinal neurodegenerative diseases.

PMID: 25668385 [PubMed - as supplied by publisher]

Hum Immunol. 2015 Feb 6. [Epub ahead of print]

HLA class II genotypes are not associated with age related macular degeneration in a case-control, population-based study.

Pappas D, Hollenbach J, Coleman AL, Study of Osteoporotic Fractures (SOF) Research Group.

Abstract: Multiple lines of evidence support an immunologic basis and genetic disposition for the development of age-related macular degeneration (AMD). Comprehensive human leukocyte antigens (HLA) class II typing at four loci (DRB1, DQA1, DQB1, and DPB1) was assessed using next generation sequencing methods and tested for association with age-related macular degeneration (AMD) in a case-control study of 456 AMD cases and 499 controls from the population-based Study of Osteoporotic Fractures (SOF) cohort. No statistically significant associations were identified for any of the class II loci and a previously identified association between DRB1*13:01 was not replicated in this dataset. These results reported here suggest that common HLA class II genetic variation does not contribute to AMD disease risk.

PMID: 25665771 [PubMed - as supplied by publisher]

Clin Experiment Ophthalmol. 2015 Feb 11. [Epub ahead of print]

Current landscape of direct-to-consumer genetic testing and its role in ophthalmology.

Sanfilippo PG, Kearns LS, Wright P, Mackey DA, Hewitt AW.

Abstract: The sequencing of the human genome, over a decade ago, was fundamental for developing personalised medicine. This is perhaps most apparent in the emergence of the direct-to-consumer (DTC) genetic testing market, which allows individuals to obtain information about their genetic profile and its many health and lifestyle implications. By circumventing the doctor-patient relationship, DTC genetic testing challenges the traditional model of healthcare delivery, and this raises concern among regulatory bodies worldwide. Genetics play an important role in the development of many eye diseases. However, little information is available describing the influence of the DTC industry in ophthalmology. In this review we examined DTC companies providing genetic test products for eye disease, giving a snapshot of the current market. Of all eye conditions, the majority of DTC companies provided susceptibility testing or risk assessment for age-related macular degeneration (AMD). For the 15 companies noted to offer products, we found considerable variation in the cost, scope and clarity of informational content of DTC genetic testing for ophthalmic conditions. The clinical utility of these tests currently remains in question and the AAO recommendations against routine testing for many conditions probably still apply.

PMID: 25676199 [PubMed - as supplied by publisher]

Diet, lifestyle and low vision

Public Health. 2015 Feb 9. [Epub ahead of print]

Certifications for sight impairment due to age related macular degeneration in England.

Bunce C, Zekite A, Walton S, Rees A, Patel PJ.

OBJECTIVES: To examine variability across England in certification rates for age related macular degeneration (AMD) between 1st April 2011 and 31st March 2012.

STUDY DESIGN: Cross-sectional survey.

METHODS: An electronic version of the CVI, the ECVI, was used at the Certifications Office, London, to transfer information from paper based certificates into a database. The electronic certifications data set was queried for all certificates completed in England between April 1st 2011 and March 31st 2012 with the main cause of certifiable visual loss being AMD or with the main cause of certifiable visual loss being multiple pathology but a contributory cause being AMD. Data were explored by type of AMD, visual status, age and sex and then directly standardized rates were computed by English region.

RESULTS: The Certifications Office received 23,616 CVIs for England between April 2011 and March 2012, of which 10,481 (44%) were people certified severely sight-impaired (blind) (SSI) and 12,689 (54%) were certified as sight-impaired (partial sight) (SI). The remainder did not have visual status classified. AMD contributed to 11546 causes of certification on the CVI forms during this period, 53% of forms being for geographic atrophy (GA)/dry AMD which is currently mostly untreatable. The median (interquartile) age at certification for AMD was 86 (81, 90) years and women were more commonly certified than men (66%). Considerable variability was seen across English regions, although there was consistency in that GA was the more common form in all areas.

CONCLUSIONS: There is considerable regional variability in CVI rates in England, which are not attributable to differences in age or sex. Reasons for such variability need examination yet this should not undermine the value of these data in terms of describing those newly registered with sight impairment due to AMD who are predominantly female and over 85 years of age.

PMID: 25677221 [PubMed - as supplied by publisher]